TABLE OF CONTENTS

Pegylated Interferon +/- Ribavirin for Children with HCV (PEDS-C)

MANUAL OF PROCEDURES

September 21, 2005

Pegylated Interferon +/- Ribavirin for Children with HCV (PEDS-C)
MANUAL OF PROCEDURES

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

CHAPTER 1

INTRODUCTION

1.1 Protocol Summary

PEDS-C is a Phase III, randomized, blinded, placebo-controlled trial to compare the safety and efficacy of peginterferon alfa-2a (PEG-2a) plus placebo vs. peginterferon alfa-2a in combination with Ribavirin (RV) for the treatment of chronic hepatitis C virus in children.

The specific aims of the study are to:

I) Assess the safety and efficacy of PEG-2a in combination with RV and PEG-2a alone for the treatment of chronic hepatitis C virus (CHC) in children.

II) Determine whether PEG-2a in combination with RV or PEG-2a alone will result in a higher sustained virological response rate in children with CHC.

III) Examine the effects of PEG-2a (with or without concomitant RV) treatment on body mass index, body composition, and linear growth in children with CHC.

IV) Characterize short and long-term outcomes, including: health-related quality of life; cognitive, developmental, and psychological functioning; and behavior in children treated with PEG-2a (with or without concomitant RV).

A total of 112 children 5-18 years of age at enrollment (not year reached 18th birthday at screening) will be recruited at 11 clinical centers. Patients not previously treated with RV or interferon and meeting all eligibility criteria will be enrolled after informed consent is obtained. They will be randomized to treatment groups in a 50:50 ratio by a computerized randomization scheme stratified by Clinical Center and HCV genotype (I vs. all others).

Enrolled patients will receive a subcutaneous PEG-2a injection once a week given with placebo or RV tablet's given once or twice daily, depending on body weight. Baseline studies will be obtained prior to the start of treatment. Following the initiation of

study drug, patients will return for evaluations at 1, 3, 5, 8 weeks, and then every 4 weeks while receiving the study drug.

Children randomized to PEG-2a plus placebo who exhibit viral disappearance at week 24 will be treated for a total of 48 weeks, followed closely for 24 weeks after stopping therapy, and have 2 annual visits during long term follow-up. Children randomized to PEG-2a plus placebo who do not exhibit viral disappearance at week 24 will be considered monotherapy treatment failures and will be moved to a compassionate "monotherapy/combination" arm with PEG-2a plus RV. This group will receive their first dose of RV at week 28 and will be assessed after 24 weeks of combinations therapy (week 52). If they do not exhibit viral disappearance after 24 weeks of combination therapy, PEG-2a and RV will be discontinued, they will be followed closely for 24 weeks after stopping medications, and will have 2 annual visits during long-term follow-up. If they exhibit viral disappearance after 24 weeks of combination therapy, they will be treated for an additional 24 weeks (for a total of 48 weeks), followed closely for 24 weeks after stopping medications, and have 2 annual visits during long-term follow-up.

Children randomized to PEG-2a plus RV who do not exhibit viral disappearance at 24 weeks will be considered combination treatment failures. PEG-2a and RV will be discontinued, they will be followed closely for 24 weeks after stopping medications, and have 2 annual visits during long-term follow-up. If they exhibit viral disappearance at 24 weeks, they will be treated for an additional 24 weeks for a total of 48 weeks. They will then be followed closely for 24 weeks after stopping medications and have 2 annual visits during the long-term follow-up.

Patients who discontinue treatment will be moved to their first scheduled untreated follow-up visit. All patients will have an untreated follow-up visit at 72 weeks which will include interim history, physical exam, laboratory analyses, review of adverse events, depression testing, and growth and body composition measures.

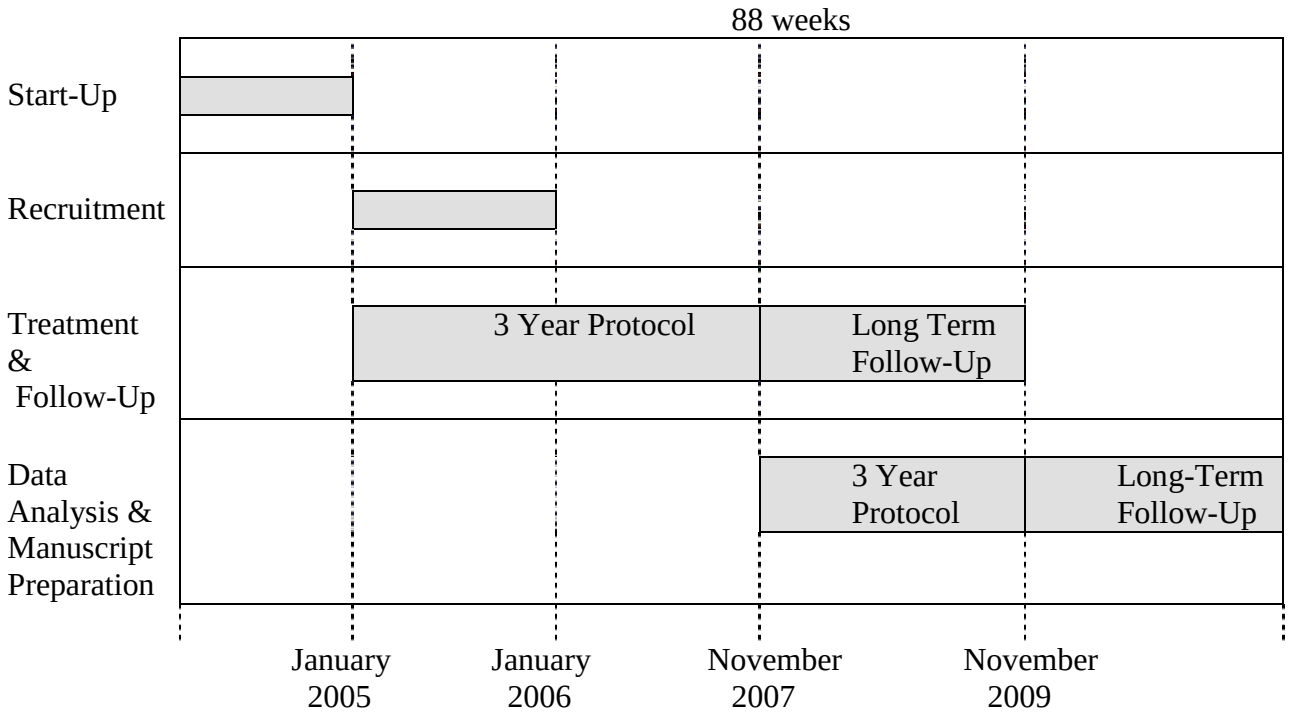
Primary outcome observations for growth and body composition will be made at baseline, 24 and 48 weeks. Some children will have 76 weeks of PEG 2a treatment, and all will be followed for 24 weeks after the end of treatment. Observations will be collected 24 weeks after the end of treatment for secondary outcomes. Health related quality of life, cognitive development and psychological functioning will be assessed at baseline, 24 and 48 weeks, and annually for 2 years post-treatment.

Procedures for collecting and storing patient identifying information are in place at Clinical Centers. Identifiers (e.g. names, address, social security numbers) will not appear on data collection forms. Unique number and letter codes will be assigned to each child and parent and will be used on all forms. Child medical information will be obtained by interview with the child or parent. Children and parents will also complete questionnaires. All forms and other patient information will be kept in locked cabinets. Forms will be collected from each Clinical Center regularly by monitors and returned to the Data Coordinating Center/Contract Research Organization (DCC/CRO) for entry into the study database. Monitors will compare individual records with reports, prepared by the Clinical Center, look for omissions and missing data, check informed consent, and maintain records of findings and actions taken to correct deficiencies. Detailed monitoring requirements are presented in Chapter 10.

1.2 Study Time Table

PEDS-C start-up will be devoted to hiring and training study personnel, designing and printing study forms, developing a Manual of Procedures, convening the Data and Safety Monitoring Board, obtaining and labeling study drugs, and obtaining required regulatory approvals. During the subsequent recruitment phase, each Clinical Center will identify and enroll between 5 and 15 patients between January 2005 and January 2006. It is expected that recruitment, screening, and enrollment of 112 children at 11 Clinical Centers will be completed by January 2006. Patients will be enrolled before screening when they have received PEDS-C patient ID number and letter code from the Data Coordinating Center. After screening eligible patients will be randomized and receive a drug kit assignment number. Drug treatment and follow-up data collection will begin immediately after patient randomization and be completed in 100 weeks (November 2007) under the three year protocol. Long-term follow-up in years four and five will be completed by November 2009. Data analysis and manuscript production for year three protocol data will begin in November 2007. Similar activities for the long-term follow-up will begin in November 2009.

PEDS-C Timeline



1.3 Description of the Participant Group

Boys and girls 5 to 18 years of age will be considered eligible for enrollment (screened prior to 18th birthday) if they have a chronic hepatitis C infection (CHC) as defined by detectable HCV RNA by any test on two determinations at least six months apart, if they are able to swallow the RV capsule, if they are RV and interferon-naïve and if they meet other inclusion and exclusion criteria detailed in Section 3.1. In addition, children must have compensated liver disease and histologic findings consistent with CHC on a liver biopsy obtained within the 24 months prior to study enrollment as assessed by a qualified pathologist. Signed informed consent will be obtained.

Total planned enrollment is 112. Enrollment goals by gender, ethnicity, and race are as follows:

TABLE 1-1: Planned PEDS-C Enrollment by Gender and Ethnic Category

Ethnic Category	**Girls**	**Boys**	**Total**
Hispanic or Latino	4	9	13
Not Hispanic or Latino	126	129	255
All Ethnic Categories	130	138	268

TABLE 1-2: Planned PEDS-C Enrollment by Gender and Racial Category

Racial Category	**Girls**	**Boys**	**Total**
American Indian/Alaska Native	1	2	3
Asian	6	9	15
Native Hawaiian or Other Pacific Islander	2	2	4
Black or African American	13	20	33
White	108	106	214
All Racial Categories	130	138	268

CHAPTER 2

DATA COLLECTION SCHEDULE AND TYPES OF DATA COLLECTED

PEDS-C data collection forms are organized around a core of scheduled bi-weekly or monthly treatment period and untreated follow-up assessment summaries which collect data and also act as check-off lists for other scheduled forms required and unscheduled forms which may or may not be part of the visit. Treatment period assessment summaries range from weeks 1 to 76 weeks. Untreated follow-up summaries range from weeks 52 to 100. Long term follow-up annual visits may take place between 80 and 180 weeks after the patient is enrolled. Scheduled data collection forms referred to in these visit summaries include the Vital Signs and Symptom Directed Physical; the Three-day Food Diary, the Physical Activity Assessment, the Ophthalmology Exam Form; the Patient=s Medication Diary; Ophthalmology Exam Summary and the quality of life battery. Forms for unscheduled data collection which may or may not be completed at the visit are the Concurrent Medication Form; the Therapy Missed Dose, Stop/Restart, and Missed Dose Forms; the Serious and Non-Serious Adverse Events Reports; the Depression Management Tracking Form; the Withdrawal/Close-Out Form; the Ophthalmology Exam Summary, and the Death Report (see the Appendix for a complete Forms List). Scheduled data collection forms will be provided with pre-printed header information when possible, unscheduled data collection forms will have header information completed at the Clinical Center.

CRF's may be used as source documents. The patient's medical record should include at a minimum the date of assessment, reason for visit and any information not captured in the CRF. CRF's can be used as a source document only after all patient study information is removed and appropriate patient information is added such as name, date of birth and medical record number. This can be accomplished by temporarily covering the top portion of the CRF with a sheet of paper on which the patient's information has already been inscribed.

2.1 Scheduled Data Collection

2.1.1 Screening to the Week 24 Treatment Assessment

PEDS-C data collection from the screening visit to the week 24 treatment period assessment is uncomplicated and is the same for patients in all therapy groups (see grayed areas in Tables 2-1, 2-2 and 2-3). Notebooks of forms in the proper sequence for each patient will be

provided by the DCC/CRO. Each notebook will be labeled with the patient ID and letter code on the spine. Patient ID and letter code will also be recorded on each data collection form. The instruction boxes on forms completed during this period say that they are to be used for all therapy groups.

All patients will have a screening visit which will take place within 35 days of the baseline visit. A liver biopsy will be performed within 24 months of screening. Before the screening visit, Clinic personnel should call the DCC/CRO ATRS system to register and obtain a patient ID and letter code. At the screening visit, the patient will be asked to demonstrate his/her ability to swallow a 100 mg tablet by swallowing a 100 mg placebo. The Screening Visit 1 Form (and the Screening Visit 2 Form, if necessary) will be completed. Then the eligibility of the patient will be evaluated using the Eligibility Summary Form. If the patient is found to be eligible, a second call to the DCC/CRO ATRS system will be made to randomize the patient and to receive medication package numbers. The patient's HCV genotype will be entered during the second call. Fill out the ATRS Voice Response Worksheet A and before making the first call. Complete the ATRS Voice Response Worksheet C before making the second call. Record information on the ATRS Worksheets as instructed and keep the worksheets for your records. Record the six-digit patient ID and the three-letter code assigned in the headers of the Screening Visit and Eligibility Summary Forms. Keep forms for ineligible participants separate from those for eligible participants and send them via a secure carrier to the DCC/CRO. Be sure to keep copies in the clinic.

At the baseline visit, the full range of assessments will be collected BEFORE the first dose(s) of study drug are administered in clinic. The Baseline Assessment Form will be completed and the parent will be instructed on how to complete the Patient=s Medications Diary. If the patient is a sexually active female over the age of 10 years with a positive urine or serum pregnancy test, DO NOT BEGIN STUDY DRUG THERAPY and withdraw the patient from the study.

After baseline, treatment period in-clinic visits will take place every two weeks until week 8 (weeks 1, 3, 5, and 8 weeks). Treatment period assessment forms for each visit have been provided and are labeled with the appropriate 3-digit visit week (001, 003, 005, or 008) in the appropriate header box. The Patient=s Medication Diary (PMD) will be reviewed at every visit but only collected at every other visit since it covers a one month period. The PMD will not be sent to the DCC/CRO but will be filed by patient ID in a secure location for future reference. All data collection visits in this initial treatment phase will be in-clinic and no telephone

assessments will be performed. If a patient discontinues drug therapy during this period, he/she will be moved to the first untreated follow-up visit at week 52 (untreated follow-up week 4) and follow the schedule as charted in Table 2-1. If the patient refuses further participation in the study and withdraws, untreated follow-up visit week 72 (untreated follow-up week 4) will be carried out as charted in Table 2-1.

After the treatment period week 8 assessment, treatment period assessments at weeks 12, 16, 20, and 24 will take place every month. Treatment period assessment forms for each monthly visit will be provided in the patient=s form notebook and will be labeled with the appropriate visit week in the header box (012, 016, 020, and 024). If a patient discontinues drug therapy during this period, he/she will skip to the first untreated follow-up visit at week 52 (untreated follow-up week 4) and follow the schedule as charted in Table 2-1. If the patient refuses further participation in the study and withdraws, untreated follow-up visit week 72 as charted in Table 2-1 will be carried out if possible.

2.1.2 Treatment Failure/Reassignment at Week 24

After the week 24 treatment assessment, the patients' HCV-RNA test results will be evaluated for viral disappearance. The DCC/CRO will monitor changes in drug therapy for each patient and sent formal unblinding notifications to Clinical Centers when patients assigned to combination therapy have shown no viral disappearance after 24 weeks of treatment. The following information will be sent to the Clinical Center PI and Coordinator:

1) Patient ID and letter code.
2) Visit date and Week #.
3) For patients at 24 weeks, information on whether the patient's treatment will be discontinued (Protocol Table 3A schedule) or changed to compassionate mono/combo (Protocol Table 3B schedule) will be given.

The DCC/CRO will send the appropriate data collection forms labeled with patient ID and letter code to each Clinical Center before the Week 28 assessment. See Chart 2-A for a flow chart of these therapy group changes after the week 24 assessment. Each arm of the diagram is labeled by a unique path number A to E.

2.1.3 Visit Assessment Schedules After Week 24

Patients in the Peg 2A + placebo therapy (original Mono therapy) group who show no viral disappearance at week 24 (Path A) will be re-assigned to compassionate Mono/Combo therapy group and follow the visit schedule outlined in Table 2-2. Their treatment assessment

week 28-52 forms will be labeled "for use in the original Mono/Combo therapy group with no viral disappearance". Members of the original Mono therapy group showing viral disappearance at week 24 (Path C) will continue to follow the visit schedule outlined in Table 2-1. Their treatment assessment week 28-48 forms will be labeled "for use in the original Mono therapy group with viral disappearance".

Patients in the Peg 2a + RV (original Combo therapy) group who show no viral disappearance at week 24 (Path D) will have their therapy stopped and will begin untreated follow-up visits at week 28. Their untreated follow-up assessment forms will be labeled "for use in all therapy groups" and they will follow the schedule of untreated week 52 to week 72 visits (untreated follow-up weeks 4-24) in Table 2-1. Untreated follow-up visits will continue until week 48 when the patients in this group have reached the end of study participation and will be closed-out. Patients in the original Combo therapy group with viral disappearance at week 24 (Path E) will receive 24 more weeks of drug therapy and then untreated follow-up assessments (4-24) until week 72. They will follow the schedule of assessments in Table 2-1 and their week 28-48 treatment assessment forms will be labeled for use in the original Combo therapy group with viral disappearance". Untreated follow-up forms for weeks 4-24 will be the same for all treatment groups.

Post 24 week visit assessment forms with preprinted AWeek #@ for each therapy group will be sent to Clinical Center personnel in a separate form notebook for each patient.

2.1.4 Treatment Failure Re-Assignment in the Mono/Combo Therapy Group at Week 52

After the week 52 treatment assessment, HCV-RNA test results for patients in the compassionate Mono/Combo therapy group with no viral disappearance at Week 24 will be evaluated again for viral disappearance at Week 52. The DCC/CRO will send a formal unblinding message to Clinics for patients who show no viral disappearance at Week 52. For patients at 52 weeks, information similar to that given at week 24 will be sent including information on whether the patient's treatment will be discontinued (Protocol Table 3A schedule) or continued (Protocol Table 3B schedule) will be given.

2.1.5 Visit Assessment Schedule in the Mono/Combo Therapy Group with Viral Disappearance After Week 52

See Chart A for a graphic illustration of the Mono/Combo therapy group therapy re-assignments after the Week 52 assessment. Patients in this group with no viral disappearance at week 52 (Path A) will continue to follow the schedule of visits in Table 2-2. Patients in this group who show viral disappearance at week 52 (Path B) will follow the schedule of measures in Table 2-3. A notebook of assessment forms for each patient pre-printed with visit week will be sent to each Clinical Center for both groups.

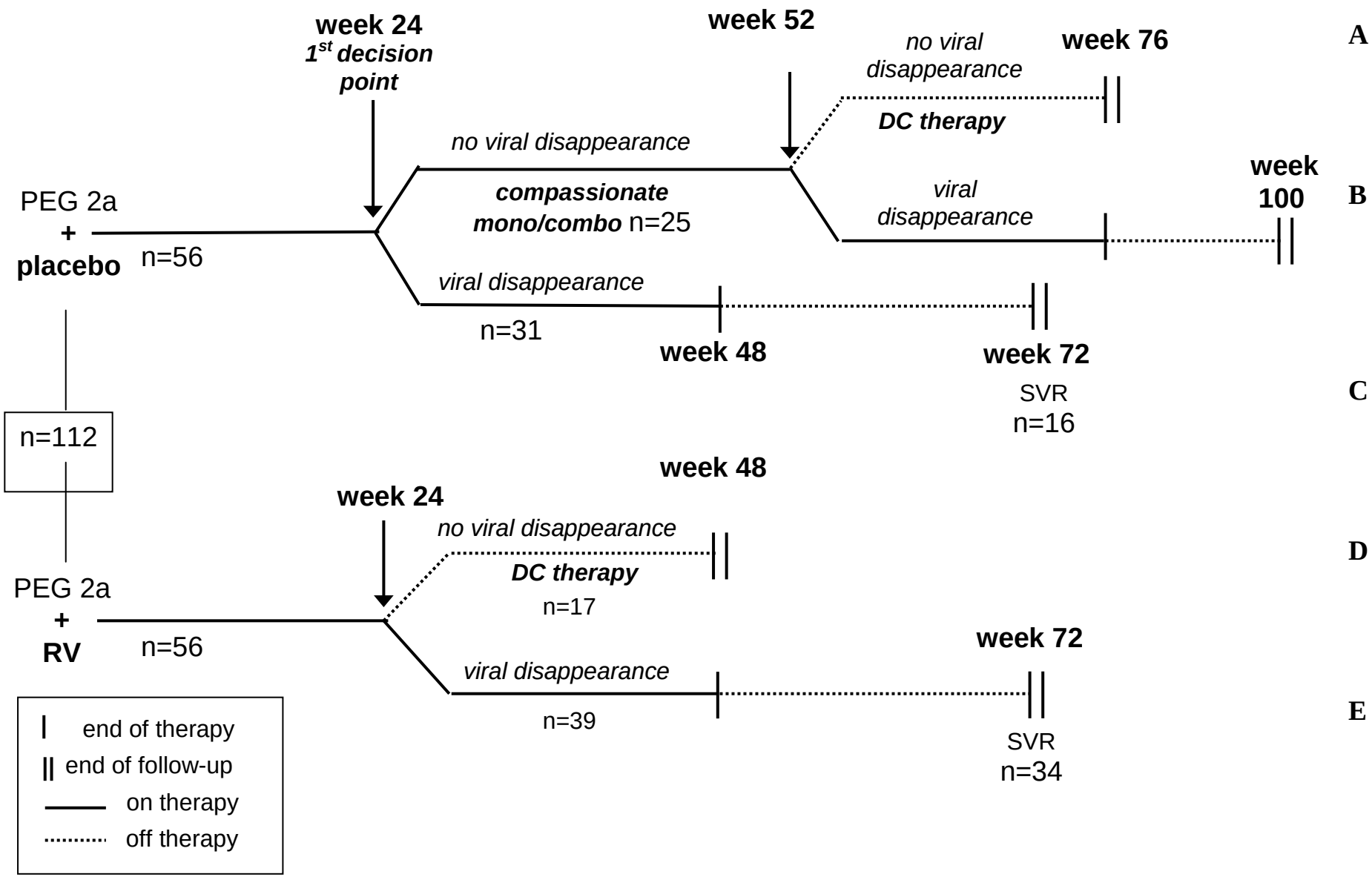
2.1.6 Long Term Follow-Up Visits

Long term follow-up visits for all therapy groups will take place one and two years after the end of study drug therapy. The first long-term follow-up visits will take place six months after the completion of follow-up week 24 (see tables 2-1, 2-2 and 2-3). The second long-term follow-up visit will take place 1 year after the completion of long-term follow-up visit 1. These visits are identical in content and a single form with a choice for Annual Visit 1 and Annual Visit 2 in the header has been provided. The instructions for this form state that it is Afor use in all therapy groups@.

Two copies of the annual visit form will be included in the last notebook of forms sent by the DCC/CRO. The visit week (AWeek #@) for these annual visits will differ according to the patient therapy group assignment and path # designation as follows:

	Annual Visit 1 at Week	Annual Visit 2 at Week
Mono/Combo Therapy Group		
Path 1	104	156
Path 2	128	180
Original Mono Group		
Path 3	100	152
Original Combo Group		
Path 4	80	132
Path 5	100	152

CHART 2-A


week 24
1st decision point
week 52
no viral disappearance
week 76
A
DC therapy
no viral disappearance
week 100
PEG 2a
+
placebo
n=56
compassionate mono/combo n=25
viral disappearance
B
viral disappearance
n=31
week 48
week 72
SVR
n=16
C
n=112
week 48
week 24
no viral disappearance
D
DC therapy
n=17
PEG 2a
+
RV
n=56
week 72
viral disappearance
n=39
E
SVR
n=34
end of therapy
end of follow-up
on therapy
off therapy

Schedule of Assessments and Procedures for Original Mono Therapy Groups with Viral Disappearance at Week 24 and for Original Combo Therapy Groups

Note that original combo patients found to be HCV + at week 24 will move to untreated follow-up
Note that BL refers to the Baseline (studies obtained prior to initiation of treatment on that day and week 1 refers to the beginning of the second week of therapy (i.e. 7 days after initiation of treatment) (Shaded area = assessment for all patients)

Table 2-1: Schedule of Assessments

Assessment	Screen Days	Study Treatment Period (weeks)															Untreated Follow-up (weeks)						Annual Visits⌂
	-35 to -1	BL	1	3	5	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72°	
Follow-up week #																	4	8	12	16	20	24	
Informed Consent	x																						
Complete Medical History	x																						
Vital Signs & Physical Exam	x															x						x	x
Vital Signs & Symptom Directed Physical		x	x	x	x	x	x	x	x	x		x		x			x	x	x				
Telephone Assessment											x		x		x					x	x		
Immunology	x																						
Hematology	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x			x	x
PT/PTT	x									x												x	x
Chemistry	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x			x	x
HCV-RNA Clinical*	x^1	x^1					x^2			x^2						x^2			x^2			x^2	x^2
HCV-RNA Research◊	x	x	x	x	x		x			x						x			x			x	
Thyroid Function Tests	x					x				x			x			x						x	
HCV Genotyping	x																						
Serum Bank	x	x					x			x				x		x			x			x	x
Pregnancy Test Serum**	x			x		x	x		x	x	x	x	x	x	x	x	x	x	x			x	
Pregnancy Test Urine**		x						x												x	x		
Urinalysis	x						x			x			x			x						x	x
Ophthalmology Exam ***	x									x						x							
Adverse Events, Concomitant Medications, and Compliance	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Depression Screen	x	x					x			x						x						x	x
Growth/Body Composition +		x								x						x						x	x
QOL/Outcomes ++		x								x						x						x	x
Patient Diary Review		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						

(See key following Table 2-3)

Table 2-2: Schedule of Assessments For Mono/Combo Group: no viral disappearance at week 24 and 52 (shaded area = all patients)

Assessment	Screen Days	Study Treatment Period (weeks) PEG 2a + placebo									Study Treatment Period (weeks) PEG 2a + RV									Untreated Follow-up						Annual Visits ⌂
Week #: a: Covance Kit Identifier	-35 to -1	BL	1	3	5	8	12	16	20	24	28 a	30 a	32 a	34 a	36 a	40 a	44 a	48 a	52 a	56 a	60 a	64 a	68 a	72 a	76E a	
Follow-up week #																				4	8	12	16	20	24	
Informed Consent	x																									
Complete Medical History	x																									
Vital Signs & Physical exam	x																		x						x	x
Vital Signs & Symptom Directed Physical		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x				
Telephone Assessment																							x	x		
Immunology	x																									
Hematology	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x			x	x
PT/PTT	x									x									x						x	x
Chemistry	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x			x	x
HCV-RNA Clinical*	x[1]	x[1]					x[2]			x[2]						x[2]			x[2]			x[2]			x[2]	x[2]
HCV-RNA Research◊	x	x	x	x	x		x			x																
Thyroid Function Tests	x					x				x					x				x						x	
HCV Genotyping	x																									
Serum Bank	x	x					x			x	x					x			x			x			x	x
Pregnancy Test Serum **	x			x		x	x		x	x			x		x	x		x	x	x	x	x			x	
Pregnancy Test Urine **		x						x			x						x						x	x		
Urinalysis	x						x			x						x			x						x	x
Ophthalmology Exam ***	x									x									x							
AE, Con Meds, and Compliance	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Depression Screen	x	x					x			x									x						x	x
Growth/Body Comp +		x								x								x							x	x
QOL/Outcomes ++		x								x								x							x	X
Patient Diary Review		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x							

(See key following Table 2-3)

Table 2-3: Schedule of Assessments For Mono/Combo Group: no viral disappearance at week 24; viral disappearance at week 52 (shaded area = all patients)

Assessment	Screen Days	Study Treatment Period (weeks) PEG 2a + placebo									Study Treatment Period (weeks) PEG 2a + RV															Untreated Follow-up (weeks)						Annual Visits ⌂
Week #: a / b: Covance Kit Identifier	-35 to -1	BL	1	3	5	8	12	16	20	24	28 a	30 a	32 a	34 a	36 a	40 a	44 a	48 a	52 a	56 b	60 b	64 b	68 b	72 b	76 b	80	84	88	92	96	100E	
Follow-up Week #																										4	8	12	16	20	24	
Informed Consent	x																															
Complete Medical History	x																															
Vital Signs & Physical Exam	x																		x						x						x	x
Vital Signs & Symptom Directed Physical		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x		x			x	x	x				
Telephone Assessment																				x		x		x					x	x		
Immunology	x																															
Hematology	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x			x	x
PT/PTT	x									x									x												x	x
Chemistry	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x			x	x
HCV-RNA Clinical*	x^1	x^1					x^2			x^2						x^2			x^2						x^2			x^2			x^2	x^2
HCV-RNA Research◊	x	x	x	x	x		x			x																						
Thyroid Function Tests	x					x				x					x				x			x			x						x	
HCV Genotyping	x																															
Serum Bank	x	x					x			x	x					x			x				x		x			x			x	x
Pregnancy Test Serum **	x			x		x	x		x	x			x		x	x		x	x	x	x	x	x	x	x	x	x	x			x	
Pregnancy Test Urine **		x						x			x						x												x	x		
Urinalysis	x						x			x						x			x			x			x						x	x
Ophthalmology Exam ***	x									x								x							x							
AE, Con Meds, and Compliance	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Depression Screen	x	x					x			x									x						x						x	x
Growth/Body Comp +		x								x								x							x						x	x
QOL/Outcomes ++		x								x								x							x						x	x
Patient Diary Reveiw		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						

(See key following Table 2-3)

Key for Tables 2-1, 2-2 and 2-3

⌂ Annual visit: Visit #1 will be 6 months after completing follow-up week # 24. Annual visit # 2 will be 12 months after annual visit #1.

a. ° Or upon discontinuation

* HCV RNA Clinical: A 3.0 mL blood sample will be collected for HCV qualitative (COBAS AMPLICOR HCV Test, v2.0™) and quantitative (COBAS AMPLICOR HCV MONITOR Test, v2.™) tests. The quantitative test will be done at screening and pre-dose at baseline. Qualitative tests will be done at weeks 12, 24 and 48 of therapy and during weeks 60 and 72 of the treatment follow-up period.

[1] Quantitative
[2] Qualitative

◊ HCV RNA Research : 3.0 mL blood samples will also be obtained at screening, baseline, weeks 1, 3, 5, 12, 24, 48, 60 and 72 for the Table 2-1 patients. Please see Tables 2-2 and 2-3 for HCV RNA research in these two groups. Plasma will be banked for performance of viral kinetic studies at a later date.

** Serum or urine pregnancy tests: As detailed above are to be performed in fertile or potentially fertile females only (age 10 years and older) within 24 hours prior to first tablet (RV/placebo) or at any time of a secondary amenorrhea of more than 1 week. Pregnancy test to be performed every 4 weeks during treatment and for the 6 months following completion of treatment.

*** Ophthalmologic exam: Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Study drug (s) should be discontinued in patients who develop severe retinopathy. Patients with severe retinopathy at screening are excluded from the trial.

+ Growth and Body Composition measurements: (with the exception of DXA scan) will be obtained by a dietitian at baseline, 24 weeks, 48 weeks and 24 weeks after end of treatment (72, 76, or 100 weeks)

++ Quality of Life/Health Outcomes will be assessed at baseline, 24 weeks, 48 weeks and 24 weeks after end of treatment (72, 76, or 100 weeks). Assessment tools include: CHQ, BRIEF, CBCL/ABCL. SF-36 and LEC. (Assessment tools can be found in Appendix)

2.2 Data Collection by Subject Area

Descriptions of data collected by subject matter area are presented below.

2.2.1 Demographics

Child birth date, gender, and ethnicity will be collected at screening. The birth date will include month, day and year of birth. Racial categories (each scored "Yes" or "No") will be: American Indian/Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. Patients are permitted to choose more than one racial category. Ethnic categories (choice of one) will be Hispanic or Latino, or Not Hispanic or Latino.

2.2.2 Complete Medical History/Vital Signs and Physical Exam/Vital Signs and Symptom Directed Physical/Depression Screen

Complete medical history, vital signs and a physical exam will be performed at the screening visit 1 to 35 days before the baseline visit. The medical history will include current and past medical conditions, date of HCV diagnosis and route of infection, current medication, and contraception. The physical exam will include body weight, height, and vital signs (pulse rate, body temperature, and respiratory rate), and blood pressure. The depression screen will consist of a check on the Children's Depression Inventory (CDI) total score (ages 5-17) or the Center for Epidemiological Studies Depression Scale total score (ages 18 or older) and symptoms of major depression.

Vital signs, a symptom directed physical, and the depression screen will be collected at baseline, before the child receives the study drug. The symptom directed physical will be performed only if the patient or parent reports that a problem has developed since the last visit. Vital signs and the symptom directed physical will be repeated regularly at study treatment period visits. The full physical exam and vital signs will be repeated at the last treatment period visit. The depression screen will be repeated at weeks 12, 24, at the last treatment period assessment, at the last untreated follow-up assessment, and at annual follow-up visits.

At untreated follow-up visits at follow-up weeks 4, 8 and 12, vital signs and the symptom directed physical will be repeated. The full physical exam with vital signs and depression screen will be repeated at follow-up week 24 and at annual visits 1 and 2.

2.2.3 Immunology

The following laboratory tests will be performed at the screening visit 1 to 35 days before the baseline visit: ceruloplasim, alpha1-antitrypsin, anti-HBc Hbc IgM Ab, anti-HAV IgM Ab, HbsAg, anti-HCV Ab, anti-mitochondrial Abs, anti-nuclear Abs, anti-smooth muscle Abs, and anti-HIV Ab.

Immunology tests do not need to be repeated if patients are not enrolled and do not receive study drug following initial screening but are subsequently re-screened. Tests will be repeated at re-screening when indicated by a change in the patient's medical condition.

2.2.4 Hematology/Chemistry

Hematology includes a complete blood count (hemoglobin, hematocrit, WBC, platelets), including differential, prothrombin time, partial thromboplastin time, INR, and hemoglobin A1C. These tests will be done at the screening visit, baseline, at all treated follow-up visits and at untreated follow-up weeks 4, 12, 24 and Years 2 and 3. Routine hematology test will be done by Covance. Re-draw and rush hematology analyses may be done at local laboratories.

Chemistries include: ALT, AST, total bilirubin, direct bilirubin, alkaline phosphates, total protein, albumin, BUN, creatinine, creatinine phosphokinase, uric acid, calcium, phosphorus, cholesterol, triglycerides, glucose, sodium, chloride, and potassium. Chemistries will be performed on the same schedule as hematology.

2.2.5 Virology

HCV RNA Clinical Tests A 3.0ml blood sample will be collected for HCV qualitative (COBAS AMPLICOR HCV Test, v2.0^{TM}) and quantitative (COBAS AMPLICOR HCV MONITOR Test v2.^{TM}) tests. The quantitative test will be done at screening and pre-dose at baseline. Qualitative test will be done at weeks 12, 24 and 48 of therapy and during weeks 60 and 72 of the treatment follow-up period.

HCV Research Tests A 3.0 ml blood sample for HCV RNA will also be obtained at screening, baseline, and at weeks 1, 3, 5, 12, 24, 48, 60, and 72 for Table 2-1 patients. Please see Tables 2-2 and 2-3 for HCV-RNA research tests in these two groups. Plasma

will be banked for performance of viral kinetic studies at a later date.

2.2.6 Thyroid Function Tests

Thyroid function tests will consist of: TSH, Free T4, T4 total and T3 uptake and thyroid peroxidase antibody. They will be performed at screening, treatment visits 8, 24, 36 and 48 and at the last untreated follow-up visit.

2.2.7 Serum Bank

Additional blood samples will be collected at screening, baseline, treatment period weeks 12, 24, 40, 48 and an untreated follow-up weeks 60, 72 and years 2 and 3 (Table 2-1 patients). (See Tables 2-2 and 2-3 for additional collection schedules.) The samples will be stored in a serum bank in the event some tests need to be repeated or additional testing is warranted. No genetic testing will be done on these samples.

2.2.8 Pregnancy Tests

Serum or urine pregnancy tests will be performed in fertile or potentially fertile girls only (age 10 years and older) within 24 hours prior to the first tablet (RV/placebo) or at any time of a secondary amenorrhea of more than one week. Tests will be performed at screening, baseline, every four weeks during treatment, and for six months following the completion of treatment. At assessments where a pregnancy test is not done, girls will be asked for the first day of their last menstrual period. If a girl shows secondary amenorrhea of 1 week or more, a serum pregnancy test will be performed. All pregnancies will be reported to the Ribavirin Pregnancy Registry (1-800-593-2214). See Section 13.5 for more information on the Ribavirin Pregnancy Registry.

2.2.9 Urinalysis

The following macro and micro panel tests will be performed on urine samples collected at screening, 3-4 times during the study treatment period, and at the last untreated assessment and at years 2 and 3:

Color
Specific Gravity
pH
Protein
Glucose
Ketones
Bilirubin
Urobilinogen

Blood (Neg., Trace, +,++,+++)
Nitrite
Leukocyte Esterase
Microscopic

2.2.10 Ophthalmology Exam

An eye exam will be performed at screening, week 24, week 48, and at the last treatment period assessment. A dilated exam is preferred for maximum visualization of the retina. Patients with severe retinopathy will be excluded at screening.

2.2.11 Adverse Events, Concomitant Medications and Compliance

These measures will be collected at all study visits.

2.2.12 Liver Biopsy

A liver biopsy will be performed within 24 months of the screening. Two slides will be sent to the PEDS-C study pathologist (Dr. Goodman) by the 8 week treatment assessment. Slides may be unstained or stained with hematoxylin – eosin and Masson's trichrome.

2.2.13 Growth and Body Composition

Growth and body composition measurements will be obtained at baseline, at treatment weeks 24 and 48, 24 weeks after the end of treatment (week 72, 76 or 100 weeks), and at years 2 and 3. All patients will be assessed at 48 weeks regardless of whether they are stopping treatment or require additional weeks of treatment. The measures will include:

1) Body composition analysis by DXA scan (dual-energy x-ray absorptiometry) including bone density scans. DXA is a radiographic technique assessing the composition and density of different body compartments (fat and lean tissue, fat free mass, and bone mineral content) and their distribution in the body.

2) Bioelectrical impedance analysis (BIA).

3) Detailed anthropometry, including body weight measured by an electronic digital scale; standing height measured by a stadiometer; triceps, biceps, iliac, and subscapular skin fold thicknesses measured with Lange skin calipers; and mid-

arm circumference measured with a flexible, non-stretchable plastic tape. All measures will be made by a single observer at each site.

4) Diet intake and physical activity will be obtained using a 3-day food diary and a physical activity assessment. The 3-day food diary will be scored at each Clinical Center using PC scoring programs. The physical activity assessment from the Dietary Intervention Study in Children (DISC) will be scored at the DCC/CRO.

2.2.14 Psychosocial Functioning/Quality of Life

Assessments are designed to evaluate the child's cognitive, developmental, and psychological functioning, and his/her health-related quality of life (QL) as well as parental stress and QL. Some of the child constructs will be collected from both the child and a parent depending on the child's age. The parent who brings the child to the baseline visit will be asked to complete subsequent assessments at treatment weeks 24 and 48, at untreated follow-up week 72, and at annual follow-up visits.

The following assessment tools will be used at all six visits:

1) Health-related QL – the Child Health Questionnaire (CHQ) completed by children at least 10 years old (child form) and a parent (parent form). The CHQ self-reports will not be collected from children younger than 10. Domains measured include: physical functioning, role/social limitations, general health, bodily pain/discomfort, parent impact, self-esteem, mental health, general behavior, and family impact.

2) Cognitive functioning – the Behavior Rating Inventory of Executive Function (BRIEF) completed by a parent. The BRIEF measures emotional and behavioral dysregulation, difficulties with response inhibition, working memory, and the ability to transition to new situations or tasks.

3) Psychosocial functioning – Parents will also complete the Child Behavior Checklist (CBCL) which measures child adaption across both internalizing (e.g. depression, anxiety) and externalizing (e.g. conduct problems, aggression) domains for children aged 5 to 18 years. Parents will complete the Adult Behavior Checklist (ABCL) for patients aged 19 or older.

4) Parental stress and QL – Parents will complete the Life Events Checklist (LEC)

which will measure their perception of 46 life events and the degree to which they are stressful for the patient. They will also complete the MOS 36 Item Short Form Health Survey (SF-36) to assess their physical functioning, social functioning, pain, psychological well-being, impairment due to emotional problems, and general health.

2.2.15 Patient Compliance

Patient Medication Diary

Parents will be asked to keep a detailed diary of the child's study drug intake. The diary will be made available in the form of a booklet labeled with patient identifiers and visit numbers, and will be identical in format for all treatment groups. Each booklet will cover approximately a one month period. The diary will be collected at regular clinic visits every month during drug therapy. For Peg-2a, parents will record: the dosage (ml) of PEG-2a injected, the date and exact time of administration, injection site, and brief comments on any difficulties with the injection. The person giving the injection will initial the diary. For the RV or placebo tablet, they will record: the date and exact time that the RV or placebo tablet was swallowed, the dosage, and brief comments on any difficulties in swallowing the tablet. The person giving the tablet(s) will initial the diary. Clinical Centers will fax copies of BL study treatment prescriptions to the DCC/CRO.

At the baseline visit parents will be instructed on how to administer the study drug and how to record administrations in the Patient's Medication Diary. At all subsequent follow-up visits during treatment, the diary for the past 2-6 weeks will be reviewed with the parent. Problems with drug administration will be discussed. Incomplete or inconsistent information will be corrected. The interviewer will complete Therapy Missed Dose, Stop/Restart or Dose Adjustment Forms to report departures from the regular drug administration schedule. The starting date and doses for both injections and tablets will be recorded on the Baseline Assessment Form. The Patient's Medication Diary will not be data entered at the DCC/CRO but will be filed at the Clinical Center in a secure location.

Returned Drug

The date(s) and quantity of drug returned by the parent/guardian will be recorded

by the research pharmacist to assess compliance. See Section 6.3 for more detail.

2.3 Visit Windows

Screening visits will be completed within 1 to 35 days before the baseline/randomization visit. Certain tests performed by Covance may require as much as 21 days turn around time. Therefore, it is recommended that the baseline visit be scheduled for more than 3 weeks after randomization.

After randomization, follow-up visits at Weeks 1, 3, and 5 will be completed within one day (plus or minus one day) of the weekly randomization anniversary. Monthly visits beginning at week 8 will be completed within one week (plus or minus one week) of the monthly randomization anniversary.

Annual long-term follow-up visits will take place one and two years after the end of study drug therapy. They will be completed within one month (plus or minus one month) of the yearly anniversary of the end of study drug therapy.

CHAPTER 3

SCREENING AND RECRUITMENT

3.1 Patient Eligibility Criteria

To be eligible for enrollment into the study, each patient must satisfy all inclusion criteria and none of the exclusion criteria.

Inclusion criteria

*Male or female patients who are 5-18 years of age at enrollment (not yet reached 18th birthday at screening).

*HCV viremia (by any test) present on 2 tests separated by at least 6 months.

*Chronic liver disease, as indicated by inflammation and/or fibrosis, consistent with chronic hepatitis C infection on a liver biopsy obtained within the past 24 months, as assessed by a qualified pathologist, not consistent with other known liver disease and not normal,

*Compensated liver disease (Child-Pugh Grade A clinical classification)

*Signed informed consent from the patient and parent/legal guardian and willingness of patient and parent/legal guardian to abide by the requirements of the study.

*Hemoglobin values $\geq$11 g/dL for females;$\geq$ 12 g/dL for males

*Normal TSH

*Able to swallow a RV/placebo tablet (demonstrated ability).

Exclusion criteria

*Any prior treatment with Interferon or RV

*Receipt of any investigational drug <6 weeks prior to the first dose of study drug

*Any systemic antiviral therapy <6 weeks prior to the first dose of study drug. Exception: patients who have taken or are expected to require acyclovir for herpetic lesions

*Positive test at screening for anti-HAV IgM Ab, HBsAg, anti-HBc IgM Ab, or anti-HIV Ab

*History or other evidence of a medical condition associated with chronic liver disease other than HCV (abnormal ceruloplasmin, alpha-1-antitrypsin, ANA>1:160, SMA>1:80, anti-LKM antibody > 60 units))

*History or other evidence of bleeding from esophageal varices

*Decompensated liver disease (e.g. conjugated bilirubin >1.5mg/dl, ascites, varices, Child-Pugh Grade B or C clinical classification)

*History of autoimmune or immunologically mediated disease (e.g. inflammatory bowel disease, idiopathic thrombocytopenic purpura, lupus erythematosus, autoimmune hemolytic anemia, scleroderma, severe psoriasis, clinical evidence of rheumatoid arthritis)

*Absolute neutrophil count <1500 cells/mm^3 , Hgb <11 g/dL for females and <12 g/dL for males, WBC>17.5 x 10^9/L, or platelet count <90,000/mm^3

*Serum creatinine level >1.5 times the upper limit of normal for age

*Major depression according to the American Psychiatric Association (see Table 7 Protocol), or a history of severe psychiatric disorder, such as major psychoses, suicidal ideation and/or suicide attempt

*History or other evidence of chronic pulmonary or cardiac disease associated with functional limitation

*History of thyroid disease poorly controlled on prescribed medications. Patients with elevated thyroid stimulating hormone (TSH) concentrations with elevation of antibodies to thyroid peroxidase and any clinical manifestations of thyroid disease are excluded

*Poorly controlled diabetes as defined by hemoglobin A1C of > 8%

*History of solid organ or bone marrow transplantation

*Coagulopathy (INR>1.5)

*Evidence of an active or suspected cancer or a history of malignancy where the risk of recurrence is $\geq$20% within 2 years.

*Hemoglobinopathy

*Hemophilia

*Severe retinopathy

*History of other evidence of severe illness or any other conditions which would make the patient, in the opinion of the investigator, unsuitable for the study

*Sexually active females of child-bearing potential (defined as age 10 years and older) and sexually active males who are not practicing two forms of effective contraception during treatment and during the 6 months after treatment has been concluded

*Females who have a positive pregnancy test within 7 days of initiation of treatment or who are breast-feeding

*Males whose female partners are pregnant

*Active substance abuse

*A sibling and/or any other child living in the same household or sharing the same primary caregiver enrolled in the study.

3.2 Patient Screening and Recruitment

Each center will enroll at least 5 and no more than 15 children, up to 112 total for the group of centers. Children 5-18 years of age at screening who are not yet 18 at enrollment will be considered eligible for enrollment if they have HCV as defined by detectable HCV RNA by any test on 2 determinations at least 6 months apart (the screening HCV test may be considered the second test), if they are able to swallow the RV/placebo tablet, if they are RV and interferon-naïve and if they meet the other inclusion and exclusion criteria detailed in the Protocol. In addition, children must have compensated liver disease and histologic findings consistent with HCV on a liver biopsy obtained within 24 months prior to screening, as assessed by a qualified pathologist. Each Clinical Center will receive a bottle of 84 100 mg placebo tablets to use in testing the patient's ability to swallow the tablet. Foster children will not be screened or enrolled in PEDS-C.

Subjects will be recruited at each of the 11 pediatric liver centers by the caring physician and/or study coordinator who will identify potentially eligible subjects. Those parents/caregivers will be contacted by phone by the study coordinator who will inform them about the study. If parents/caregivers are interested a screening visit will be scheduled.

3.2.1 Screening Visit

Screening will begin within 35 days prior to the first dose of study drug after written informed consent is obtained.

The following screening assessments must be obtained within 35 days prior to the initiation of study drug.

Screening Assessments

Medical History and Physical Exam	Body weight, height, vital signs, body temperature, complete medical history and concomitant medications, Depression screen
Immunology	Ceruloplasmin*, alpha1-antitrypsin*, anti-HBc IgM Ab*, anti-HAV IgM Ab*, HBsAg*, anti-HCV Ab*, anti-mitochondrial Abs*, anti-nuclear Abs*, anti-smooth muscle Abs*, anti-HIV Ab*
Hematology	Complete blood count (hemoglobin, hematocrit, WBC, Platelets), including differential, prothrombin time, partial thromboplastin time, INR
Hematology	Hemoglobin A1C
Chemistry	ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, total protein, albumin, BUN, creatinine, creatinine phosphokinase, uric acid, calcium, phosphorus, cholesterol, triglycerides, glucose, sodium, chloride, and potassium
Virology	HCV genotype, quantitative HCV RNA (clinical), research HCV RNA (stored frozen)
Thyroid Function Tests	TSH, Free T4, T4 total and T3 uptake, Thyroid Peroxidase Antibody
Serum Bank	Samples will be stored in a serum bank in the event some tests need to be repeated or additional testing is warranted
Pregnancy test	Serum pregnancy test to be performed in fertile or potentially fertile females only
Urinalysis	Urine sample to be sent to central lab for analysis
Liver Biopsy	Within 24 months before screening

Note: Tests marked above with an asterisk (*) do not need to be repeated if patients do not receive study drug following initial screening but are subsequently re-screened for this protocol, unless dictated by a change in the patient's medical condition.

Additional blood samples will be collected at screening. The samples will be stored in a serum bank in the event some tests need to be repeated or additional testing is warranted.

If any future research of these samples other than delineated in this protocol is desired, the sera will not be released unless an IRB approves a protocol for this purpose. Samples will be transferred to the NIDDK repository where they will be stored for an indefinite period of time. No genetic testing will be done on these samples as they do not contain DNA.

3.2.2 Liver Biopsy

The patient must have had a liver biopsy within 24 months of screening. He/she must have compensated liver disease and histologic findings consistent with HCV on a liver biopsy as assessed by a qualified pathologist. If an exemption to standard eligibility criteria is requested or granted for an out of date liver biopsy, the date of the biopsy should still be entered in the appropriate place on the Eligibility Criteria Exemption Form 07.

For purposes of analyzing the relationships between study endpoints and initial hepatic histology the initial liver biopsies will be processed as follows. Sections of the liver biopsies will be stained with hematoxylin-eosin and Masson's trichrome for histologic evaluation by Dr. Zachary Goodman, study pathologist. Each biopsy will be evaluated for degree of hepatocellular injury, inflammation and fibrosis with the three scoring systems most widely used in hepatitis treatment studies: Knodell score(55), Ishak score(56) and Metavir score(57). Other histologic features, such as steatosis and dysplastic foci will be noted when present.

Liver biopsy slides will be sent to Dr. Goodman before the week 8 assessment visit. Slides should be packaged in plastic slide protectors and wrapped in bubble wrap. They will be sent by FedEx or a similar service. A PEDS-C Slide Submission Form will be included in the packet. The specimens will be identified with the patient ID number and letter code assigned by each Clinical Center. See the Appendix for Slide Submission Procedure and Slide Submission Form.

3.2.3 Concomitant Medication and Treatment

All concomitant medications taken or treatments administered at anytime between screening and study termination will be recorded in the source document and on the Concurrent Medications Form. This includes any medication that is new, discontinued or changed in dose.

Systemic antiviral, anti-neoplastic and immunomodulatory treatments (including steroids and radiation) are not allowed during the study. Exception: patients who have taken or are expected to require acyclovir for herpetic lesions. Steroids given as physiologic replacement are permitted or as a short course (<7 days) for asthma

management. Any investigational drugs, herbals and remedies being taken by the patient for possible or perceived effects against HCV are excluded.

The total daily dose of acetaminophen will not exceed 1 gram per day.

3.2.4 Use of Screening Visit 1 and 2 Forms and Eligibility Screening Forms

The Screening Visit 1 Form will be completed at the time of the screening visit. A second screening visit will be scheduled and the Screening Visit 2 form used if it was not possible to obtain sufficient blood at Screening Visit 1. The Eligibility Summary Form (ESF) will be used as a checklist to document whether or not a patient fulfills the entry criteria. All forms will be signed and dated by the investigator for all patients considered for enrollment in the study. A copy of the Screening Visit Forms and the ESF will be kept with the patient's records, or if the patient is excluded, the ESF will be kept as the patient's exclusion record. Patients must meet the entry criteria to be enrolled in the study.

General Instructions for completing the ESF:

1. Review the Screening Visit 1 (and 2 if appropriate) Form.
2. Verify the answer to each question.
3. Maintain the source document that validates the inclusion/exclusion criteria.

Header information

1. Week #: Enter the 3 digit study week number. For example the week 1 visit = 001.
2. Date of Assessment: Enter the date the data is collected in mm dd yyyy format. Do not leave a box empty. Enter a 0 if applicable (e.g. enter May as 05)
3. Patient Letter Code: Enter a 3 letter code that you assigned for each patient. This code must remain the same during the entire study.
4. Patient Number: After consent has been obtained and before the screening process begins, call the DCC/CRO to register the patient and get the Patient Identification (ID) Number. Enter in the appropriate boxes. These identification codes will remain the same throughout the study. If the patient

is eligible, make a second call to the DCC/CRO to randomize the patient and obtain Peg 2a and RV/placebo package numbers. You will need to enter the patient's ID, letter code, and HCV genotype to obtain the package numbers. (See ATRS Worksheets Forms A and B for a list of all information needed.)

Inclusion criteria

#'s 1-8	Fill the Yes or No bubble for each question
#9	Enter "1" in the box if any inclusion criteria is answered No

Exclusion criteria

#'s 10-35	Fill the Yes or No bubble for each question
#36	Enter "1" in the box if any exclusion criterion is answered Yes.

Concomitant Medication and Treatment

#'s 37-39	Fill Yes or No bubble for each question
# 40	Enter "1" in box if any concomitant medication or treatment is answered Yes

Eligibility Summary

# 41	Have one or more questions in the boxes numbered 9, 36 or 40 been answered "1"? Fill the Yes or No bubble.
#42	Indicate if the patient was ineligible but has received an exemption.

If the patient is eligible, make a second call to the DCC/CRO to randomize the patient and obtain drug package assignment numbers. You will need to enter the patient's ID, letter code, and HCV genotype to obtain the package numbers.

3.3 Re-Screening

The PEDS-C initial screening process will take from 1 to 35 days after the first screening visit. Within that window, tests determining eligibility may be delayed or

repeated with the approval of the Exemptions Committee. At the end of the initial screening period, patients who are ineligible, e.g. and Eligibility Summary Form has been returned to the DCC/CRO, can be re-screened if they were ineligible on a reversible eligibility criteria and have had a change in status. Patients who are ineligible on other eligibility criteria or have been randomized and then withdrawn (a Withdrawal/Close-Out Form has been returned to the DCC/CRO), will not be re-screened.

Reversible eligibility criteria are the following:

1) Age – The patient has not yet reached their fifth birthday

2) At least one positive HCV test 6 months or more before screening visit 1 (SV1). For example, the patient had a positive HCV test 4 months before SV1 and was ineligible, but can be re-screened 2 months later.

3) Swallowing the 100 mg placebo tablet. For example, the patient cannot swallow the 100 mg tablet within the initial screening window. However, he/she is able to swallow the tablet later.

4) The patient received an investigational drug within 6 weeks of the first dose of study drug. For example, the patient has taken an investigational drug 2 weeks before the first dose of study drug. He/she can be re-screened 1 month later.

5) The patient received anti-viral therapy within 6 weeks of the first dose of study drug. An example would be similar to #4 above.

6) Patients who are ineligible in the initial screening period because they are taking concurrent medications and treatments mentioned in the Concomitant Medication and Treatment section of the Eligibility Summary Form may be re-screened if the treatments or drugs are discontinued.

Patients may NOT be re-screened if there is a change of mind about consent, if the site PI changes their mind about the appropriateness of enrolling the patient, if the patient discontinues active substance abuse, if a patient not practicing 2 forms of birth control begins practicing birth control, or if a male patient's sexual partner who was pregnant has given birth.

Patients who are ineligible based on lab results will be considered for re-screening on a case-by-case basis. Site PIs will work with Dr. Schwarz and the PEDS-C

Exemption Committee in order to be as inclusive as possible and to make sure that patients are not excluded from PEDS-C because of artifactual laboratory results.

See section 3.2.1 for screening laboratory tests that do not need to be repeated when patients are re-screened. Forms that must be repeated when a patient is re-screened are:

Screening Visit 1 Form 02

Screening Visit 2 Form 03 (if necessary)

CDI Form 06

Baseline Ophthalmology Summary 05

Eligibility Summary Form 04

Complete a Patient Re-Registration Form for patients who are re-screened. A patient may be re-screened one time. The patient's ID number will not change at re-registration.

3.4. Screening Siblings

Siblings (patients from the same household or who share the same primary caregiver) may not be randomized in PEDS-C. However, more than one patient from the same household or sharing the same primary caregiver may be screened in order to select a participant. A possible strategy is to screen the oldest sibling(s) first. In the event that older siblings are ineligible, younger siblings may not have become 18 years old at the first screening visit.

During screening, patient IDs will be assigned to siblings in the order that they are seen. The last digit of the ID for first sibling screened will be 0. If that sibling is not eligible, the next sibling screened will have the same patient ID only ending in 1. For example, the first sibling screened at Johns Hopkins may be assigned patient ID number 10-222-0. Then the second sibling screened in that household would be assigned the ID number 10-222-1. The last possible ID for siblings in this household is 10-222-4. The letter codes assigned for all siblings and parent/guardians will be the same.

Multiple siblings will not be screened at the same time. Only after a sibling is determined to be ineligible and the Eligibility Summary Form has been completed may another sibling be screened.

Once a patient is determined to be eligible and the patient is randomized, no additional siblings from that household or sharing the same primary caregiver will be screened. In the event that a patient is withdrawn from the study, closed out (completed his/her scheduled study visits), or is sent to untreated follow-up, no additional siblings from that household or sharing the same primary caregiver will be screened.

3.5. Monitoring Patient Recruitment and Follow-up:

DCC/CRO staff will prepare regular patient recruitment reports showing the number of patients recruited by each Clinical Center for that week and cumulatively. In addition, a comparison to recruitment goals will be included. Regular follow-up reports will also be generated, showing the number of patients that have been seen as part of the follow-up by month, by visit, and cumulatively. These reports allow the study leadership to monitor the recruitment and follow-up efforts at each clinical site and to discuss with a Clinical Center director any problems with follow-up. In addition, each Clinical Center director will be aware of his or her standing with respect to the other Clinical Centers in the study.

CHAPTER 4

INFORMED CONSENT

4.1 Obtaining informed consent/assent

Prior to beginning the screening process, signed informed consent from parent/legal guardian and the patient and willingness of parent/legal guardian and patient to abide by the requirements of the study is required.

Consent will be obtained before screening and before the patient is given a Patient ID number and lettercode. The study will be discussed in detail by the physician and study coordinator and the consent/assent form reviewed. The consent will include study purpose, description of procedures, risks and benefits, alternative treatments, costs, compensation, and issues of confidentiality. Signed and dated informed consents will be obtained from the parent/legal guardian and assent will be obtained from the child. Procedures for obtaining assent from children younger than 7 will be based on the institutional policy of the Clinical Centers. The consent/assent will be signed and dated by the investigator.

Failure to give informed consent renders the patient ineligible for the study. No testing or physical examination will occur before informed consent has been obtained.

4.2 Storage of Signed Consent/Assent Forms

Four copies of the signed informed consent and assent forms will be generated. The original signed consent and assent forms will be maintained in the patient's medical record. One copy of the signed consent and assent forms will be maintained in the study regulatory file. The DCC/CRO will maintain a third copy of the signed consent and assent forms. One copy of each consent and assent will be given to the family.

4.3 Re-Consenting

Patients must be re-consented with a revised consent/assent if there is a significant change in study procedures. All revisions to consents/assents must be approved by the clinical center's IRB.

4.4 HIPAA Compliance

To assure compliance with HIPAA regulations, each clinical site will include in their consent/assent forms specific language to permit the transmittal of patient information to the DCC/CRO, both in the form of CRFs and in the form of laboratory and genetic data.

CHAPTER 5

RANDOMIZATION AND DRUG ASSIGNMENT

5.1 Randomization

Patients will be enrolled into the study and allocated to a treatment group at random using the Automated Telephone Response System (ATRS), implemented by DCC/CRO staff. This system uses a touch tone phone to enter information about a new participant, including age, gender, ethnicity, race, and checks on eligibility and informed consent. The system will then assign a study ID number. After lab results have been obtained, a second call will be made to randomize the patient and assign drug package numbers. Information will be announced by the system to the caller and confirmatory faxes will be sent to the clinic coordinator and to the clinical site pharmacy after the calls. This system is available 24 hours per day, 7 days per week. In case of system failure, manual randomizations are available through a DCC/CRO staff member who is available by pager at all times.

Access to the system is over 1-800-731-3103 using assigned PIN numbers and pass code. Each clinic coordinator (and any other designated staff at the clinical site who might enroll a participant) will be assigned a PIN and pass code. Each person assigned a PIN must perform at least one practice randomization to become certified in the system and to be allowed to perform a real randomization. See Manual section 5.3 for detailed instructions.

Randomization schedules will be generated within clinical sites with stratification by HCV genotypes (1 vs all others). The ration of PEG-2a + RV to PEG-2a + placebo treatment assignments will be 1:1. The randomizations will be blocked using random blocking factors of 2 or 4, due to the relatively small sample size within a clinical site (approximately 10 participants for each of 11 sites). The resulting randomization schedules will be sorted in the ATRS database for reference by the system.

5.2 Study Drug Labeling

Study medications will be packaged with unique medication numbers on each package. These numbers (MCN) will be used during randomization to assign study drug

to patients. MCN numbers will be transmitted to Clinical site pharmacies at the time of the second ATRS randomization call to the DCC/CRO. The local pharmacy at each Clinical Center will prepare the medications for distribution by labeling them with PEDS-C patient ID and lettercodes. Each patient will receive separate packages (Peg 2a) and bottles (RV/placebo) of drug according to their dosage.

5.3 PEDS-C ATRS Practice / Certification Call Instructions

1.) Every person who has a PIN card must activate their PIN number before they can register patients, randomize patients, or re-supply medication. The PIN number is activated by performing a successful ATRS practice / certification call.

2.) ATRS practice / certification calls can be performed as many times as desired, but it is required at least once. The practice / certification call can be used to become familiar with the ATRS and train others to use the ATRS.

2.) Use the PEDS-C Registration and ID Assignment ATRS Worksheet (Form A) for this practice / certification call. Complete this form using fictitious data before making the ATRS call.

3.) The DCC provided you with your personal ATRS PIN cards. These laminated cards contain your name, your site's name, your personal identification number (PIN), the site's password (HP), and the site number. This PIN card contains all the information that is needed to access the Automated Telephone Response System (ATRS).

5.) Follow the instructions on the PEDS-C Registration and ID Assignment ATRS Worksheet (Form A). Dial 800-731-3103.

6.) Enter your PIN number – 5 digit number found on your laminated PIN card.

7.) For practice / certification calls **DO NOT** enter your site's password (HP) – 4 digit found on your laminated PIN card. **Enter 9999.** This signals the ATRS that this is a practice / certification call.

8.) You will hear a message giving you options, to register a patient press 1.

9.) Follow the Registration and ID Assignment ATRS Worksheet A

10.) Patient's fictitious Letter Code – Use the table included on the Worksheet to translate the letters to numbers which can be entered . For example, the number codes for HCV are 42 23 83.

11.) First Scheduled Screening Visit Date – Enter the fictitious date in mmddyyyy format.

12.) Enter the Patient's fictitious gender 1 – Male or 2 – Female

13.) Enter the Patient's fictitious date of birth. Enter the date in mmddyyyy format. The patient must be greater than or equal to 5 years of age and less than eighteen. If the patient's age doesn't fall within these age constraints, they will not be eligible for screening in PEDS-C.

14.) Is the patient Hispanic or Latino? Press 1 – Yes
Press 2 – No
Press 3 – Not Specified

15.) Patient's fictitious race codes (Choose all that apply). You enter all the codes that apply and end your selection by pressing the "#" button on your phone. For example: If the patient was Black & White. Press 35#

16.) Has another sibling been registered for screening in PEDS-C? In this case the answer will be 2 (No).

17.) Has the patient been previously screened for PEDS-C? In this case the answer will be 2 (No).

18.) The system will then give you the patient's ID number. For the practice / certification call, the patient ID number will be 99-999-9. The system will ask you to re-enter the numeric portion of the ID number. If you do not re-enter the patient ID number, the patient isn't registered and no fax will be sent.

19.) You are then asked whether to send the fax to the default fax number. This is the fax number that you entered on the ATRS Clinic Application Form. Press 1 to use the default fax number. Press 2 if that fax number is incorrect or out of service. You will then be asked for the alternate fax number. You must enter the area code and phone number. We would like you to use the default fax number if possible to verify that it works.

20.) The system will state that a fax will arrive shortly and thank you for using the ATRS system.

21.) If you do not receive the confirmation fax, please let us know.

If you have any questions or problems, call the pager number that is found on the bottom of the PEDS-C Registration and ID Assignment ATRS Worksheet (Form A). 410-416-3935.

CHAPTER 6

STUDY DRUG MANAGEMENT

6.1 Dose Adjustments and Toxicity Management

6.1.1 Dose Regimen and Dose Adjustment

After the first 30 patients enrolled have been treated for 4 weeks (or, if enrollment begins slowly, 3 months after the first patient is enrolled), there will be a safety checkpoint (interim analysis) during which the DSMB will review all clinical and laboratory data for safety.

6.1.2 Investigator Dose Modification Guidelines for Intolerance

The intention of the protocol is that patients demonstrating a response to therapy remain on study drug until the completion of the study. However, it is possible that some patients will encounter adverse events during their participation in the trial necessitating study drug dosage adjustment. Decrement adjustments should be uniform across centers and patients. When appropriate, downward dose adjustments in one level increment should be considered. (See Appendix for PEG-2a and Ribavirin dosing guidelines).

Suggested dose adjustments to PEG-2a and RV are for guidelines to maintain consistency between centers. These guidelines are given below for neutropenia, thrombocytopenia, anmeia, indirect hyperbilirubinemia, and elevated alanin aminotransferase (ALT) activity. When possible, abnormal lab results should be confirmed as soon as possible following notification. If laboratory abnormalities improve or resolve, the dose of PEG-2a or RV may be increased back to the original dose at the discretion of the investigator with continued close monitoring.

For other adverse effects considered to be possible related to PEG-2a and/or RV investigators should utilize the "Toxicity Table for Grading Severity of Pediatric AEs") see Appendix E). Dose reduction for non-laboratory related adverse events will be based upon severity ratings in accordance with modified WHO criteria as noted in this appendix.

- For grade 1 toxicity, no dose reduction is needed.
- For grade 2 toxicity that persists over two consecutive safety visits and does not respond to symptomatic management, a level 1 dose decrease of PEG-2a and/or a decrease in RV may be required.

- For grade 3 toxicity not responsive to adjunctive management, a level 1 dose decrease of PEG-2a and/or a decrease in RV may be required. Stepwise reduction will continue until symptoms resolve. Patients with grade 3 toxicity will be followed closely, visits at more frequent intervals or through close telephone contact to monitor in between regularly scheduled safety visits. If symptoms improve or resolve, return to previous dosing will be done at the discretion of the investigator.
- For grade 4 toxicity, treatment will be discontinued.

If adverse events continue at the same intensity despite maximal dose reductions, PEG 2a and/or RV may require discontinuation at the discretion of the investigator. It will be noted that certain toxicities carry different levels of significance for each patient and therefore, the investigator will use these as guidelines only, within the context of clinical judgment. Growth factors may not be used to maintain normal levels of hemoglobin, neutrophils or platelets.

The alert level for triglycerides is a fasting level of 500 mg/dL or above. Fasting is not required for routine safety visits. If the patient is at or above this level the patient will be asked to repeat the non-fasting test. If the patient's triglyceride level is 500 mg/dL or more on two non-fasting tests, the patient will be asked to repeat the test at the next scheduled visit after an overnight fast. If the patient's triglyceride level remains at or above 500 mg/dL, then the study drug will be adjusted according to the Toxicity Table in Appendix E.

PEG-2a

Original Dose	One Level Adjustment	Two Level Adjustment	Three Level Adjustment
180 mcg/1.73 m^2	135 mcg/1.73 m^2	90 mcg/1.73 m^2	45 mcg/1.73 m^2
(104 mcg/$m^{2)}$	(78 mcg/m^2)	(52 mcg/m^2)	(26 mcg/m^2)

Pegasys Dosing Guidelines – Full Dose (180 µg/1.73 m^2 * BSA m^2)			
BSA m^2	**Dose (µg)**	**Vial concentration (µg/mL)**	**Volume per injection (mL)**
0.5 – 0.6	54	180	0.3
0.7	72	180	0.4
0.8 – 0.9	90	180	0.5

1.0 – 1.1	108	180	0.6
1.2	126	180	0.7
1.3 – 1.4	144	180	0.8
1.5 – 1.6	162	180	0.9
≥ 1.7	180	180	1.0

Pegasys Dosing Guidelines – 1 level adjustment (135 µg/1.73 m^2 * BSA m^2)			
BSA m^2	**Dose (µg)**	**Vial concentration (µg/mL)**	**Volume per injection (mL)**
0.5	36	180	0.2
0.6 – 0.8	54	180	0.3
0.9 – 1.0	72	180	0.4
1.1 – 1.2	90	180	0.5
1.3 – 1.4	108	180	.06
≥ 1.5	126	180	0.7

Pegasys Dosing Guidelines – 2 level adjustment (90 µg/1.73 m^2 * BSA m^2)			
BSA m^2	**Dose (µg)**	**Vial concentration (µg/mL)**	**Volume per injection (mL)**
0.5	18	180	0.1
0.6 – 0.8	36	180	0.2
0.9 – 1.0	54	180	0.3
1.3 – 1.4	72	180	0.4
≥ 1.6	90	180	0.5

Ribavirin

Original Dose	Dose Reduction
15 mg/kg/day divided bid	7.5 mg/kg/day divided qd or bid based on dose

Ribavirin Dosing Guidelines				
Weight Rounded to nearest 0.5 kg	Full dose per day	Schedule	Reduced dose Per day	Schedule
13.5 to 16.6	200 mg	100 mg BID	100 mg	100 mg QD (am or pm)
16.7 to 23.3	300 mg	100 mg q AM: 200 mg q PM	100 mg	100 mg QD (am or pm)
23.4 to 29.9	400 mg	200 mg BID	200 mg	100 mg BID
30.0 to 36.6	500 mg	200 mg q AM; 300 mg q PM	200 mg	100 mg BID
36.7 to 43.3	600 mg	300 mg BID	300 mg	100 mg q AM; 200 mg q PM
43.4 to 49.9	700 mg	300 mg q AM; 400 mg q PM	300 mg	100 mg q AM; 200 mg q PM
50.0 to 56.6	800 mg	400 mg BID	400 mg	200 mg BID
63.4 to 69.9	1000 mg	500 mg BID	500 mg	200 mg q AM; 300 mg q PM
70.0 to 76.6	1100 mg	500 mg q AM; 600 mg q PM	500 mg	200 mg q AM; 300 mg q PM
≥ 76.7	1200 mg	600 mg BID	600 mg	300 mg BID

PEG-2a Dose Adjustments for Low Absolute Neutrophil Counts

Parameter	Response
ANC (cells/mm3)	

1000	None
750-999	Week 1-2: Immediate Level 1 adjustment Week 3-48: None
500-749	Week 1-2: Delay or hold dose until 750 then resume dose with a Level 1 adjustment. Assess weekly x 3 to verify WBC's >750.
250-499	Week 1-2: Delay or hold dose until 750 then resume dose with a Level 2 adjustment Week 3-48: Delay or hold dose until 750 then resume dose with a Level 1 adjustment
<250 or febrile neutropenia	STOP DRUG

PEG-2a Dose Adjustments for Low Platelet Counts

Parameter	Response
Platelets (cells/mm^3)	
50,000	None
35,000-49,000	Delay or hold dose until 50,000 then resume dose with a Level 1 adjustment
25,000-34,000	Delay or hold dose until 50,000 then resume dose with a Level 2 adjustment
<25,000	STOP DRUG

Ribavirin Dose Adjustments for Anemia and Indirect Hyperbilirubinemia

Parameter	Response
Hemoglobin (gm/dl)	
<10 gm/dl	Reduce ribavirin dose by one half. Follow weekly and increase dose when > 10 gm/dl
<8.5 gm/dl	Permanent discontinuation of ribavirin
Indirect Bilirubin (mg/dl)	
>5 mg/dl	Stop drug, follow indirect bilirubin weekly. If reduces to <2.5, restart ribavirin at one half dose. If <2.5 mg/dl for 4 weeks, increase to full dose. If recurs at > 5 mg/dl, reduce dose or stop for 1-2 weeks and restart at a reduced dose if indirect bilirubin is <2.5 mg/dl. Indirect bilirubin must remain at <2.5 mg/dl to continue ribavirin even at a reduced dose.
>5 mg/dl for > 4 weeks	STOP DRUG

PEG-2a Dose Adjustments for Elevated Serum ALT

On Treatment serum ALT	Response
< 5 X ULN	None
5 X ULN but < 10 X ULN	Repeat in 1 week **If ALT decreased**, continue at present dose, follow every 1-2 weeks to assure stability. **If ALT stable or increased but 10 X ULN**, Level 1 dose adjustment and follow weekly until stable or decreasing
10 X ULN	Repeat in 1 week **If ALT decreased below 10 X ULN but 5 X ULN**, Level 1 dose

	adjustment and follow weekly until stable or decreasing **If ALT still 10 X ULN** stop drug permanently

6.2 Dosage Adjustments for Significant Weight Gains/Losses

6.2.1 Peg2a

Peg2a (PEG-IFN-alpha-2a) is dosed according to the patient's Body Surface Area (BSA) which is computed by the Mosteller's formula:

BSA (m^2) = ([Height(cm) x Weight(kg)]/3600)$^{1/2}$

Investigators will adjust the dose of Peg2a upward or downward to reflect the most current BSA if there is a significant increase or decrease (i.e. a change of greater than 10%) from the beginning of the study (screening BSA).

6.2.2 Ribavirin

Ribavirin is dosed according to body weight and administered PO daily (BID) with food. Ribavirin "with food" means taking their doses within 1 hour before or two hours after a meal. The meal should be considered "regular" as opposed to "fat restricted".

The investigator will adjust the dose upward or downward to reflect the most current weight if there is significant weight loss or gain (i.e. > 10%) from the beginning of the study (weight at screening).

6.3 Dosage Delays

6.3.1 Peg2a

If a Peg2a dose was delayed but eventually administered, the following guidelines for the next scheduled dose(s) will be used:

Dose delayed 1 or 2 days: administer on usual dosing day of the week (e.g., if Monday is the usual dosing day and the dose is delayed until Wednesday, the next dose may be administered as usual on Monday).

Dose delayed 3-5 days: administer subsequent doses every 5th or 6th day until the patient is back to his or her original schedule (e.g., if Monday is the usual dosing day and the dose is delayed until Saturday, the next dose should be administered on Thursday, the following dose on Tuesday, then the dose after that as usual on Monday).

Dose delayed 6 days: hold the dose for that week then continue on the usual schedule the following week (e.g., if Monday is the usual dosing day but the patient is not ready to be

dosed until the following Sunday, the dose is considered to have been held and the next injection should be for the following week's dose on Monday).

Dose delayed 7 or more days: the investigator may reintroduce study drug at any time and, if necessary, dose the patient every 5^{th} or 6^{th} day until the patient resumes weekly dosings on their usual scheduled day.

6.3.2 Ribavirin

If a dose of Ribavirin was missed, the patient should take the dose as soon as they remember during the same day. They should not take two doses too close together in time. If it is late in the day, they should wait until the next day and go back on schedule. They should not double the next dose.

6.4 Injection Procedures

Information and teaching materials given to parent/guardians on injections procedures will follow the institutional guidelines established at each Clinical Center. Any problems or resources needed by Clinical Centers will be brought to the attention of the PEDS-C Steering Committee.

Clinical Centers will be provided with injectable supplies. These will include: syringes, needles, gauze, alcohol wipes, band aides, and sharps containers. Roche will supply cooler bags and ice for medical transport.

6.5 Patient Medication Diary Review

The family will bring the Patient's Medication Diary (PMD) to each study visit. The information will be reviewed with the family by the Clinic Coordinator at each study visit.

It is mandatory that each PEG-2a injection and RV dose be recorded in the PMD. The parent/guardian will be instructed to record the date and exact time and dose of PEG-2a and RV. The person giving the PEG-2a injection must initial the PMD. During the diary review, the reviewer will correct unreadable information and ask the patient to supply missing information. Reviewers will report missing doses on the Therapy Missed Dose Form, dose adjustments on the Therapy Dose Adjustment Report and therapy stops or restarts on the Therapy Stop/Restart Form. The dates and amounts of initial doses at baseline will be reported on the Baseline Assessment. The patient diaries will be maintained with the source documents at each site.

6.6 Drug Returns

Instructions for inventory of controlled on non-controlled clinical drug returns at the investigator site.

6.6.1 Materials

The following materials are enclosed:

- Clear, plastic bags
- Tamper evident seals
- Controlled or Non-Controlled Drug Return Record (DRR) forms

(depending on study)

6.6.2 Inventory Procedures

1. Start a new DRR form for each drug return shipment. If a DRR form is not completed and drug is sent to Returned Goods Room personnel, then the CRA will be notified and will be responsible for completing a DRR form prior to destruction of drug.
2. a. Drug reconciliation will be performed by collecting patient's Drug Dispensing Log, emergency codes or treatment allocation, previously completed Drug Return Records Forms, all remaining drug supplies, undistributed, partially used and empty packs from investigator.
   b. Calculate the total amount of drug that will have been used collectively by all subjects. Add together the undispensed drug supplies and those dispensed to all subjects. The result will equal the amount of drug shipped to the study site.
   c. Attempt to reconcile any discrepancies with the study coordinator or the person responsible for dispensing study medication at the investigational center. Have that person adequately document discrepancies in drug count on the Drug Dispensing Log and Case Report Form. Additional procedures for further reconciliation or documentation may vary for specific programs.
3. Complete the white section of the DRR form as follows (referring to the appropriate section shown on the attached example):
   a. Make an imprint of the clic card to include the protocol number, Investigator name, etc.
   b. Record the DRR page number and total number of DRR forms completed (e.g. Page 1 or 2, Page 2 of 2, etc.)
   c. Record the Monitor name and telephone number

d. If drugs are returned to Roche, record the date that the returns are sent to Roche

e. Record the number of bags sent to Roche

f. Indicate the type of container

g. For open studies, enter the Lot Number

h. For coded studies, enter the package ID#, the patient numbers (RDC#s) and bottle letter (if applicable)

i. **Non-Controlled Drugs**: Enter the number of full, partial and empty containers. Do not use check marks.

Controlled Drugs: Enter the number and type of units. DO not use check marks.

j. Signature of Investigator and date

k. Signature person destroying the drug and date. **ALL CONTROLLED DRUGS MUST BE RETURNED TO ROCHE**. Check off where the drug is destroyed for non-controlled drugs.

Note: The gray section of the DRR form will be completed by Hoffmann-La Roche Clinical Supplies Packaging Returned Goods personnel.

4. The CRA will keep the canary copy of the DRR form.
5. Place the pink copy of the DRR form in the study files.
6. If drug supplies are permitted (by the Project Account Leader) to be destroyed at the investigator site, the CRA will arrange to have drug supplies destroyed following country-specific legal and GMP requirements, according to local procedures.
7. If non-controlled drugs are destroyed at the investigator site, it is the responsibility of the CRA to send the white copy of the DRR form to CDC.

6.6.3. <u>Shipping Instructions for Drug Destruction at Roche</u>

1. Place the returns into the plastic bags. Glass bottles will be carefully packed in a cushioned box to avoid breakage. Place cushioned box inside plastic bags. Seal each bag with a tamper evident seal. The CRA will initial the tamper evident seal.

2 Place the sealed bags into shippers. Place the white copy of the DRR forms into a shipper. PLEASE DO NOT PLACE THE DRR FORMS INTO THE PLASTIC BAGS. Send all of the shippers together to:

Hoffmann-La Roche, Inc.
340 Kingsland Street Bldg. 59/01
Returned Goods Room/Attn: Susan Sarzo
Nutley, NJ 07110

Note: The drug will then be destroyed at Roche and the white copy of the DRR form will be stamped with a "Destruction" stamp and sent to the CRA. The CRA will make a copy of the DRR form and send the original white copy to the CDC.

3. If study drugs need to be returned to stock or if you have any other questions, please contact Medical Stock at (973) 325-5756.

TO SEND DRUGS BACK TO ROCHE

When sending drugs back to Roche, always make shipment using US mail; never use overnight express courier services.

After packing all drugs to be returned to Roche, affix the enclosed postage paid sticker addressed to Ms. Susan Sarzo, centered on top of the box.

The second sticker (enclosed) is filled out with the protocol number, investigator name, investigator address and the Roche Clinical Operation's department code 22-6821. This sticker is to be affixed in the upper left-hand corner, on top of the box.

F11337 8/22/96 10:04 PM Page 1

Protocol No NV14256 CRTN 19523

Study Title A PHASE III Safety AND Efficacy Study of Saquinavir

Rx No 31-8959 CRDF No 01093

Investigator JANE DOE, M.D. ATLANTA, GA.

Investigator No 24792 Center No 20143 Country USA

Roche Hoffmann-La Roche
A Member of the Roche Group

Non-Controlled Drug Return Record

NOTE: DO NOT PLACE DRUG RETURN RECORD FORM IN SEALED BAGS

Page 1 of 1

FOR HOFFMANN-LA ROCHE RETURNED GOODS USE ONLY
Date Received: Month Day Year RC #
Package seal intact? ☐ Yes ☐ No
Number of bags received:
By:

Monitor Name: MARY JONES
Telephone Number: 201-235-1234
Date Sent to Roche: 12/1/96
Number of Bags Sent: 1

Type of Containers:
☒ Bottles ☐ Blister cards ☐ Vials
☐ Other

If seal is broken, Returned Goods Personnel will complete below:

Lot Number (C# for Open Studies or Package ID# for Coded Studies)	Patient Numbers (RDC # for Coded Studies; use additional forms as necessary)	Bottle Letter (if any)	Number of Containers Being Returned (Do not use (✓) marks) FULL	PARTIAL	EMPTY
C123456-01	151	A			1
		B		1	
	152	A			1
		B	1		
	153	A		1	

Roche Count Agrees	Roche Count DOES NOT Agree	If count DOES NOT agree, please note discrepancy.
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶
☐	☐	▶

Signature of Investigator: Jane Doe, M.D. Date: 12/6/96
Signature of Person Completing Drug Return Record: Mary Jones Date: 12/1/96
Drug Destroyed By: Date:
Drug Destroyed At: ☐ Roche ☐ Investigator Site
Verified by: Month Day Year

F 11337 (Rev. 7/96) White Copy: Send with Drug – (If Drug is Destroyed at Site, Send to CDC) Canary Copy: Monitor Keeps Pink Copy: Investigator Files

F11337A 8/22/96 10:07 PM Page 1

Protocol No. NV14256 CRIN 19523
Study Title A PHASE III Safety and Efficacy Study of Saquinavir
Rx No 31-8959 CRDP No. 01093
Investigator JANE DOE, M.D. Atlanta, GA.
Investigator No. 24792 Center No. 20143 Country USA

Roche Hoffmann-La Roche
A Member of the Roche Group

Controlled Drug Return Record

NOTE: DO NOT PLACE DRUG RETURN RECORD FORM IN SEALED BAGS

Page 1 of 1

FOR HOFFMANN-LA ROCHE RETURNED GOODS USE ONLY
Date Received: Month Day Year RC #
Package seal intact? ☐ Yes ☐ No
Number of bags received:
By:

Monitor Name: MARY JONES
Telephone Number: 201-235-1234
Date Sent to Roche: 12/1/96
Number of Bags Sent: 1

Type of Containers:
☒ Bottles ☐ Blister cards ☐ Vials
☐ Other

Twenty Percent (20%) of Controlled Drug Returns will be counted by Returned Goods Personnel and listed below. If seal is broken, Returned Goods Personnel will also complete below:

Lot Number (C# for Open Studies or Package ID# for Coded Studies)	Patient Numbers (RDC # for Coded Studies) (use additional forms as necessary)	Bottle Letter (if any)	Number of Units Being Returned (e.g. Vials, Capsules, Tablets)
C123456-01	151	A	2
		B	10
	152	A	1
		B	5

Roche Count Agreed	Roche Count DOES NOT Agree ▶ If count DOES NOT agree, please note discrepancy.
☐	☐ ▶
☐	☐ ▶
☐	☐ ▶
☐	☐ ▶
☐	☐ ▶
☐	☐ ▶
☐	☐ ▶
☐	☐ ▶
☐	☐ ▶
☐	☐ ▶
☐	☐ ▶
☐	☐ ▶
☐	☐ ▶
☐	☐ ▶
☐	☐ ▶
☐	☐ ▶

Signature of Investigator: Jane Doe, M.D. Date: 12/1/96
Signature of Person Completing Drug Return Record: Mary Jones Date: 12/1/96

Drug Destroyed at Roche By: Date:

Verified by: Month Day Year

F 11337A (Rev. 7/96)

White Copy: Send with Drug Canary Copy: Monitor Keeps Pink Copy: Investigator Files

FROM: NAME _____

FACILITY _____

_____

ATTN: MS. SUSAN SARZO
RETURN GOODS ROOM - BUILDING 59/1
HOFFMANN-LA ROCHE INC.
NUTLEY, NEW JERSEY 07110

PROTOCOL # _____ DEPT. CODE _____

Drug Return Labels (small)

FROM: NAME _____

FACILITY _____

_____

ATTN: MS. SUSAN SARZO
RETURN GOODS ROOM - BUILDING 59/1
HOFFMANN-LA ROCHE INC.
NUTLEY, NEW JERSEY 07110

PROTOCOL # _____ DEPT. CODE _____

FROM: **NAME** _____

FACILITY _____

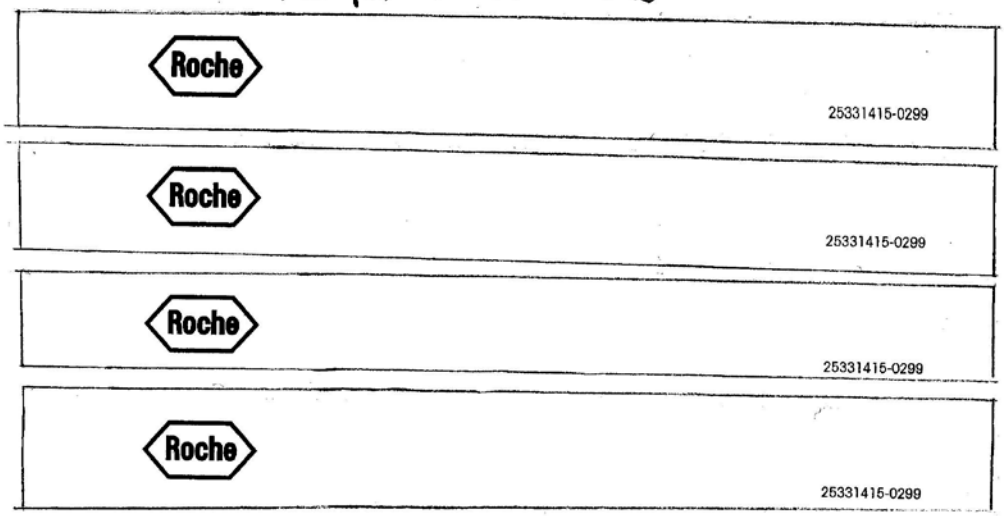
_____

ATTN: **MS. SUSAN SARZO**
RETURN GOODS ROOM - BUILDING 59/1
HOFFMANN-LA ROCHE INC.
NUTLEY, NEW JERSEY 07110

PROTOCOL # _____ **DEPT. CODE** _____

Drug Return Label (Large)

Tamper-Proof labels



Drug Return Form

Roche

Non-Controlled Drug Return Record

Protocol No.	CRTN
Study Title	
Ro No.	CRDP No.
Investigator	
Investigator No. Center No.	Country

NOTE: DO NOT PLACE DRUG RETURN RECORD FORM IN SEALED BAGS

Page _____ of _____

[redacted]

Monitor Name:	Telephone Number:
Date Sent to Roche:	Number of Bags Sent:

Type of Containers:

☐ Bottles ☐ Blister cards ☐ Vials

☐ Other _____

If seal is broken, Returned Goods Personnel will complete below:

[redacted]

Lot Number **C#** for Open Studies *or* **Package ID#** for Coded Studies	**Patient Numbers** **RDC #** for Coded Studies *(use additional forms as necessary)*	**Bottle Letter** *(if any)*	**Number of Containers Being Returned** (Do not use (✓) marks.) FULL	PARTIAL	EMPTY

Signature of Investigator: Date:	Drug Destroyed By: Date:
Signature of Person Completing Drug Return Record: Date:	Drug Destroyed At: ☐ Roche ☐ Investigator Site

[redacted]

F 11337 (Rev. 3/98) White Copy: Send with Drug – (If Drug is Destroyed at Site, Send to CDC) Canary Copy: Monitor Keeps Pink Copy: Investigator Files

CHAPTER 7

DATA COLLECTION PROCEDURES

7.1 General Instructions for Completing PEDS-C Forms

7.1.1 Identifying Information

PEDS-C forms will be identified by the Patient ID, Patient Letter Code, Visit Week # and Date of Assessment. If more than one visit is possible in a week, a sequence number (starting with 01) will also be recorded. Identifying information (at the top of each form above the black line) is to be used on all study forms, reports and pages of documentation.

The Patient's ID Number is assigned by the DCC/CRO ATRS System (Automated Telephone Response System) before screening and after the consents/assents are signed and are recorded on all data collection forms. Once assigned, the Patient's ID Number remains the same throughout the study and follow-up. Because parents (possibly more than one parent) will be contributing data on patients, the Patient ID Number will be structured to allow these IDs to be linked in the database. The Patient's ID Number is composed of the Clinical Center number for the first two digits, a sequential 3-digit number representing the family for the second 3 digits, and then a one digit code (0-4 for the patient or siblings, 5 for female parent/guardian, 6 for male parent/guardian, 7 for other caretaker) e.g., 02-002-0 for a patient and 02-002-5 for the patient's mother, 02-002-6 for the patient's father, and 7 for the patient's grandmother.

When calling the DCC/CRO for drug package assignments, it is important to be sure that all necessary approvals and consents have been obtained and that a firm commitment to participate has been obtained. When a randomization is made, the Teleform data entry system will be prepared to receive patient forms containing that patient ID. Premature assignments and possible withdrawal of ID numbers will require DCC/CRO programmers to delete the ID from the Teleforms System. Similarly, each randomized package assigned by the DCC/CRO will effect the balance of subsequent randomizations assigned to later callers from all Clinical Centers. Premature randomization assignments and subsequent withdrawal of the assignment must be carefully avoided.

The patient is also identified by his/her 3-digit letter code which consists of three letters assigned by the Clinical Center. Clinical Centers will receive lists of random letter codes from the DCC/CRO. As each code is used it will be struck from the list. Patients and each parent completing forms should be assigned the same letter code. The code should remain the same for each individual throughout the study.

Each patient's study forms will be identified by his/her ID number and letter code. They must be provided on the form header for every form and form page being completed in the study. Any mismatch of headers on the pages of the same form will result in the form being rejected for data entry until the identifying information is corrected. Also the CBCL, food diary coding results, and any copies of documentation, such as hospital medical records or laboratory specimens will be identified by the patient ID number, letter code and date. No personal identifiers, e.g., name, SS#, address, phone number, hospital access number, next of kin personal identifiers, etc., will appear on any copies of numbered data collection forms for a PEDS-C patient or parent/guardian.

Forms administered on a regular schedule, e.g. every 1 or 5 weeks or every year, will include a week number in the header information. The week numbers will be three letters or 3-digit consecutive numbers: ELG for screening, 000 for baseline, 001 for the 1 week follow-up visit after baseline, 003 for the second follow-up visit at 3 weeks, 005 for the five week visit, etc. In many cases, week numbers will be pre-printed on forms distributed to the Clinical Centers.

7.1.2 Instructions for Completing Teleform Forms

PEDS-C forms will be printed on pages with binder holes on the left hand side of the sheet. At the beginning of data collection, Clinical Centers will receive a binder for each patient containing forms for treatment assessment visits screening through week 24. The DCC/CRO will be in touch with each Clinical Center to report treatment group reassignments at weeks 24 and 52. Additional forms notebooks will be sent for each patient after weeks 24 and 52.

7.1.2.1 Completion of Each Item

1. Use a black, medium tip, gel-writer type pen, DO NOT use a ball point pen.
2. Completely darken the bubbles; do not check or X the bubbles.

3. Make sure to write inside the boxes. DO NOT TOUCH THE SIDES OF THE BOXES. However, do not write so small that the letters are unreadable.
4. Write all your letters in block UPPER CASE, capital letters.
5. Write all numerals clearly.
6. If you do not have a response, use the "Unknown" or Unavailable" bubble if available. If a text field, do not fill the field with dashes. Leave it blank.
7. Use leading 0's to fill in numerical fields, i.e., 0 0 9 1. If there is no value, do not fill the field with 0's or dashes. Leave it blank.
8. Use forms sent to you in the patient data collection notebook. To obtain copies of event forms, download a PDF form from the web site. Do not use copies of copies.
9. Time fields must be in military 24 hour clock time as defined in Section 7.1.8. Exceptions to this rule will contain AM/PM bubbles to indicate that clock time should be recorded.
10. Dates will be recorded as detailed in Section 7.1.7.

Do not write data or corrections on the form outside the spaces for answers – comments will be seen at the DCC/CRO but not recognized as data by the data entry program. See "Examples for Completing FAX ENTRY Forms" Section 7.1.3 for examples of how to fill out answer spaces.

7.1.2.2 Yes/No Items

Answer Yes or No for every item, not just the "Yes" responses. Fill in each bubble completely, but do not leave marks outside the bubble.

7.1.2.3 Pre-Coded Multiple Choice Items

Fill in only one bubble unless directed to "Answer each part". Fill in each bubble completely, but do not extend marks outside the bubble.

7.1.2.4 Numeric Write-In Items

Write numerals legibly.

Be sure to write so that 1 can be distinguished from 7, and 4 from 9. Do not cross 7. Do not close the top of 4.

Right justify numbers in the spaces provided, and fill in leading zeros, e.g., if the number 12 is the answer, and three spaces are available, write in 0 1 2.

If an item has a built-in decimal point for a numeric response, fill in the number to fit around the decimal and add zeros as needed to fill all spaces, e.g., write in 0 1 2.0, if that many spaces are provided around the decimal point. Do not use hyphens or dashes.

Fill in missing numeric data according to the missing data convention described above.

7.1.2.5 Alphabetic Write-In Items

Use clearly-written capital block letters.

Complete alphabetic write-in fields starting from the left. Leave blank spaces on the right if the response does not completely fill the spaces provided.

Separate words with blanks. Do not use hyphens or dashes. Avoid special characters.

If the entry is longer than the spaces allow, truncate at the last available space.

7.1.2.6 Form Corrections

Do not use correction fluid.

To make a correction:

A. If the form has not yet been FAXed to the DCC/CRO, fill out a new form with the correct data items. Alternatively, you may overwrite the erroneous response on the old form as follows:

An incorrect numeric or alphabetic response must be completely crossed out, using an X, and the correct numeric or alphabetic response written clearly and neatly above or below the original response.

If the response bubble has been written over to change the response, the response is considered missing, unless the correct bubble response is clearly circled and initialed, and the incorrect response crossed out using an X.

The correct response will be circled and initialed by the individual making the corrections. An incorrect response will never be circled or initialed.

B. If the form has already been FAXed to the DCC/CRO:

1) Complete a new form with the same identifying information at the top (e.g., Patient's ID number, Letter code and the original form's date).

2) Fill in the bubble marked “correction” at the top of the form.

3) Complete the item(s) to be corrected. Leave other data items blank.
NOTE: All parts of a conditional item must be answered.

4) Sign the corrected form, and fill in your certification number at the bottom of the form.

5) FAX the corrected page to the DCC/CRO.

6) File the corrected page with the original (uncorrected) page in the patient’s files.

7.1.2.7 Edit Messages

Items on the data collection forms are sometimes overlooked, information is sometimes recorded in the wrong format, or items are answered inconsistently. In order to identify such problems as well as errors that may have occurred during fax entry and to retrieve as much information as possible, all data are subject to a DCC/CRO computer edit to detect missing or improbable answers to each item.

Problems detected by the special computerized edit procedures trigger “edit messages” printed at the DCC/CRO and sent to each Clinical Center. The data transmitted to the DCC/CRO are edited within one week of receipt.

Types of Problems Listed on Edit Statements

1. Inconsistencies

   Within an item on a form, the responses to different parts of an item are checked for consistency. For example, if certain parts of the item are to be answered only if the first part of the item is answered “YES”, a message is generated for each item that is answered if the first part is answered “NO”.

2. Out-of-Range Checks

   Values that are outside specified limits are identified.

3. Unanswered Items

   All unanswered items are listed on the edit statement. An unanswered item is indicated on the edit statement by an empty space under the current value column. A message will say “Item must be answered”.

An edit message is printed for each error identified by the computer to "correct" the item in question, as well as to limit the possibility of additional "error" in processing the corrections at the Clinical Center. The Edit Statement consists of basic identifying information and the edit message. An illustration of a typical edit statement is attached.

The upper left corner of the edit statement contains the Patient's Identification Number. The upper right corner identifies the Form Number, Revision Letter, Page Number and the date of completion for that particular form. The date the edit was printed also appears on the edit statement. The edit statement consists of four columns with the following information:

Column 1: The number of the item in question

Column 2: The description of the item in question, if applicable

Column 3: Brief edit message

Column 4: Current value: The value given in this column is:

a. The value of the remark recorded on the form for write-in responses, or a blank space if the answer is missing.

Column 5: Space to write in the correct value

Specific Procedures for Correcting Edit Statements

You will set aside time, at least one day a week, to respond to edit statements. Each form failing edit will be checked against the edit statement. The particular item will be located and corrected on the original form. The correct value is recorded on the edit statement under the "correct value" column if you choose to do so. The original edit statement is filed with the forms to which they refer so they are available for audits.

Corrections Sent to the DCC/CRO

Forms that require correction will have the corrected information returned to the DCC/CRO. Complete a "corrections form" with identifying information in the header: the Patient's Identification Number, Patient's Letter code, and the date of the <u>original form being corrected</u>. The bubble labeled "correction" in the header will be filled in, and only the items requiring correction to be completed on the rest of the form. This form labeled "correction" will be FAXed to the DCC/CRO.

Procedures for correcting different types of errors are given below:

1. <u>Missing Items</u>

Complete a correction page by filling in the missing items with the correct response.

2. Out-of-Range Values

The DCC/CRO has specific upper and lower ranges for all numeric items. Complete a correction page with the out-of-range item filled in. If the corrected page has the same value for the out-of-range item as the original page, the value will be "flagged" in the computer system as "Out-of-range – verified OK." This will allow the form to pass edit and prevent an out-of-range message for this item from being issued again during a re-edit.

3. Change of Item

Complete a correction page by filling in the items that need to be changed.

4. Deletion of a Write-in Response

To delete a numeric or alphabetic write-in response, complete a correction page. For numeric and date items fill in all boxes for the item to be deleted with asterisks (*). A numeric value could look like (***.*). A date will look like (**/**/****). For character items with more than three boxes, fill in the first three boxes with asterisks (***).

5. Deletion of Bubble Item

The edit statement has a "delete bubble" box in the Action Column. To delete the answer to a bubble item, check the box and give the edit statement to the CRA. The edit statement is not computer processed, but handled by the data coordinator at the DCC/CRO.

7.1.3 Answer ALL Items Unless There is a Conditional Skip

A conditional skip is an instruction to answer a question based on a previous question's answer or to skip to another question further down on the form. Answering questions that will be skipped will create inconsistencies in answering and will result in edit queries.

7.1.4 Unknown, N/A or N/D Check Box

Some form items are required, i.e., leaving them blank will result in an edit query that will need to be resolved, and will be reported in performance monitoring reports as delinquent study data (required but not received) as long as it remains blank. Required

items do not have an "unknown" check box available. However, other items may be answered from the outset as "Not Available" (N/A), or "Not done". When this check box is checked, the item will be reported as missing and not available, and will not appear on an edit statement as a missing, required item. History-type items are designed as "Not Available" or "No answer"; X-rays and other special procedures may be designated as "Not Done" (N/D).

7.1.5 Missing Data

Too much missing data may result in not having sufficient data to answer scientific questions. The Executive Committee will review performance reports frequently, including rates of missing data. Every attempt will be made to identify problems and correct problems leading to missing data.

7.1.6 Dates on Study Forms and Study Data

All dates on study forms will be in the form of 05-01-2005 (May 1, 2005). Valid codes for month are JAN = 01, FEB = 02, MAR = 03, APR = 04, MAY = 05, JUN = 06, JUL = 07, AUG = 08, SEP = 09, OCT = 10, NOV = 11 and DEC = 12. Valid codes for day are 01-31, depending on the number of days in the calendar month.

Some dates may not be known in full. Ask the patient to give his/her best estimate. Do not leave boxes in the date field blank.

7.1.7 Military Time

In most cases, times will be recorded as 24-hour military time in hours only (rounded to the last hour). For example:

Record Midnight as 00

Record 1:00 AM – 11:59 AM as 01 – 11

Record Noon as 12

Record 12:01 PM – 12:59 PM as 12

Record 1:00 PM – 11:59 PM as 13 – 23

Use 99 for an unknown hour.

Times recorded as hours 1-5 will receive edit messages to verify that the time recorded is military, not clock time. Some times labeled with an AM/PM bubble are recorded in clock time. If the question is not so labeled, it should be recorded in military time.

7.1.8 Zero Filling

When you record an answer involving dates or amounts, all boxes (spaces) for that answer must be filled. Zero fill the empty boxes starting from the left. For example, if the patient said she/he was born in July, you would record | 0 | 7 | rather than | | 7 | or | 7 | | |

Always fill every box in the answer space and always zero fill starting from the left.

7.1.9 Coordination

The last part of every form is for recording the certification number and signature of the person responsible for the data being reported on the form.

7.2 Adherence Aids

Adherence Aids are used to help the study data management system flow smoothly. These aids will be used by each Clinical Center and DCC/CRO Staff.

Patient Follow-Up Visit Schedule and Windows

Visit windows for treatment assessment visits 1, 3, and 5 will be ∀ 1 day. For monthly treatment assessments beginning at week 8, the visit window will be ∀ 1 week. For long-term annual follow-up visits the window will be ∀ one month. Clinic Coordinators will receive a list of ideal dates for visits as well as two dates defining acceptable limits. An assessment schedule with visit windows based on the study protocol and date of patient enrollment, will be e-mailed to the site coordinator at the time of patient ID assignment.

Delinquent Forms List

The delinquent forms list will be generated at the DCC/CRO approximately once every two weeks. It will contain information on expected but not received forms based on the patient's follow-up visit schedule and visit windows. The list may also contain forms expected by not received for patients who are on "hold". They may remain on the list until their status changes.

7.3 Electronic Transfer of Data from the Central Laboratory

Laboratory results will be transferred electronically from the Central Laboratory (located at Covance Central Laboratory Services, Inc., Indianapolis, Indiana). The use of a bar code system for specimens will eliminate errors in the recording of identifying

information. Unique accession numbers will be assigned to each collection kit. One accession number will be assigned per visit/per patient. These numbers will identify results in the Covance database and will provide an audit trail for the specimen. The system will alert DCC/CRO staff of any missing specimens or results on a daily basis for immediate follow-up. All laboratory data will be subjected to editing at the DCC/CRO.

Transmission of results from Covance to the DCC/CRO will be based on the Covance LabLink system of posting results on a secure web site for downloading by DCC/CRO staff. The web site will also permit the movement of specimens to be tracked from the Clinical Centers to the Central Laboratory and facilitate the timely reporting of results. In addition, laboratory results will be faxed to the Clinical Center by test group (hematology, chemistry, etc.) as completed. To insure prompt delivery, sites will monitor their fax service regularly. Hard copies will be mailed weekly. Results out of reference ranges will be flagged. See Chapter 12 for details on alerts and flags. Covance will supply each PEDS-C site with a detailed Investigator Manual.

Any problems with the transmission of laboratory results or missing specimens will be referred to Covance Site Support Services contacts. See Chapter 12 for contact telephone numbers.

7.4 FAXing Data Collection Forms to the DCC/CRO

7.4.1 Introduction

The DCC/CRO will receive forms for all patients assigned a Patient Identification Number, for forms completed by Clinical Center staff (Certification Number Report, De-Certification Report), and for forms completed by site monitors (CRA Report) by FAX transmission (410-323-4729) or by FedEx (or other trackable service) in case of temporary interruption of FAXing services. Forms received by mail will be scanned into the computer at the DCC/CRO. Forms FAXed by the Clinical Centers will be transmitted directly into the same computer. The computer system will read the data forms using optical character recognition (ICR) algorithms. Each form image will be verified by a data manager to resolve any characters or bubble responses that the ICR engine has trouble interpreting. The identifying information on each form (header information) will be automatically checked by the data management system to confirm that the patient's identification number and letter code, the staff certification number, or

the CRA's identification number are correct. Any problems encountered (e.g., incorrect patient letter codes) will be promptly resolved with the appropriate Clinical Center staff. If the form fails identification checks, it will held for correction and not added to the main database file. If the form passes the review, it will added to the main study data base and edited.

7.4.2 The Test FAX Form

Clinical Center staff will be required to complete a Test FAX Form to test their FAXing equipment. It is recommended that Clinical Centers use a dedicated FAXing line and have their equipment cleaned and serviced beforehand. Complete and FAX the Test Form to the DCC/CRO as soon as possible. The Clinical Center PI or Project Coordinator will be contacted if the test indicates that the Clinical Center FAX machine is not of acceptable quality for valid data transmission.

7.4.3 FAX Procedures

The original copy of the form should be FAXed. It is recommended that you handle the original copy carefully in order to avoid tearing or misshaping the sheet which will be FAXed. If the fax machine jams, be careful to extract the page carefully so that it does not tear.

Use FAX Form Transmittal Lists (Forms G, H and I) as cover sheets when FAXing completed forms. Use Form G to transmit forms for patients, Form H to transmit forms for Clinical Center staff, and Form I to transmit CRA Reports. The use of cover sheets allows DCC/CRO staff to determine if the FAX transmission is complete. Use one cover sheet for each patient, Clinical Center staff member, or CRA. A single FAX transmission may contain more than one cover sheet.

Cover sheets are filled out with the Clinical Center number 01-11 (see the Address Directory), the date the FAX is being sent, the total number of pages for the patient, staff member, or CRA (not the number of pages in the total transmission if there is more than one ID), and the ID numbers for each patient, staff member, or CRA. Also indicate the Week # for event forms. It is recommended that a single transmission not exceed 30 pages. The patient must be registered with the DCC/CRO (received a Patient ID) and been assigned a letter code before patient forms will be accepted by the computer system. After FAXing, file the original form with the patient's or staff member's records.

When received at the DCC/CRO the bottom box of the cover sheet will be completed with information on any problems with the forms or the transmission. Any

forms to be re-FAXed will be circled and a note written to explain the problem. Annotated cover sheets will be FAXed back to the Clinical Center to acknowledge the receipt of forms. They should be filed with the original forms as a record of the transmission.

7.4.4. It is preferable that the CRF's are completed during the patient visit. However, CRF's must be completed within 24 hours of the patient visit. All CRF's must be faxed into the CRO within 2 weeks of the patient visit.

Form G
Rev 1

PEDS-C TRANSMITTAL LIST OF FAX DATA ENTRY FORMS – PATIENT

Site #: ___ ___ Date sent: _____

Record the patient's ID number below for the forms being sent. Send all pages for each form. If multiple week and/or sequence numbers are being sent, use the spaces provided to indicate the week # and sequence #. Remember that the patient must have been registered with DCC/CRO first before forms can be FAXed.

Forms sent for patient ID number: ___ ___-___ ___ ___-___ Total number of pages FAXed: _____

Form Number	Rev#	# Pages	Week #	Seq #	Comments	Comments from DCC/CRO

Staff Name Faxing Transmittal List: _____ FAX #: _____

This section will be completed by the DCC/CRO staff and returned to the Clinical Center:

Date received: _____ Received by: _____

All forms were receive and were legible: YES _____ No _____

If no, some forms were ineligible or missing. Please see comments above and reFAX.

FAX TO DCC/CRO AT 410-323-4729

7-26-05
Page 1 of 1

TRANSMITTAL LIST OF FAX DATA ENTRY FORMS - STAFF

CLINICAL CENTER # DATE SENT # PAGES FOR STAFF MEMBER

__ __ __ __-__ __-__ __ __ __ __ __

Record the staff member's certification number below for the forms being sent. Send all pages for each form.

Forms sent for Staff Certification Number: __ __ - __ __ __

Form Number Comments

___ ___ _____

___ ___ _____

___ ___ _____

___ ___ _____

___ ___ _____

___ ___ _____

___ ___ _____

___ ___ _____

___ ___ _____

This section will be completed by the DCC/CRO staff and FAXed back to the Clinical Center:

Date received __ __-__ __-__ __ __ __ Received by: _____

All forms were received and were legible ___ Yes ___ No

Some forms were illegible or missing. See circled forms above and re-FAX. ___ Yes ___ No

FAX TO DCC/CRO at 410-323-4729

TRANSMITTAL LIST OF FAX DATA ENTRY FORMS - CRA

CLINICAL CENTER # DATE SENT # PAGES FOR CRA

__ __ __ __-__ __-__ __ __ __ __ __

Record the CRA certification number below for the forms being sent. Send all pages for each form.

Forms sent for CRA Certification Number: __ __ - __ __ __

Form Number Comments

___ ___ _____

___ ___ _____

___ ___ _____

___ ___ _____

___ ___ _____

___ ___ _____

___ ___ _____

___ ___ _____

___ ___ _____

This section will be completed by the DCC/CRO staff and FAXed back to the Clinical Center:

Date received __ __-__ __-__ __ __ __ Received by: _____

All forms were received and were legible ___ Yes ___ No

Some forms were illegible or missing. See circled forms above and re-FAX. ___ Yes ___ No

FAX TO DCC/CRO at 410-323-4729

CHAPTER 8

DIETARY AND PHYSCIAL ACTIVITY DATA COLLECTION

8.1 Diet

A three-day food intake diary will be collected to obtain information on dietary intake. The diary will be collected at Baseline, Week 24, Week 48, Week 72 or 100 (24 weeks after the end of treatment), and at both annual visits (long-term follow up). At the baseline visit, the parent (patient) will be provided with detailed instructions on how to keep the 3-day food diary at home. The parents (patient) will also be provided with instructions on visualizing food portion sizes to be used when keeping the diary. The subject will have one week after the visit to record the three days of the patient's food intake. The 3-day food record will include two weekdays and one weekend day. For example, if a weekday record is collected in person at the visit, the patient will complete one weekday and one weekend day. The parent or patient should bring the food diary to the next scheduled visit where it will be reviewed. The total intake of calories, protein, carbohydrate, fat and micronutrients will be analyzed using the Food Processor SQL© Nutrition Analysis Software from ESHA Research, PO Box 13028, Salem, OR 97309 USA. Dietary interviews with parents, including baseline instruction and regular food diary de-briefing, as well as the computer scoring of completed food diaries will be done by a nutritionist. Both printed scoring results and an electronic results file in an ASCII comma delimited format should be sent to the DCC/CRO promptly.

8.2 Physical Activity

A physical activity questionnaire will be collected in conjunction with the food diary instruction/review at the same clinical center visits. An interviewer will administer the assessment to the parent or to the parent and patient together.

8.2.1 Introduction

Physical activity in PEDS-C patients will be evaluated using the Physical Activity Assessment.

Two approaches to estimating physical activity will be used. The approaches and the questions on the form that address them are as follows:

1. Assessment of the patient's level of physical activity in comparison to other people of the same age and gender (Q1). Based on information obtained, patients will be categorized by activity level.
2. The patient's usual daily activity pattern on a weekday and weekend day during the past month (Q2).

8.2.2 General Instructions

The Physical Activity Assessment will be administered by an interviewer to the parent or the parent and patient together.

The interviewer will read each question from the form in the order in which it appears. When asking questions, the interviewer will insert specific information when directed by the question. For example, when "patient" is written in the question, the interviewer will use the patient's name. After reading a question, the interviewer can use his/her own words while probing. However, he/she will be careful not to lead the parent or patient while probing. When completing the form, the interviewer will clearly mark the parent's (patient's) response.

8.2.3 Instructions for Specific Questions

1. Item 1, activity level. The interviewer will read the categories to the parent (patient).
2. Item 2, activity accounting. The interviewer and parent or patient will work together to complete a table that describes the patient's activity level for a typical weekday and a typical weekend day during the last month. Use the activity level table on the next page to place activities into levels of intensity. The following stepwise approach will be followed: (a) begin with a 24-hour day; (b) ask for the usual number of hours spent sleeping and enter on line A (usual: 8-11 hours); (c) probe for amount of time spent in sustained intense activities and enter on line E (usual: 0-1.5 hours); (d) ask for the number of hours spent in moderate activities and enter the number of hours on line D; (e) subtract A+D+E from 24 hours; (f) ask the parent or patient to divide the remaining hours between light and sedentary activity and enter the appropriate numbers of hours on lines C and B; (g) check to

make sure that the entries in lines A through E add up to exactly 24.0 hours. Hours spent in physical activity classes and lessons will be included in this activity accounting.

ACTIVITY LEVEL TABLE

Sleeping

Sedentary or Seated Activities
Eating
TV, radio, music, videos, etc.
Reading
Cards, board games
Playing musical instruments
Computer activities
Other seated activities

Light or Casual Activities
Household chores
Standing, walking, activities which require standing or walking
Volleyball, ping pong, boating , sailing, bowling, fishing, horseback riding, archery
Easy bike riding
Playing on swings or jungle gym
General play

Moderate or Stop/Start Activities
Heavy yard chores
Calisthenics
Skate boarding, scooters
Fast walking, hiking, hard bike riding, carrying heavy objects
Frisbee, playing catch, softball, golf, recreational skating, recreational swimming in pool or at beach, dancing, aerobics, ballet, gymnastics, cheerleading, surfing, water skiing, weight lifting, doubles tennis
All sports participation with start/stop rather than a sustained activity level

Intense or Sustained Activities*
Running, swimming laps, jogging, jump rope, cross country or downhill skiing, basketball, full court soccer, field hockey, ice hockey, singles tennis, racquetball, figure skating, paddle ball, lacrosse, touch football, rowing

*Code as intense only if you are certain activities are sustained for the entire period of time

CHAPTER 9

PSYCHOSOCIAL DATA COLLECTION

9.1 General Purpose

The general purpose of the psychosocial assessment is to characterize short- and long-term outcomes, including health-related QOL, cognitive and developmental and psychological functioning, and behavior in children in the PEDS-C study.

9.2 Summary of Assessments and Administration Timeline

The following table summarizes the administration schedule of the psychosocial assessment battery:

Measure	Baseline		Week 24		Week 48		24 Weeks After the End of Tx		Annual Visits	
	C	P	C	P	C	P	C	P	C	P
CHQ	X*	X	X*	X	X*	X	X*	X	X*	X
BRIEF		X		X		X		X		X
CBCL (or ABCL if 19+)		X		X		X		X		X
LEC		X		X		X		X		X
SF-36		X		X		X		X		X

[C = Child self-report or administered to child; P = Parent report].
* Not completed by patients younger than age 10

9.3 Description of Assessment Tools and Their Administration

1. Child Health Questionnaire (CHQ)

Description. The Child Health Questionnaire (CHQ) assesses the general and health-related quality of life of children. This paper-and-pencil questionnaire gathers information on several quality of life domains, including physical functioning, role/social limitations, general health, bodily pain/discomfort, parent impact, self-esteem, mental health, general behavior, and family impact. Most of the items pertain specifically to the child's health and others focus on the impact of the child's health on parents and family.

Administration. In this study, the CHQ-PF50 is completed by every study parent and the CHQ-CF87 is completed by every enrolled child who is at least 10 years old. For children younger than 10, comparable information on the same CHQ constructs will be collected from the parent/guardian. The cover page of the rating form includes instructions for completing the form and examples for marking responses. The CHQ-PF50 will take parents about 10 to 15 minutes to complete, while the CHQ-CF87 will take children about 20 to 25 minutes to complete. Both forms will be labeled with the patient's ID number, letter code, date of assessment, and week number.

2. Behavior Rating Inventory of Executive Function (BRIEF)

Description. The Behavior Rating Inventory of Executive Function (BRIEF) is a paper-and-pencil questionnaire that measures emotional and behavioral dysregulation, difficulties with response inhibition, working memory and the ability to quickly transition into new situations or tasks. The BRIEF contains 86 items in 8 non-overlapping clinical scales and 2 validity scales. The clinical scales measure different aspects of executive functioning: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor. The two validity scales are labeled Inconsistency and Negativity. The clinical scales form two broader Indexes: Behavioral Regulation (3 scales) and Metacognition (5 scales), as well as an overall Global Executive Composite score.

Administration. In this study, the standard version of the BRIEF will be completed by all study parents. The first page of the PEDS-C form will include instructions for completing the form and examples for marking responses. The BRIEF will take parents about 10 to 15 minutes to complete. The form will be labeled with the patients ID number, letter code, date of assessment, and week number.

3. Child Behavior Checklist (CBCL)

Description. The Child Behavior Checklist (CBCL) is a paper-and-pencil questionnaire that measures child adjustment across both internalizing (e.g., depression, anxiety) and externalizing (e.g., conduct problems, aggression) domains. The first section of this questionnaire consists of 20 competence items (participation in sports, nonsports

activities, organizations, jobs, friendships, and relationships with other individuals). The second section consists of 112 items focusing on the frequency of behavior or emotional problems observed during the past 6 months.

Administration. In this study, the CBCL will be completed by all study parents. A purchased standardized (blue) form will be used. The cover page of the rating form includes instructions for completing the form and examples for marking responses. The CBCL will take parents about 10 to 15 minutes to complete.

Since the CBCL can only be administered to patients 5 to 18 years of age, the Adult Behavior Checklist (ABCL) will be completed by parents of patients 19 years of age and older. Since the copyright holder will not permit the form to be copied, a purchased standard ABCL form (blue) will be supplied by the DCC/CRO. The ABCL has 126 questions and the summary scores measure the same constructs as those measured by the CBCL. The form will be labeled with the patient's ID number, letter code, assessment date, and week number in the top margin.

4. Life Events Checklist (LEC)

Description. The Life Events Checklist (LEC) is a paper-and-pencil questionnaire that measures perception of 46 life events and the degree to which they represent positive or negative stressors for the patient. These 46 life events are representative of life changes frequently experienced by children and adolescents. Parents will report whether the events were experienced by the child since the last evaluation, indicate whether the life event was "good" or "bad," and the degree to which each event impacted their life.

Administration. In this study the LEC will be completed by all study parents. The LEC will take parents about 5 minutes to complete. The form will be labeled with the patient's ID number, letter code, assessment date, and week number.

5. Short Form-36 Health Survey (SF-36)

Description. The SF-36 is a paper-and-pencil questionnaire that measures parental health-related quality of life across 8 domains: physical functioning, role functioning (physical and emotional), social functioning, pain, general health, vitality,

and mental health. The form will be labeled with the **parent's ID number**, letter code, date of assessment, and week number.

Administration. In this study the SF-36 will be completed by all study parents. Parent will report information about themselves (not the patient). The SF-36 will take parents about 5 minutes to complete.

Once the QL assessment battery has been completed, review each questionnaire for blanks, missing responses, or multiple responses before the family leaves the Clinic Center. If any are found, ask the respondent to go back and answer any skipped items or to clarify any ambiguous responses. (See Chapter 20 for more detailed instructions.)

9.4 Questionnaire Administration by Patient Age

Quality of life (QL) questionnaires will be administered to the following individuals in the following order.

<u>If the enrolled patient is younger than age 7:</u>

1. The patient does not complete any QL questionnaires.
2. The parent completes (in order): CDI Form (depression screen), Child Health Questionnaire- Parent, BRIEF Form, Physical Activity Assessment, Child Behavior Checklist, Your Health and Well-Being (SF-36), and LEC Form- Parent.

<u>If the enrolled patient is 7 to 9 years old</u>:

1. The patient completes (or Clinic Coordinator reads to patient): CDI Form
2. Parent completes (in order): Child Health Questionnaire-Parent, BRIEF Form, Physical Activity Assessment, Child Behavior Checklist, Your Health and Well-Being (SF-36), and the LEC Form- Parent.

<u>If the enrolled patient is at least 10 years old</u>:

1. The patient completes (in order): CDI Form (or the CES-D Form if the patient is 18 or older), Child Health Questionnaire-Patient, and Physical Activity Assessment.
2. The parent completes (in order): Child Health Questionnaire- Parent, BRIEF Form, Child Behavior Checklist (or the Adult Behavior Checklist if the patient is 19 or older), Your Health and Well-Being (SF-36), and the LEC Form- Parent.

9.5 Scoring the Children's Depression Inventory

The Children's Depression Inventory (CDI) will be used for patients aged 5 to 17 years old. It will be scored at the Clinical Center at the time of the screening visit and subsequently at baseline, weeks 12, 24, 48, 72, and at the two long term annual visits (Table 1 schedule. See Tables 1a and 1b for other schedules). Scoring will be done while the patient is still present in the Clinic. Deriving the Total CDI Score is a relatively simple process and will take no longer than 5 minutes. Three CDI scoring templates, one for each page of the form, and the CDI Scoring Worksheet will be used for scoring.

The CDI Form in Teleform format is three pages long and contains 27 questions. All questions must be answered in order to compute the CDI Total Score. During coding each response is assigned a code of 0, 1, or 2. The codes for 13 of the questions (# 2, 5, 7, 8, 10, 11, 13, 15, 16, 18, 21, 24, and 25) have been reversed so that patients will not form the habit of choosing answers according to their order of presentation (first, last, etc). To use scoring templates, place each template over the correct CDI page and align the cornerstones (black boxes in each corner). Using the CDI Scoring Worksheet, copy the codes appearing beside the darkened bubbles for each response in the appropriate column of the Worksheet (Page 1, 2, or 3). When all page columns have been completed, total each column and record the totals for each page in the space provided below each column. Finally, add the three page totals to derive the CDI Total Score and record it in the space provided in the bottom right of the Worksheet. Double check the score by adding the columns and column totals a second time. Using a calculator may improve accuracy.

The CDI Total Score is the score used in the depression screen section of PEDS-C forms. If the Total CDI score is greater than 19, the Clinical Center Principal Investigator will be informed and a Depression Management Tracking Form will be started. CDI subscale scores will be computed at the Data Coordinating Center when needed.

9.6 Scoring the Center for Epidemiological Studies Depression Scale (CES-D)

The CES-D will be used INSTEAD OF the CDI for patients 18 years of age or older. Deriving the total CES-D score is a relatively simple process and should take no longer than 5 minutes. The questionnaire has 20 questions. All questions must be answered to compute the total score. You will need two CES-D scoring templates, one for each page of the form, and the CES-D Scoring Worksheet. During scoring, each response is assigned a code of 3= Most or all of the time (5-7 days), 2= Occasionally or a moderate amount of the time (3-4 days), 1= Some or a little of the time (1-2 days), or 0= Rarely or none of the time (less than 1 day). The codes for questions 4, 8, 12, and 16 are reversed. To score the CES-D, place each template over the correct page and align the cornerstones so that the codes and question responses line up. Using the CES-D Worksheet, copy the codes appearing beside the darkened bubbles for each response in the appropriate column of the worksheet (Page 1 or Page 2). When both page columns have been completed, record the total for each page in the space provided below each column. Finally, add the two page column totals together to derive the total CES-D score. The total score is the score used in the depression screening section of PEDS-C forms for patients aged 18 and older. If the total CES-D score is greater than 15, start a Depression Management Tracking Form for the patient.

CHAPTER 10
MONITORING REQUIREMENTS

10.1 Clinical Center Records Checklist

The Principal Investigator at each site is responsible for ensuring that the study is conducted properly and in accordance with the protocol, Good Clinical Practice (GCP), relevant regulatory guidelines and sound medical practice. The DCC/CRO (or their designee) will ensure that the Investigator is familiar with GCP and the appropriate regulatory requirements.

STUDY DOCUMENTATION AND RETENTION OF DOCUMENTS

Before the study can commence at a PEDS-C Clinical Center, the Investigator must provide the DCC/CRO with the following documents:

1. Signed final protocol
2. Investigator's CV
3. A signed copy of the IRB/IEC approval letter

The Investigator will also be expected to help provide a list of the IRB/IEC members, plus their constitution/qualifications. Where local laboratories are used, a copy of the lab reference ranges and certification of their participation in quality assurance schemes will be required throughout the study.

The Investigator will also be expected to maintain a study file to retain all documentation relating to the trial.

The minimum requirements for the Investigator's study file are:

- the signed original protocol and amendments
- signed FDA Form 1572
- copies of the investigator's and co-investigator'(s) CVs, plus a study personnel identification list and sample signature page
- IRB/EC approval(s), annual study updates and all IRB/EC correspondence

- regulatory approvals
- updated laboratory certification and reference ranges covering the entire duration of the study
- all signed informed consents
- all completed CRF's (these can be added at the end of the study)
- all correspondence to/from the sponsor
- a blank copy of the informed consent documents and CRF
- clinical trial supplies
- all documentation relating to the study medication including drug receipt forms, accountability forms and return/destruction of study medication (this can be added at the end of the study)
- Investigator brochure and updates
- confidential patient list (to include patient name, date of birth, study number and a hospital number if possible)
- SAE's
- Visit log

The Investigator's study file will be retained in a known location for a period of 2 years after the final anticipated marketing application or until 2 years have elapsed since the formal discontinuation of the clinical development of the investigational product. It is the responsibility of the sponsor to inform the investigator as to when the retention of the study file is no longer needed.

10.2 SOURCE DOCUMENTATION VERIFICATION (SDV) REQUIREMENTS

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) require that the investigator prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the study on each patient. Patient records support the data included in the CRF's and may provide additional information on the patient prior to and after the study. CRF's alone cannot serve as the complete investigational record and patient medical records are necessary to authenticate

the information presented in the CRF and to provide, where appropriate, the possibility of completing or correcting the CRF entries.

10.2.1 Contacts and Visits

The amount of monitoring required shall largely depend on the number of patients enrolled at each study site. However, as a general rule, it is estimated that it will take approximately 4 to 6 hours per patient to verify source data against CRF's.

This trial shall involve on-site monitoring by personnel designated by DCC/CRO who shall follow the DCC/CRO Standard Operating Procedure (SOP) for this trial. It is recommended that the first monitoring visit will take place as soon as possible after the first subject has completed their screening visit. Another visit will happen as soon as possible after the first patient has been randomized. Subsequently the frequency of monitoring visits will not be less than every 3-4 months before all patients have passed their 24 Week visit and every 6 months thereafter. The appropriate visit intervals may increase or decrease depending on the phase of the study and the recruitment rate.

A Data Safety Monitoring Board (DSMB) has been defined for the study to which safety and efficacy information will be disseminated regularly and reviewed on an ongoing basis. The DSMB will be able to call an 'alert' meeting if any data gives cause for concern. In conjunction with this, a Safety Committee will review all AE's and SAE's on a monthly basis. Concerns arising from this review will be forwarded to the sites for follow-up or may be referred to the lead PI or DSMB as needed.

10.2.2 Monitoring Schedule

Clinical Centers will be visited before the study begins (pre-study visits) and at initiation visits after DSMB approval when CRF's and drug supplies have been received at the Clinics. After the study has started, visits will occur every 3-4 months before all patients in a clinic have completed their 24 Week visit and every 6 months thereafter. Clinical sites will also be visited in order to remedy any problems that may arise. Special visits may include Dr. Schwarz and representatives from the DCC/CRO and Project Office.

10.2.3 SOURCE DOCUMENT VERIFICATION and HOW TO RECORD SOURCE DOCUMENTATION

What is a Source Document?

Source documents are the original medical records i.e. the place where data are first recorded. These include, but are not limited to, clinic and hospital charts, laboratory reports, X-rays, other diagnostic reports and patient-generated documents (e.g. diaries and questionnaires). The CRF may in some circumstances become the source document if it is the first place where certain observations are noted and provided that the necessary minimum information has been recorded in the patient's medical records. For example the CRF asks in detail for the patient's race. This would not routinely be added the patient's notes and the CRF might therefore be the first and only place where this information is noted, in this case the CRF will therefore form the source document.

Photocopied CRF's

Blank CRF pages may be photocopied and used to capture source data as necessary. If these are used, ensure they are retained in the patient's clinic notes. These will be more easily identified as source documents if the word 'source' is indicated in a non-data section such as the CRA comment column. The author's signature should be included as normal for source documentation.

If a completed CRF is to be used in a medical chart, they must be photocopied with the study related header data covered and replaced with the appropriate patient information such as name, date of birth and hospital medical record number.

Investigators will enter medical information into the clinic notes as they would for any patient under their care (all entries must be signed and dated by the person making the entries). They must, in addition, make it clear in these records that the patient is participating in the clinical study. As a guideline, the following data will be verifiable in the medical records:

Minimum Information Required in Medical Notes

An entry must be in the patient's medical records each time the patient is contacted or visits the clinic during the study.

For study visits, the minimum acceptable documentation must include:

- Date of every visit
- At Screening:
    - The patient's clinical status/details of disease under study
    - Confirmation that written Informed Consent has been obtained. Written informed consent must be obtained prior to performing any pre-treatment procedure. The patient must be given a copy of the signed and dated consent form that they have personally signed and dated with the Investigator and witness, if applicable. The original document must be filed in the patient's chart as a permanent part of the record (source document). A copy will also be filed in the site file. It must be made available to the study monitor upon request, during monitoring visits.
    - A statement that the patient has been enrolled into the PEDS-C study
    - Record of the patient number
- Details of the primary efficacy parameter whenever assessed with a copy of the supporting assessments
- All changes to concomitant medications including dose and start/stop dates. If no adverse events, occurred this must be documented.
- Details of any adverse events including diagnosis/symptom and start/stop dates. If no adverse events occurred, this must be documented.
- If the patient withdraws from the study, this must be documented and a reason provided.
- When the patient completes the study, this must be documented.

Please note: If source data is electronic, then a signed and dated hard copy is required to be filed in the medical notes. The investigator must sign the hard copy.

DIRECT ACCESS BY THE DCC/CRO (OR THEIR REPRESENATIVE) IS REQUIRED TO ALL PATIENT MEDICAL RECORDS THAT RELATE TO THE PATIENT'S PARTICIPATION IN THE STUDY.

Source Data Verification (SDV)

ICH GCP guidelines requires that the study monitor have direct access to all subject files to verify that all data recorded in the CRF is correct (that is to undertake "direct access source data verification'). In general, monitors will verify subject entry criteria, principal measures of efficacy and safety, concomitant medications and subject compliance as these are items that, if recorded incorrectly, might influence the outcome of the study. In addition, one chart will have all measures checked against source documents.

It is important that the investigator appreciates that this is a necessary quality control; no one investigator is singled out. All sponsors of trials must undertake this process and if it is not properly undertaken the regulatory authorities might reject the study.

The matter of SDV will be discussed with the investigator at the initial discussions. Due to the strict regulatory requirements, any investigator who does not allow direct SDV cannot be invited to take part in the study.

Patient confidentiality is a prime concern in PEDS-C. The patient is fully informed that SDV is required and they will be asked to give their written permission on the consent form. The monitor will behave professionally to ensure that patient confidentiality is respected.

10.3 Records Retention

As per the Code of Federal Regulations (part 312.62): an investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such an indication, until 2 years after the investigation is discontinued and the FDA is notified.

The exact period for archiving is not well defined and investigators will be advised by the DCC/CRO of the study how long to store documentation.

10.4 Study File Checklist

Study File Checklist **Study No. :** **Site No. and Name :**

Documentation Required Before the Clinical Phase of the Trial Commences

Document	Purpose	Located in files (tick if present)		
		N/A	Site File	MMRI File
Signed Confidentiality Agreement	To document agreement	☐	☐	☐
Investigator's Brochure **List below:**	To document that relevant and current scientific information about the investigational product has been provided to the investigator	☐	☐	☐
Insurance Statement (where required)	To document that compensation to subject(s) for trial-related injury will be available	☐	☐	☐
Signed Protocol and Amendments (if any)	To document investigator and MMRI agreement to the protocol/amendment(s)	☐	☐	☐
Signed Financial Agreement(s) between involved parties **List below:**	To document all financial agreement(s) relating to the trial	☐	☐	☐
Regulatory Authority(ies) Authorization/Approval/Notification of Protocol (where required)	To document appropriate authorization/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirements	☐	☐	☐

Document	Purpose	Located in files (tick if present)		
IRB/EC Composition	To document that the IRB/EC is constituted in agreement with GCP	☐	☐	☐
IRB/EC Submission(s) **List below**	To document the protocol and other documents which were subject to IRB/EC review	☐	☐	☐
Information given to Trial Subject		☐	☐	☐
- Informed Consent Document **List below:**	To document the informed consent	☐	☐	☐
- Any other written information **List below:**	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	☐	☐	☐
- Advertisement for Subject Recruitment (if used) **List below:**	To document that recruitment measures are appropriate and not coercive	☐	☐	☐
Dated, Documented IRB/EC Approval/Favorable Opinion of the following: **List below:**	To document that the trial has been subject to IRB/EC review and given approval/favorable opinion. To identify the version number and date of the document(s)	☐	☐	☐

Document	Purpose	Located in files (tick if present)		
Completed FDA Form 1572 (if applicable)	Statement of investigator to document appropriateness to conduct clinical trial	☐	☐	☐
Curriculum Vitae and/or other Relevant Documents Evidencing Qualifications of Investigator(s), Co-Investigators and Relevant Study Personnel **List below:**	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	☐	☐	☐
List of MMRI and Study Site Personnel **List below:**	To document names and contact details for all relevant study personnel	☐	☐	☐
Laboratory References/Range(s) for Medical/ Laboratory/Technical Procedure(s) and/or Test(s) Included in the Protocol **List below:**	To document normal values and/or ranges of the tests	☐	☐	☐
Medical/Laboratory/Technical Procedures/Tests – certification, accreditation, established quality control and/or external quality assessment or other validation **List below:**	To document competence of facility to perform required test(s), and support reliability of results	☐	☐	☐

Document	Purpose	Located in files (tick if present)		
Specialist Medical/Laboratory/Technical Procedures/Tests – methodologies **List below:**	To document the methodology for non-standard tests used in the trial	☐	☐	☐
MMRI approved blank Case Report Form	To document MMRI's approval of the CRF	☐	☐	☐
Blank Case Report Form	To document the CRF	☐	☐	
Other Sample Clinical Trial Supplies **List below:**	To document other supplies provided to site	☐	☐	☐
Monitoring Guidelines (if used)	To assist with CRF interpretation and completion	☐	☐	☐
Sample of Label(s) Attached to Investigational Product Container(s)	To document compliance with applicable labeling regulations and appropriateness of instructions provided to the subjects	☐	☐	☐
			☐	☐
Certificate(s) of Analysis of Investigational Product(s) **List below:**	To document identity, purity and strength of investigational product(s) to be used in the trial			
Pharmacy Handling Instructions (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials		☐	☐
Master Randomization List	To document method for randomization of trial population			☐ (third party if applicable)

Document	Purpose	Located in files (tick if present)	
Decoding Procedures/Envelopes for Blinded Trials (if not included in protocol, Investigator's Brochure or Pharmacy Handling Instructions)	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for remaining subjects' treatment	☐	☐ (third party if applicable)
Completed Investigator and Site Qualification/ Initiation Form	To document that the investigator and site is suitable for the trial and that the trial procedures were reviewed with the investigator and the investigator's trial staff	☐	☐
Trial Medication Release Form(s)	To document that the essential study documentation is in place prior to sending trial medication to study site		☐
Trial Medication Despatch Form	To document the request to ship trial medication to the study site		☐
Trial Medication Delivery Note	To document shipment dates batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	☐	☐

Please sign when Study File Checklist is complete:

Signed: _____ Date:_____

Name: _____ Title:_____
(block capitals)

Documentation Required During the Clinical Conduct of the Trial
(In addition to filing the previous documents, the following should be added to the study files during the trial as evidence that all new, relevant information is documented as it becomes available.)

Document	Purpose	Located in files (tick if present)	
		Site File	MMRI File
Investigator's Brochure Updates **List below:**	To document that the investigator is informed in a timely manner of relevant information as it becomes available	☐	☐
Any Revisions to:	To document revisions of these trial related documents that take effect during trial		
• **protocol/amendment(s)** **List below:**		☐	☐
• **CRF** **List below:**		☐	☐
• **informed consent document(s)** **List below:**		☐	☐
• **any other written information provided to subjects** **List below:**		☐	☐
• **advertisement(s) for subject recruitment (if used)** **List below:**		☐	
IRB/EC Submissions **List below:**	To document the protocol and other documents which were subject to IRB/EC review	☐	☐

Document	Purpose	Located in files (tick if present)	
		Site File	MMRI File
Interim or Annual Reports to IRB/EC and Authority(ies) **List below:**	Interim or annual reports provided to IRB/EC and authority(ies)	☐	☐ (where required)
Dated, Documented Approval/Favorable Opinion of IRB/EC of the following: **List below:**	To document that the amendment(s)and/or revision(s) have been subject to IRB/EC review and were given approval/favorable opinion. To identify the version number and date of the document(s)	☐	☐
Regulatory Authority(ies) Authorizations/ Approvals/Notifications (where required) **List below:**	To document compliance with applicable regulatory requirements	☐	☐
Updates to FDA Form 1572 **List below:**	Statement of investigator to document appropriateness to conduct clinical trials	☐	☐
Curriculum Vitae for New Investigator(s) and/or Co-Investigator(s) and Relevant Study Personnel **List below:**	To document qualifications and eligibility to conduct trial and/or to provide medical supervision to subjects	☐	☐
Updates to Laboratory Reference Range(s) for Medical/Laboratory/Technical Procedure(s)/ Test(s) Included in the Protocol **List below:**	To document the methodology for non-standard tests used in the trial	☐	☐

Document	Purpose	Located in files (tick if present)	
		Site File	MMRI File
Updates of Medical/Laboratory/Technical Procedure(s)/Test(s) – certification, accreditation, established quality control and/or external quality assessment, other validation (if required) **List below:**	To document that tests remain adequate throughout the trial period	☐	☐
Updates of Specialist Medical/Laboratory/Technical Procedure(s)/Test(s) – methodologies **List below:**	To document the methodology for non-standard tests used in the trial	☐	☐
Certificate(s) of Analysis for New Batches of Investigational Products **List below:**	To document identity, purity and strength of investigational product(s) to be used in the trial		☐
Trial Medication Release Form(s) (if required) **List below:**	To document that the essential study documentation is in place prior to sending trial medication to study site		☐
Trial Medication Dispatch Form(s) **List below:**	To document the request to ship trial medication to the study site		☐
Trial Medication Delivery Note(s) **List below:**	To document shipment dates batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	☐	☐

Document	Purpose	Located in files (tick if present) Site File	MMRI File
Drug Accountability Form	To document that investigational product(s) have been issued according to the protocol	☐	
Site Visit Log	To document site visits by the monitor	☐	
Signed Informed Consent Forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission	☐	
Monitoring Visit Reports **List below:**	To document site visits by, and findings of, the monitor	☐ (if appropriate)	☐
Correspondence **Subdivide and List below if required:**	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	☐	☐
Notification of Serious Adverse Events and Related Reports to MMRI	Notification by originating investigator to sponsor of serious adverse events and related reports	☐	☐
Notification by MMRI and/or Investigator, where applicable, to Regulatory Authority(ies) and IRB(s)/EC(s) of Unexpected Serious Adverse Drug Reactions and of other Safety Information **List below:**	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/EC(s) of unexpected serious adverse drug reactions and of other safety information	☐ (where required)	☐
Notification by MMRI to Investigators of Safety Information **List below:**	Notification by sponsor to investigators of safety information	☐	☐
Subject Screening Log	To document identification of subjects who entered pre-trial screening	☐	☐ (where required)

Document	Purpose	Located in files (tick if present)	
		Site File	MMRI File
Subject Recruitment Log	To document chronological enrolment of subjects by trial number and provide a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/ institution to reveal identity of any subject	☐	
Sample Handwriting	To document signatures and initials of all persons authorized to make entries and/or corrections on CRF's	☐	☐
Updates to List of MMRI and Study Site Personnel **List below:**	To document names and contact details for all relevant study personnel	☐	☐
Record of Retained Body Fluids/Tissue Samples (if any)	To document location and identification of retained samples if assays need to be repeated	☐	☐
Other Documents Added **List below:**		☐	☐

Please sign when Study File Checklist is complete:

Signed: _____ Date:_____

Name: _____ Title:_____
(block capitals)

Documentation Required After Completion or Termination of the Trial

(After completion or termination of the trial, all of the documents described previously plus the following should be in the file together)

Document	Purpose	Located in file (tick if present)	
		Site File	MMRI File
Signed, Dated and Completed CRF's	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded	☐ (copy)	☐ (original)
Documentation of CRF Corrections	To document all changes/additions or corrections made to CRF after initial data were recorded	☐ (copy)	☐ (original)
Completed SDV Checklists (if used)	To document the existence of the subject and substantiate integrity of trial data collected	☐ (optional)	☐
Completed Site Visit Log	To document site visits by monitor	☐	☐
Drug Accountability Forms	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by subjects, returned to MMRI, or destroyed on site	☐	☐
Documentation of Investigational Product Destruction (if applicable)	To document destruction of unused investigational products by sponsor or at site	☐ (if destroyed at site)	☐
Completed Subject Recruitment Log	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner for an agreed time	☐	
Audit Certificate (if available)	To document that audit was performed		☐
Site Closure Form	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		☐

Document	Purpose	Located in file (tick if present)	
		Site File	MMRI File
Treatment Allocation and Decoding Documentation	Returned to MMRI to document any decoding that may have occurred		☐
Final Report by Investigator to IRB/EC where required, and where applicable, to the Regulatory Authority(ies)	To document completion of the trial	☐	
Clinical Study Report	To document results and interpretation of trial. Full copy of text to Principal Investigators - other sites may only require summary	☐ (if appropriate)	☐
Publications (if available)	To document publications concerning clinical trial	☐	☐

Please sign when Study File Checklist is complete:

Signed: _____ Date:_____

Name: _____ Title:_____
(block capitals)

CHAPTER 11

PHYSICAL EXAM PROCEDURES

11.1 Medical History, Physical Examination and Vital Signs

11.1.1 Procedures for Taking the Medical History

Past Medical History and Physical Exam

Patients are required to have a past medical history at screening. Patients are required to have a full physical at screening, end of treatment, end of untreated follow-up and annual visits.

Patients will have a symptom directed physical at any other study visit as needed or at any time during the study as needed.

A competent medical professional must perform the History and Physical Exam. The assessments should be done in a private area. Based upon the age, developmental level and wishes of the patient, the adult caregiver may accompany the patient. The examiner must introduce himself to the patient and explain what will be done during this section of the study.

Procedure for Taking a Past Medical History

The past medical history is background information related to the patient's physical and mental health and well being assessed in a systems approach. The questions are worded to reflect a variance from normal limits.

If the answer to a question is ‘within normal limits’, the physician will answer yes under #1 Yes/No. If the answer to a question is outside of normal limits, the physician will answer no under #1 Yes/No and give a brief description of the problem under #2 Specify/Comment.

Include only brief comments neatly printed in this section; further details can be placed in the patient’s clinical chart if needed. It is important to remember that only information recorded on the CRF will be collected in the database.

Indicate if problems are on-going by darkening the appropriate bubble under #3: ‘Still a problem Yes/No.’

The medical history section includes a list of the current medications the patient is taking. There is an opportunity to record 7 different medications. If the patient is taking

less than 7 medications leave all unused boxes blank (Do not draw lines or mark in the boxes in any way).

Procedure for Performing a Physical Exam

The physical exam is as assessment of the patient's current physical and mental health and well being. The questions are worded to reflect a variance from normal limits.

If the answer to a question is ‘within normal limits’, the physician will answer yes under #1 Yes/No. If the answer to a question is outside of normal limits, the physician will answer no under #1 Yes/No and give a brief description of the problem under #2 Specify/Comment.

Include only brief comments neatly printed in this section; further details can be placed in the patient’s clinical chart if needed. It is important to remember that only information recorded on the CRF will be collected in the database.

11.1.2 Taking Vital Signs

Procedure for obtaining vital signs:

Wash hands.

Explain procedure to the patient.

Temperature:

May be measured via oral, axillary or tympanic route.

How to Take an Oral Temperature:

For accuracy, wait at least 10 minutes after hot or cold fluids have been taken, or cigarettes have been smoked.

Use a digital thermometer, make sure it is in the correct "on" mode.

Place the thermometer in the person's mouth under the tongue on one side, and slide well back into the mouth. Have person close the lips, and avoid biting the thermometer.

Hold thermometer in place until the alarm signals complete.

Remove the thermometer from the mouth and record the temperature.

How to Take an Axillary Temperature:

Use a digital thermometer.

Hold the thermometer in the clean, dry armpit, making sure that the bulb is completely covered between the person's arm and side. Hold the arm down.

Hold the thermometer in position until the alarm signals complete.

Remove the thermometer and record the temperature.

How to Take a Tympanic Temperature:

Use a thermometer especially designed for ear temperatures.

Hold the thermometer firmly at the opening to the child's ear. For the sensor to detect heat from the drum, not from the cooler canals, the ear canal must be straightened as when using an otoscope -- the pinna pulled up and back for all children in the study. Press the button.

When the alarm signals complete, remove the thermometer and record the temperature.

Record result in Centigrade.

To convert from Fahrenheit to Centigrade you must take the Fahrenheit reading and subtract 32 then divide by 1.8 (TF – 32 ÷ 1.8 = TC)

Pulse:

Must be taken with a stethoscope.

Listen to the heart for 30 seconds and multiply by 2 to obtain beats per minute (bpm).

Blood Pressure:

Blood pressures may be taken manually or by an electronic device. Try to maintain consistency on type of device and size cuff used for each visit.

The bladder inside the cuff should encircle 80% of the arm in those ages 13 and above and 100% of the arm in children less than 13 years old. If in doubt, use a larger cuff.

Palpate the brachial artery and place the cuff so that the midline of the bladder is over the arterial pulsation, then wrap and secure the cuff snugly around the subject's bare upper arm. Avoid rolling up the sleeve in such a manner that it forms a tight tourniquet around the upper arm. Loose application of the cuff results in overestimation of the pressure. The lower edge of the cuff should be 1 inch (2 cm) above the antecubital fossa (bend of the elbow), where the head of the stethoscope is to be placed

If performing a manual BP, place the manometer so the center of the mercury column or aneroid dial is at eye level and easily visible to the observer and the tubing from the cuff is unobstructed.

Place the earpieces of the stethoscope into the ear canals, angled forward to fit snugly. Switch the stethoscope head to the low-frequency position (bell). The setting can be confirmed by listening as the stethoscope head is tapped gently.

Place the head of the stethoscope over the brachial artery pulsation just above and medial to the antecubital fossa but below the lower edge of the cuff, and hold it firmly in place, making sure that the head makes contact with the skin around its entire circumference.

Inflate the bladder rapidly and steadily until your desired maximum is reached. Partially unscrew (open) the valve and deflate the bladder at 2 mm/s while listening for the appearance of the Korotkoff sounds.

As the pressure in the bladder falls, note the level of the pressure on the manometer at the first appearance of repetitive sounds and at the muffling or total disappearance of the sound. After the last sound is heard, the cuff should be deflated slowly for at least another 10 mm Hg, to ensure that no further sounds are audible, then rapidly and completely deflated. The systolic and diastolic pressures should be immediately recorded, rounded off (upwards) to the nearest 2 mm Hg. In children, and when sounds are heard nearly to a level of 0 mm Hg, the reading at the muffling of sounds should be recorded

Reference: Adapted from the American Heart Association, “Human Blood Pressure Determination by Sphygmomanometry” Copyright 1994.

Weight:

The weight should be assessed with the child in normal street clothes with shoes, and all outerwear removed. The weight must be recorded in kg. To convert from pounds to kilograms, take the weight in pounds and divide by 2.2 (lbs ÷ 2.2 = kilograms).

Height:

A standing height board or stadiometer is required. The device has a flat vertical surface on which a measuring rule is attached. It has a movable headpiece and either a permanent surface to stand on or the entire device is mounted on the wall of a room with a level floor.

Procedure for measuring a child:

1. Remove the child's shoes, hats, and bulky clothing, such as coats and sweaters. Undo or adjust hair styles and remove hair accessories that interfere with measurement.

2. The child should stand erect, with shoulders level, hands at sides, knees or thighs together and his weight evenly distributed on both feet. The child's feet should be flat on the floor or foot piece, with both heels comfortably together and touching the base of the vertical board. When possible, all four contact points (i.e., the head, back, buttocks, and heels) should touch the vertical surface while maintaining a natural stance. Some children will not be able to maintain a natural stance if all four contact points were touching the vertical surface. For these children, at a minimum, two contact points — the head and buttocks, or the buttocks and heels — should always touch the vertical surface.

3. Lower the headpiece until it firmly touches the crown of the head and is at a right angle with the measurement surface. Check contact points to ensure that the lower body stays in the proper position and heels remain flat.

4. Read the stature to the nearest 1 mm. Record.

5. Record the result in centimeters.

1 inch = 2.54 cm and 1 foot = 30.48 cm.

To convert from inches to centimeters multiply height in inches by 2.54.

H" x 2.54 = H cm

Adapted from The Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion

11.2 Anthropometry

11.2.1 Procedures for Measuring Height

Standing height will be measured by a stadiometer to the nearest 0.1 cm. Measures will be taken twice by the same measurer as instructed on the data collection form.

The patient will be barefoot. It is important to avoid including tight braids or other hairstyle features between the head projection and the crown of the head.

The stadiometer will be checked for accuracy every two months with a rigid rod of known height. A log of checks, results and re-calibrations will be kept at the Clinical Center

11.2.2 Procedures for Measuring Weight

Body weight will be measured with an electronic scale accurate to 0.1 kg. The scale will be checked every two months with standard weights.

The patient will be barefoot with indoor clothing only reduced to a practical minimum. Measurements will be taken twice by the same measurer.

11.2.3 Procedures for Measuring Arm Circumference

Circumferences will be measured with a fiberglass or paper tape reading in centimeters. Circumferences will be recorded with the zero end of the tape held by the left hand above the remaining part of the tape measure, which is held by your right hand. The tape measure around the arm will be perpendicular to the long axis of the body.

To locate the midpoint of the arm, the patient's elbow is flexed at a 90-degree angle with their palm facing up. The person measuring will stand behind the patient and locate the lateral tip of the acromion by palpating laterally along the superior surface of the spinous process of the scapula. The tape measure is placed from the acromion process to the tip of the olecranon and the midpoint is marked on both the anterior and posterior sides of the arm. (Both of these marks will be further utilized during the triceps and biceps skin fold measurements.) The arm will now be repositioned to hang loosely at the side with their palm facing in. The tape measure will be passed around the arm from left to right. Making sure that the tape is at the same level as the mid-upper-arm mark, the person measuring will tighten the tape measure so that it touches the skin all around the circumference, but does not compress the skin or alter the contour of the arm. The circumference is then read. Perform this measurement twice and record the results to the nearest 0.1 cm.

11.2.4 Procedure for Measuring Skinfolds

Each center will use the same equipment for all skinfold measurements.

Skinfold measurements: Lange Calipers and a calibration block

A grease marking pencil or a washable felt-tip marker

Lange Caliper Skin Fold Measurement Guidelines

Calibration of skin fold calipers will be performed on each day prior to usage. A log of calibrations and servicing will be kept by the Clinical Centers. Calibrations must be

within 0.9mm or less at the following test distances; 10-, 20-, 30-, 40- and 50-mm. If these standards are not met, calipers must be serviced prior to use.

To grasp the fold of skin to be measured, without including musculature) first pinch and raise the fold two or three times to be certain the correct tissue is obtained. The amount of tissue to be measured will be as accurately determined as possible prior to placement of the calipers. Right-handed measurers will use the left index finger and thumb to firmly grasp the skin fold. Left-handed measurers will use the right index finger and thumb.

The skin fold will be grasped approximately 2 cm above the marked point at which point the calipers will be placed; the caliper jaws will contact the point of the skin fold at the mark previously made; the finger and thumb will be above the mark.

Place the caliper jaws around the skin fold, below the thumb and finger and release the caliper grip. Hold this position for 3 seconds prior to reading the measurement on the dial. Do not release the firm grasp (bearing in mind the subject's pain threshold) of the skin fold with the left hand until the measurement is complete and the caliper is removed.

The calipers must be placed at a specific depth of the skin fold to yield accurate measurements given a skin fold lifted by one hand is likely to be unparallel (i.e., larger near the base vs. the crest). The skin fold surfaces must be as parallel as possible to one another and thus to the jaws of the calipers; a measurement will likely be inaccurately large if the caliper jaws grasp the base of the skin fold.

Accurate measurements are of the utmost importance. It is possible to make errors, even for the most experienced practitioner, if the dial is incorrectly read or the caliper jaws are misplaced.

Measurements will be obtained two times by the same measurer for each skin fold (triceps, biceps, subscapular and suprailiac). Remove the calipers and release the skin fold in between each reading. All measurements will be recorded to the nearest 0.1 cm or mm.

Unless contraindicated, all measurements will be taken on the right side of the subject.

Triceps Skin Fold

Instruct the subject to drop their arm by their side and allow it to hang loosely, palm facing in. The posterior midpoint between the acromion and the olecranon processes (previously marked for the mid-arm circumference measurement) will be used for the measurement. Grasp the skin fold between the index finger and thumb above this point, taking care to separate the skin fold form the underlying muscle tissue. Calipers will be placed along the vertical fold below the thumb and index finger. Read the measurement to the nearest millimeter, record and repeat the procedure.

Biceps Skin Fold

The arm will again be hanging loosely by the subject's side, palm facing in, for this measurement. The anterior midpoint between the acromion and the olecranon processes (previously marked for the mid-arm circumference measurement) will be used for the measurement. Grasp the skin fold between the index finger and thumb above this point, taking care to separate the skin fold from the underlying muscle tissue. Calipers will be placed along the vertical fold below the thumb and index finger. Read the measurement to the nearest millimeter, record and repeat the procedure.

Subscapular Skin Fold

The subject will be instructed to lie prone or stand with his/her back facing the practitioner for this measurement. Again, shoulders will be relaxed and arms loosely hanging by the patient's sides. An accurate measurement is dependent on the patient's posture to prevent the scapulae from moving. Palpate and mark the point of measurement directly below the inferior angle of the scapula (the lower most point of the scapula). Grasp the skin fold with the index finger and thumb. Place the calipers below the finger and thumb, at the mark, at a slight diagonal angle along the cleavage of the skin fold. Read the measurement to the nearest millimeter, record and repeat the procedure.

Suprailiac Skin Fold

The patient will be instructed to stand with his/her feet together, weight evenly distributed, arms hanging at the sides. Locate and mark the point of measurement directly above the superior anterior iliac crest of the hip along the midaxillary line. Using the index finger and thumb, grasp a double fold of skin and fat approximately one centimeter from the superior anterior iliac crest (again, approximately 2 cm above the marked point). Place the calipers below the finger and thumb at a slight diagonal (45 degree) angle along the cleavage of the skin fold. Read the measurement to the nearest millimeter, record and repeat the procedure.

11.3 Bioelectrical Impedance Analysis

11.3.1 BIA

Bioelectrical impedance analysis will be measured with a four terminal portable impedance analyzer. Measurements will be made while the child is in the supine position. Current-injector electrodes will be placed just below the phalangeal-metacarpal joint in the middle of the dorsal side of the right hand and below the metatarsal arch on the superior side of the right foot. Detector electrodes will be placed on the posterior side of the right wrist, midline to the pisiform bone of the medial (fifth phalangeal) side with the wrist semiflexed.

11.3.2 Proper Care of Your BIA Instrument

Instrument Do's and Don'ts

Never eat or drink near the instrument: Beverages spilled on the instrument will permanently damage the sensitive electronic components of the instrument.

Never yank on the subject cables: The subject cables should be treated with care. When removing them, pull on the lead clips. Remove the subject cables by first unplugging the subject cables from the subject connector and then lifting them out of the subject connector. Clean them occasionally with rubbing alcohol.

Take care of the software CD: Your Cyprus manual came with a plastic CD holder. When CD is not in use, the CD should remain in the holder to avoid damage to the disk.

Replacing the BIA-QUANTUM Batteries

When the Quantum battery is weak, decimal points will be displayed on the impedance meter (e.g.: .5.0.0.). When they are displayed, the results will not be accurate! Prior to using the Quantum, replace the battery by following these steps:

1. Turn the BIA-QUANTUM off
2. Remove the battery compartment cover (located on the back of the unit) with a small screwdriver
3. Replace the battery with fresh 9V battery
4. Replace the cover
5. Test the analyzer with the supplied 500 ohm resistor

Charging Your BIA-101A BIA-101S Instrument

Your BIA-101A or BIA-101S instrument contains an internal battery and charging instrument that allows it to be used continuously for up to three hours without an external power supply. The length of use depends on the amount of charge in the battery initially. Charging for 8-12 hours with the instrument off will ensure that the batteries contain the maximum amount of charge.

Even if the batteries are very low (battery indicator in red), the impedance meter can still run off the wall outlet, but it will not be charging while the power is on.

NOTE: Even though the battery indicator arrow may not indicate that the batteries are extremely low, they may still not be fully charged. Charged batteries are essential for correct operation of the instrument. RJL Systems recommends charging the instrument for 8 to 12 hours (overnight) before a full day of use.

Follow these steps in charging your BIA-101A BIA-101S Instrument: Make sure the power switch is off.

1. Plug the female end of the power cord into the connector labeled “AC INPUT” located on the back of the unit.
2. Plug the male end of the power cord into a 110 VAC wall outlet. (The charger is on as soon as the power cord is connected.)
3. Charge the instrument for 8 to 12 hours in order to guarantee a full charge.

11.3.3 Storing Your Instrument

Because of its sensitive components, the BIA Instrument requires some care even when you are not using it.

When storing the instrument for a day or two:

Turn the power switch off.

Disconnect the subject cables from the unit.

When storing the unit for more than a few days:

Turn the power switch off

Disconnect the subject cables from the unit.

Charge the instrument for 8 to 12 hours.

Store the instrument in a cool, dry place.

11.3.4 Shipping and Transporting Your Instrument

Follow these rules whenever shipping or transporting your instrument:

Place the instrument in its original packing material, if possible. The instrument is fragile and should not be exposed to unnecessary shock.

Make sure the power switch is off

Protect the instrument from extreme heat and cold. The instrument may not function properly if exposed to inhospitable temperatures.

If the instrument needs to be returned to RJL Systems, ALWAYS include the subject cables so that the entire instrument can be checked.

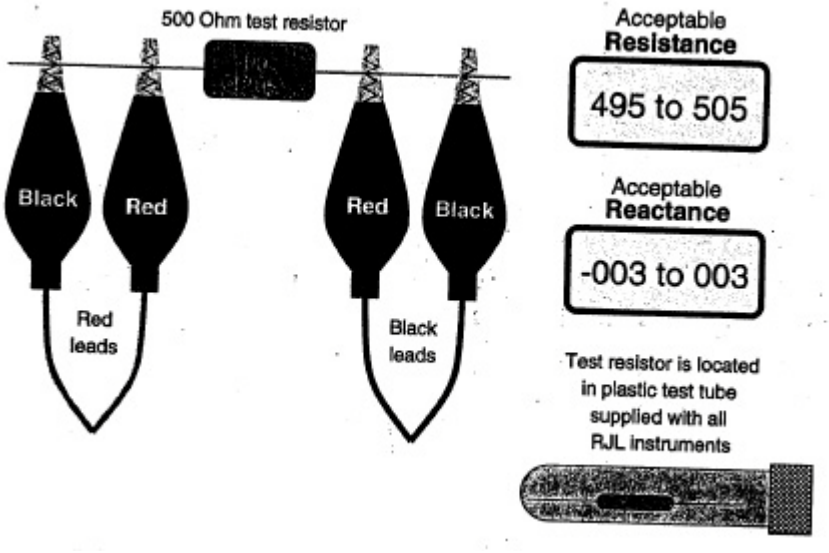
Do not return the instrument to RJL Systems without first calling. The majority of problems can be solved over the phone. If the instrument needs to be returned, you will be issued a Return Merchandise Authorization (RMA) number to be included on the returned package. Any unit returned without a RMA number will not be serviced.

11.3.5 Testing Your BIA Instrument

Your BIA instrument should be tested periodically to verify that the impedance measurements are as accurate as possible.

The 500 ohm resistor supplied with your BIA instrument is used to verify the integrity of your instrument. The resistor is shipped in a plastic test tube and looks like a piece of wire with a small brown cylinder on the middle of it.

Connecting the leads and clips to the test resistors



Testing Your BIA-101A BIA-101S BIA-QUANTUM QUANTUM-II QUANTUM-X

The following steps will test the impedance circuitry, the subject cables, the subject cable connector and the instruments batteries. Follow these steps to test your BIA instrument:

First make sure that your instrument is fully charged. It is very important that your instrument is fully charged before continuing.

BIA-Quantum user: make sure your instrument has a fresh 9 volt battery meter will be displayed. If this is the case, replace the battery with a fresh 9V alkaline battery by opening the cover on the bottom of the instrument with a small screw driver.

Disconnect the charging cord from the wall outlet. Set the resistance/reactance switch to resistance.

Attach the 500 ohm resistor (located in the test tube) to the subject cables. Note that the two red clips should be adjacent to the plastic middle of the resistor and

that the clips of the red cable should be on one side, the black on the other (see diagram above).

Turn the power switch on, and note the resistance value displayed

If all the previous steps were performed with good results, your BIA instrument has checked out OK. If you experience unusual results while a subject is being tested, review the sections Subject Interfacing and Electrode Placement. If the results are still correct, call RJL Systems service department. When you call, please have the results of the above tests available for reference.

Testing Your Spectrum II System

The following steps will test the impedance circuitry, the subject cables, the subject cable connector and the system's batteries. Follow these steps to test your BIA system:

First make sure that your system is fully charge, it is very important that your system is fully charged before continuing.

Disconnect the charging cord from the wall outlet.

Boot the computer and run the Fluid & Nutrition Status program.

From the main menu press A or select Analyzer Test. The RJL Systems BIA Analyzer test form will be displayed.

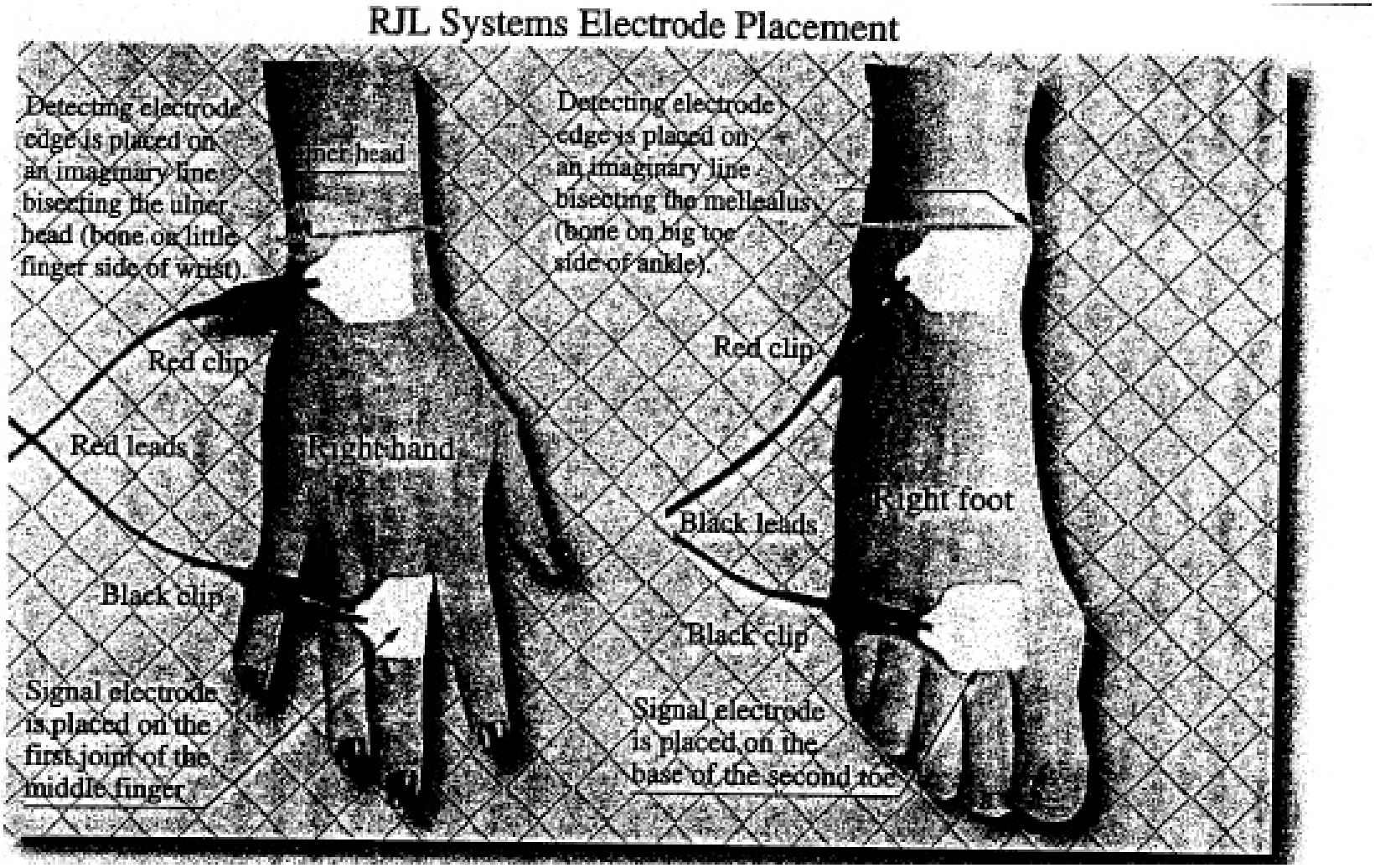
Attach the 500 ohm resistor (located in the test tube) to the subject cables. Note that the two red clips should be adjacent to the plastic middle of the resistor and that the clips of the red cable should be on one side, the black on the other (see diagram above).

Press F7. The resistance and reactance values should be displayed. The resistance displayed should be between 495 and 505 ohms. If the resistance is inside of this range, then the impedance circuitry and batteries are in good working order. If the resistance is outside of this range, record the resistance value and continue with the next steps.

To check the subject cable connector, press lightly on the base of the cables where they attach to the BIA system (labeled SUBJECT). If the resistance fluctuates more than 10 or 15 ohms, the connector may be damaged. Record the amount of fluctuation, and continue with the next step.

To check the subject cables, move the cables to difference positions and note the resistance displayed on the screen. Should the resistance fluctuate more than 5 ohms, there is probably a break in the cables, and you should call RJL Systems to order a replacement pair of subject cables.
Press ESC to end the machine test and return to the main menu.

If all the previous steps were performed with good results, your BIA system has checked out OK. If you experience unusual results while a subject is being tested, review the sections Subject Interfacing and Electrode Placement. If the results are still correct, call RJL Systems service department. When you call, please have the results of the above tests nearby reference.


RJL Systems Electrode Placement
Detecting electrode edge is placed on an imaginary line bisecting the ulner head (bone on little finger side of wrist).
ner head
Red clip
Red leads
Right hand
Black clip
Signal electrode is placed on the first joint of the middle finger
Detecting electrode edge is placed on an imaginary line bisecting the mellealus (bone on big toe side of ankle).
Red clip
Right foot
Black leads
Black clip
Signal electrode is placed on the base of the second toe

11.3.6 Patient Testing Procedures

BIA TESTING PROCEDURE

The exam area should be comfortable and free of drafts and electrical source heaters.

The exam table surface must be non-conductive and large enough for the subject to lie supine with their arms 30 degrees from their body and legs not in contact with each other.

The analyzer and patient cable clips should be cleaned with an alcohol dampened cloth as needed.

The analyzer battery should be a new 9 volt battery.

The analyzer calibration and patient cables should be checked regularly (see manual).

SUBJECT PREPARATION

The subject should not have exercised or taken a sauna within 8 hours of the study.

The subject should not have exercised or taken a sauna within 8 hours of the study.

The subject's height and weight should be accurately measured and recorded

The subject should lie quietly and without motion during the entire test

The subject should not have a temperature or be in shock

The study and testing procedure should be explained to the subject

TESTING PROCEDURE

The subject should remove their right shoe and sock (generally the study is completed on the right side of the body), whichever side is used should always be used subsequently.

The subject should lie supine with their arms 30 degrees from their body and legs not touching and remove jewelry on the electrode side.

The electrode sites may be cleansed with alcohol, particularly if the skin is dry or covered with lotion.

Attach the electrodes and patient cables as shown in the illustration

Turn the analyzer on and make sure the subject refrains from moving when the measurements have stabilized, read the displayed Resistance (R) and Reactance (Xc) and record with the name, age, gender, height, weight, ID number.

Remove and dispose of the electrodes so as to not injure the subject's skin or contaminate the operator.

The entire testing time is less than 5 minutes, the BIA analyzer is on for less than one minute.

The results are available immediately from the software program.

The study may be repeated as often as necessary.

Operator/examiners must demonstrate the following level of proficiency:

Two consecutive measurements made on a single, stable subject must result in values within one percent.

11.4 DXA Scan

OPERATORS' MANUAL FOR PEDS-C Study

SCANNING PROCEDURES FOR HOLOGIC SYSTEMS

PEDS-C INTERFERON ALFA-2A

Hologic, Inc.

35 Crosby Drive
Bedford, MA

MQIR
University Of California, San Francisco
Dept. Of Radiology Box 0946
San Francisco, Ca 94143-0946

Draft 5
NOVEMBER 2004

Table of Contents

Introduction to Quality Assurance

This manual serves as the official Hologic DXA Operator's Guide for the PEDS-C study. The purpose of this manual is to standardize the DXA scanning acquisition procedures between the clinical centers participating in the PEDS-C study. The success of the DXA study will depend on several factors, including the qualifications and dedication of the scanner operators, clear specification and understanding of the study requirements as set forth in this manual, and good lines of communication between the sites participating in the study, the UCSF Quality Assurance Center (MQIR- Muscoluskeletal and Quantitative Imaging Research), NIDDK, and the members of the PEDS-C Study.

This manual is intended to serve as the DXA operator's guide for the PEDS-C study and builds upon (rather than replaces) the operator training and documentation provided by the Hologic Corporation. It is expected that each person performing scan acquisition for the PEDS-C is familiar and competent with the scanning system employed at their study site. In addition, the material in this manual should be read and understood before beginning to scan subjects for this study. The MQIR will certify that each DXA technologist is qualified by performing Expert Review of 5 DXA whole body scans acquired and analyzed prior to the study by each technologist. These scans can be from volunteers or from recent patients with patient identifiers removed.

Other requirements for DXA in this study are as follows:

No scanner hardware changes - without prior notification of MQIR
No scanner software upgrades - without prior notification of MQIR
No scanner relocation – without prior notification of MQIR

Notification of the above can be made by e-mail to MQIR. Procedures, if required before changes, will be described using MQIR specific forms.

Any questions or comments concerning the DXA procedures of this study should be directed to the UCSF, Musculoskeletal and Quantitative Imaging Research Ctr. (MQIR):

Chyi Huang
UCSF / MQIR
Attn: PEDS-C
185 Berry Street, Suite 350, Box 0946
San Francisco, CA 94107

Tel: (415) 353-4938
Fax: (415) 353-9425

e-mail: chyi.huang@radiology.ucsf.edu

Other questions regarding the study protocol should be directed to the site Study Coordinator.

HOLOGIC DXA OPERATOR'S LOG

Dear DXA Technologist and Study Coordinator,

UCSF/MQIR and PEDS-C require that all DXA technologists using the Hologic densitometer read and fully understand the Hologic DXA Operator's Guide for PEDS-C.

Please print your name, sign and date this form to confirm completion of this requirement. For MQIR's documentation, please send a copy of this information including the 5 DXA certification scans as described in section D4, to Chyi Huang at MQIR. Please keep the original at your site to document any future changes in personnel.

Lead Site Investigator: _____
Study Coordinator: _____
Site: _____

DXA Technologists:

Printed Name	Signature	DD/MMM/YY	Initials

Introduction to the PEDS-C Protocol

DXA Procedures Introduction:

The primary objective of the PEDS-C trial is to assess the safety and efficacy of PEDS-Cinterferon alfa-2a (PEDS-C) for treatment of chronic hepatitis C virus (CHC) infection in 112 children, ages 5 to 18 years of age, at 11 Clinical Centers. Recruitment is for 1 year with continued follow-up for 5 years. The subjects' body composition will be tracked with the use of Dual X-Ray Absorptiometry (DXA) Whole Body scans at baseline, 24 weeks, 48 weeks, and 72, 76 or 100 weeks or at discontinuation. There will also be a one year and two year follow up scan. This section describes the DXA procedures to be followed for the duration of the study.

Please read this manual carefully before scanning subjects. These instructions assume you are familiar with correct scanning procedures.

Schedule of DXA Scans - Please be sure to enter the codes exactly as presented in the table.

Exams	Baseline Visit Code	24 week Visit Code	48 week Visit Code	72/76/100 week visit or Discontinuation	1 Year follow up	2 year follow up
DXA Whole Body	**000**	**024**	**048**	**072/76/100 or correlating #of weeks**	**1 year**	**2 year**

Figure 1. Schedule of DXA scans and visit codes

A. Subject Registration

Enter the subject's **"letter code"** into the *last name field*. The subject's 6 digit ID number is entered into the ID field exactly as it is entered on the Case Report Form. For this

reason, you should always get the subject's "letter code" and ID number from the Study Coordinator to ensure accuracy.

DOB and Sex should be entered in the appropriate fields. Ethnicity should be entered for all subjects as white. Enter appropriate height and weight. PEDS-C followed by the site's 3 letter code (section F) should be entered into the Ref MD field. All leading zeroes must be included. Be sure to use zeroes (Ø) and not the letter "O" when entering the Subject ID into the Pat ID field. (Figure 1a)

The visit code appropriate to the visit is entered in the **Scan Comment** field on the Scan Property page (following the fields for Operator's Initials and subject's height and weight). The Visit Code is a 3-digit code: **000 for the Baseline visit, 024 for 24 weeks, 048 for 48 weeks, and 072 for 72 weeks, (or the number of weeks that correlate with the number of weeks at discontinuation) and 1 year and 2 year,** as shown in Figure 1b. Be sure to use zeroes and not the letter "O" when entering the visit code in the Scan Comment field. The Scan Comment field must be updated at each visit. (Figure 1b)

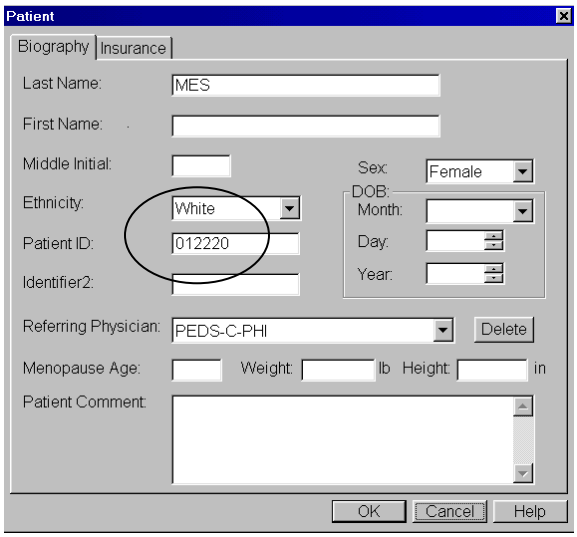


Figure 1a Biography

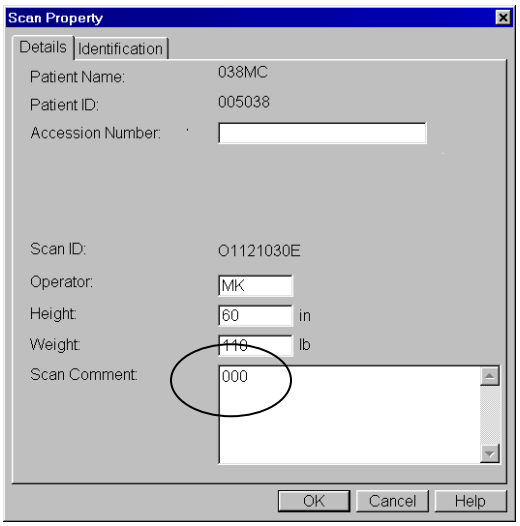


Figure 1b 2nd page, visit code

B. DXA Scan Acquisition

The following sections describe in detail the MQIR's requirements for acquiring subject scans for the PEDS-C study, above and beyond those mentioned in the Hologic operator's manual. In order to get the most consistent subject results it is important to follow consistent procedures in acquiring all scans. These include the following:

Use the same scan mode throughout the study.

Remove all radio-opaque objects from the scan areas.(underwire bras, jewelry, belts, etc.)

Ensure correct positioning of the subject on the baseline exam.

Ensure that no movement occurs during scanning.

Keep a printout of the baseline scan to use as a reference for follow up scans.

Monitor the scan during acquisition. If positioning is not correct, or the subject moves, etc., abort the scan, reposition the subject if necessary and restart the scan.

The subject should be dressed in a hospital gown or scrubs wearing only underpants and, if necessary, thin socks. A thin sheet may be placed over the subject for warmth.

NOTE: when scanning subjects it is important to keep in mind that it is much less time consuming to rescan the subject immediately if a problem is detected, rather than having to recall

the subject for a repeat of the scan on another day. Please note any problems with scan acquisition in the comment field of the DXA log sheet.

When performing follow-up scans refer to a printout of the baseline scan to assure duplicate positioning and scan parameters.

B.1 Whole Body Scans

Details specific to the PEDS-C Study are noted below.

Keep the scan width and length set to the default settings – scan the entire table.

Position the subject in the center of the table aligned with the long axis of the scanner, head near the head end of table. The subject's head should face straight up, not turned to the left or right. If required for subject comfort, use only radiolucent pillows. If pillows are used however, make a note to use the same pillow again during follow-up measurements.

The legs and feet **must** be positioned together with a Velcro strap around the ankles to help avoid movement. **Please keep the feet relaxed with the toes pointed upwards.** (Figure 3)

Position hands with palms flat against the scan table. **Please maintain space between the arms and the torso when possible**. If necessary, with larger or heavier subjects, the hands may be placed in a lateral position next to the hips. **Do not** tuck the hands under the hips to keep them in the scan field. If necessary, tape the subject's hands to the scan table. For patients who are too tall to fit within the scanning limits, it is acceptable for the feet to extend beyond the lower scan limit line. Do not bend the knees to keep the feet within the scan field.

Monitor the scan during acquisition for patient movement so the scan may be stopped and restarted. Do not engage the patient in conversation because it may cause motion, but give them encouragement and updates on the scan's progress.

No analysis.

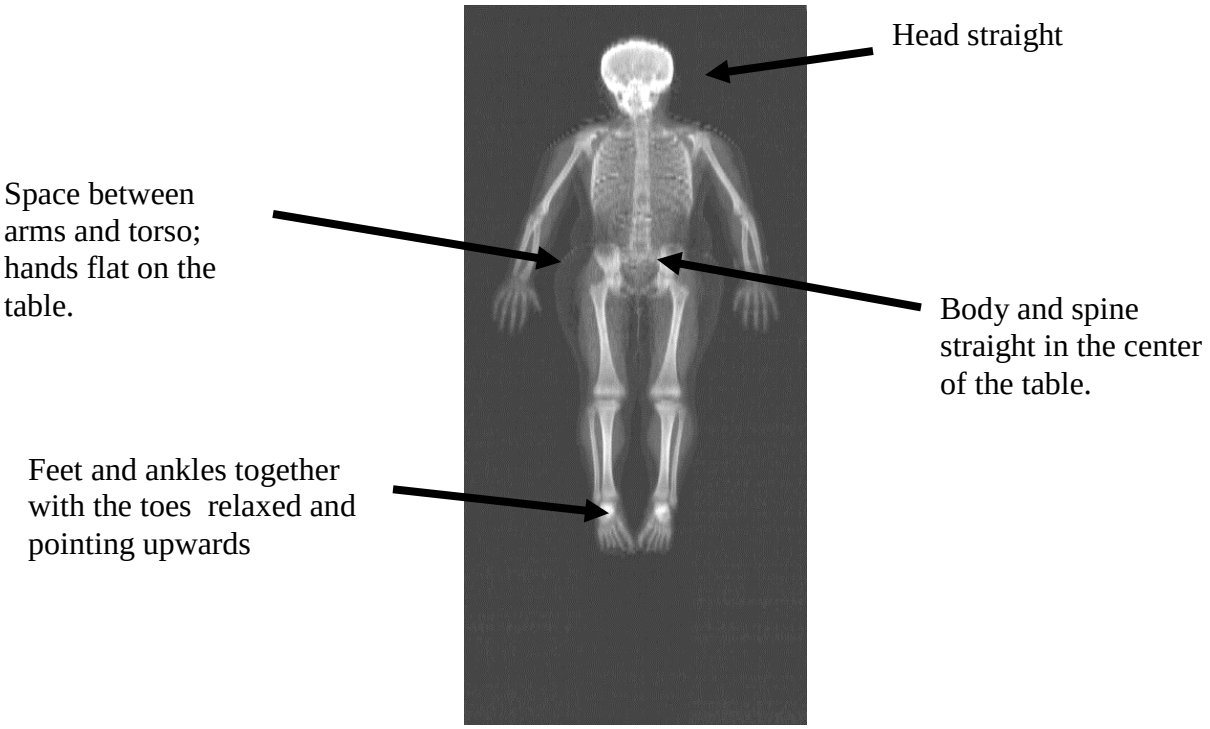


Figure 3: Correctly Positioned Pediatric Whole Body Scan

C. Data Security

When preparing to send patient scan files to UCSF, use the **Copy** command to transfer subject scan files to transfer modality. Do **not** use the Archive command to make a copy to send to UCSF.

For data security, archive your scan files on a regular basis.

The System Backup function is used to back up your Hologic database. The Hologic database contains all biography, report summaries and, location information for all patients scanned on your system. Your site should perform a System Backup on a weekly basis.

D. Quality Control Data (Longitudinal and Cross-Calibration)

Scanner Quality Control (QC) procedures are used to monitor scanner performance throughout the course of the study. Longitudinal QC procedures consist of daily procedures used to monitor

the performance of a single scanner over time. Cross–calibration procedures are used to monitor scanner variation from machine to machine. An additional QC measure is the use of the "DXA Bone Densitometer Report" (see E.3 and appendix). The investigator site completes and sends this report monthly to UCSF in addition to a copy of the QC scans including the air scans on site-specific transfer modality. Both longitudinal Quality Control and cross–calibration will be discussed in this section.

D.1 Normal Longitudinal QC Procedures

This study will make use of data obtained by your standard daily QC procedures using the Hologic Spine Phantom and an Air Scan procedure.

Typical Schedule for Phantom Scanning – Longitudinal QC

	Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Tissue Bar		X					
Hologic Spine Phantom		X	X	X	X	X	
Air Scan		X					

D1.1. Hologic Spine Phantom

(The assumption is made that a biography already exists.)

Make sure that the phantom serial number is entered in the Pat ID field. The phantom number may be read from the label on the side of the phantom.

Scan the Hologic Spine phantom at least every day that a study subject is scanned, but at a minimum of three days per week for the duration of the study.

These scans are analyzed automatically and added to the QC database.

Review the QC plot for BMD. If the BMD for L1-L4 falls outside acceptable limits, rescan the phantom. If the BMD from the second scan also falls outside the limits, call for service at Hologic. If the BMD from the second scan falls within the limits, continue with normal scanning for the day.

D1.2 Air Scan Procedure (Table Top Radiographic Uniformity)

Perform a scan of the table once per week, the same day that the tissue bar is scanned. For users with software version 12.1 or higher, this is an automatic procedure called “Table Top Radiographic Uniformity”. No biography needs to be created. Users with a software version less than 12.1 need to create a Patient Biography in the following manner:

Please use zeros in the biography, not the letter "O.”

Name : Air Scan

Patient ID :

Sex: F

Referring Physician: 3 Letter Site Code

Patient Comment: AIR SCAN

Remove everything from the table and perform a scan of the entire table using the whole body scan mode.

Analysis: (automatic with versions 12.1 and higher)

Windows/Delphi

Using Windows Explorer, go to the **C:\QDR\Utilities** directory

Copy the Service icon onto your desktop as a shortcut (This should remain on the desktop.)

Enter the Delphi Software in the usual manner.

Acquire an Air Scan

Exit from the Delphi software without shutting down.

Double click on the SERVICE Icon Shortcut. This puts you back into the Delphi software in service mode.

From the Menu on top of the screen, select Utilities->Service Utilities->Table Top Radiographic Uniformity

Select the most recent air scan and press ok.

You will be presented with an image of the air scan and a scan printout similar to the output below. The image will typically not look very pretty. It should ideally look like random white noise (i.e. static on a TV set). You may see streaks.

Report Date: 8/8/02
Selected scan = P:\DXA_DATA\CTASC\[PA02626A.R0P
Total points per phase in row: 109
Total lines in column: 150

Lines with a standard deviation greater than 2.0
Phase Line mean stdev min max
Global Stats:
1 586.92 1.03 582 590

Note: If the global standard deviation is less than 2.0, the scanner is functioning properly. If the results are above 2.0, please repeat the air scan and review results. If the SD remains over 2.0, please email to Mary Sherman for immediate review. The number to look at is shown above in bold. (1.03 in this example.)

No further analysis should be performed on these scans.

D1.3 Copying And Archiving:

Use ***Copy*** for copying scans to diskette, CD or superdisc. Archive to your site's regular archive modality.

D.2 Scanner Cross-Calibration Plan

In order to accurately assess differences in scanner performance among investigator sites, cross-calibration phantoms will be sent to each site at least once during the course of the study. Coordination will be made in advance between the QA Center and each site for delivery of the cross-calibration phantoms. The Hologic Block Phantom, European Spine Phantom, and Hologic Whole Body Phantom will be used for cross-calibration. Detailed scanning and analysis procedures will accompany the phantoms.

D.3 DXA Bone Densitometer Report (BDR)

The BDR is completed at the end of each month by the site technologist and submitted to the Study Coordinator. It provides a record of additional information about each study scanner. The BDR tracks scanner maintenance and repairs as well as technologist changes, which are then reviewed by the MQIR. The scanner serial number and the Hologic spine phantom serial number are critical identification numbers.

For reference purposes, an original blank BDR form is supplied with this DXA Operator's Guide. Copies of the form are included in your supply packet.

IMPORTANT:

Changes in scanners, software, or location of scanners can have a large impact on the integrity of study data. For this reason, such changes are NOT ALLOWED for the duration of this study without prior notification of the MQIR and NIDDKD.

Requests for changes may be made by telephone or e-mail to MQIR (Chyi Huang at 415-353-4938, chyi.huang@radiology.ucsf.edu).

D.4. Operator Qualification

All technologists must be qualified by the QA Center prior to scanning any study subjects. Qualification consists of on-site training by a QA Center staff person and the QA Center's evaluation of printouts of 5 total body scans acquired before the study and analyzed by the

technologist. Each study technologist should provide a copy, if available, of their manufacturer's training certificate and license to the QA Center. Please forward with a copy of the Hologic Operator's Form found at the beginning of this manual as soon as possible after receiving and reviewing this Procedures Manual. When a new technologist is employed, please follow the above instructions.

E. Data Export Procedures / Timelines

This section details the data export items and delivery schedules

E.1. Subject Data

All subject scans for all visits are to be sent on labeled diskettes, CDs, or superdiscs with a copy of DXA Examination Form to UCSF for analysis by the MQIR on a monthly basis.

E.2. Instrument Quality Control Data

Instrument Quality Control data should be sent to UCSF once monthly. QC data transfers should consist of the following:

Completed DXA Bone Densitometer Report (BDR) .

Labeled diskettes, CD, or superdisc containing a copy of the QC scans of the Hologic Spine and air scans for the past month.

Please Note:

You may copy both subject and QC scans to the same modality. Please check the appropriate data types, even if the modality contains both sets of data. (Figure 6)

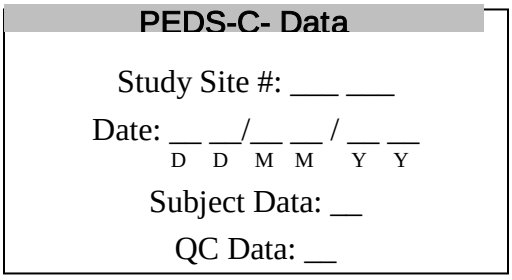


Figure 6 – Modality Label

Data to be submitted on a monthly basis to:

Address:

Chyi Huang
MQIR, University of California, San Francisco
Attn: PEDS-C
185 Berry Street, Suite 350, Box 0946
San Francisco, CA 94107
Fed Ex zipcode : 94107

Telephone: (415) 353-4938
FAX: (415) 353-9425
E-Mail: chyi.huang@radiology.ucsf.edu

F. Site Codes and Numbers

SITE CODE	SITE NUMBER	SITE
CIN	01	University of Cincinnati
FLO	02	University of Florida
PHI	03	Children's Hospital of Philadelphia
HAR	04	Children's Hospital, Boston
GWU	05	George Washington University
IND	06	Indiana University
UOW	07	University of Washington
DEN	08	University of Colorado
SFO	09	University of San Francisco
JHU	10	John Hopkins University
COL	11	Columbia University

G. Bone Densitometer Report

USE ONE FORM FOR EACH SCANNER IN THIS STUDY

THIS FORM ONLY PERTAINS TO STUDIES IN WHICH DXA DATA ARE SENT TO UCSF. DXA SCANNER OPERATORS SHOULD SEND THIS FORM ALONG WITH A COPY OF THE QC SCANS FOR THE MOST RECENT MONTH.

DXA Bone Densitometer Report • PEDS-C

Site number _____

Scanner Serial Number _____ Spine Phantom Number _____

1) Has a new / different scanner been used for any study patients? ☐☐ Yes ☐No

If yes, explain:_____

Was scanner change approved in advance by UCSF? ☐☐ Yes ☐No By Whom? _____

2) Have there been any software changes ? ☐☐ Yes ☐No If yes, indicate:

Old software version: _____ New software version: _____ Date installed: _____

Was software change approved in advance by UCSF? ☐☐ Yes ☐No By Whom? _____

3) Were there any technologist changes? ☐☐ Yes ☐No If yes, indicate:

Technologist	Add/Departed	Date of Change	Date of Manufacturer's Training

4) Were there any maintenance/recalibration/repair problems? ☐☐ Yes ☐No If yes, indicate:

Service performed	**Date of Service**

5) Additional comments (Use reverse side if necessary) :

Main Technologist: _____ Date: _____ Telephone:_____

Please make copies of this blank form. Complete this form each reporting period and send the original to the MQIR and keep a copy for your records.

H. FED EX Transfer Log

FEDEX TRANSFER LOG

Complete this form and place it on top of the contents in the FedEx package. Send to an email to:

chyi.huang@radiology.ucsf.edu ***with the expected delivery date and tracking # for the package.***

FedEx to: Chyi Huang

UCSF/Musculoskeletal and Quantitative Research Imaging

185 Berry Street, Ste.350

San Francisco, CA 94107

Tel: 415-353-4938

Subject Data Enclosed in this FedEx:

PATIENT ID #	**PATIENT CODE**	**DXA FORM**

Note: For each patient ID listed above, a subject intake sheet must be included in FedEx; All CD's, diskettes, superdiscs, etc. must be labeled!

___ Tot. # transfer media (CD's, diskettes, etc.)

Quality Control Data Enclosed in this FedEx:

DXA: **(all of the following should be included):**

☐ QC Archive data diskette/superdisc with label

☐ Bone Densitometer Report

Study Coordinator Signature: _____ Site# _____

DATE: / /

OPERATORS' MANUAL FOR PEDS-C Study

SCANNING PROCEDURES FOR GE LUNAR PRODIGY SYSTEMS

PEDS-C

INTERFERON ALFA-2A

GE Lunar Corp.
313 West Beltline Hwy.
Madison, WI 53713

MQIR
University Of California, San Francisco
Dept. Of Radiology Box 0946
San Francisco, Ca 94143-0946

Draft 4
OCTOBER 2004

TABLE OF CONTENTS

INTRODUCTION TO QUALITY ASSURANCE

This manual serves as the official GE Lunar Prodigy DXA Operator's Guide for the PEDS-C study. The purpose of this manual is to standardize the DXA scanning acquisition procedures between the clinical centers participating in the PEDS-C study. The success of the DXA study will depend on several factors, including the qualifications and dedication of the scanner operators, clear specification and understanding of the study requirements as set forth in this manual, and good lines of communication between the sites participating in the study, the UCSF Quality Assurance Center (MQIR- Muscoluskeletal and Quantitative Imaging Research), NIDDK, and the members of the PEDS-C Study.

This manual is intended to serve as the DXA operator's guide for the PEDS-C study and builds upon (rather than replaces) the operator training and documentation provided by the GE Lunar Prodigy Corporation. It is expected that each person performing scan acquisition for the PEDS-C is familiar and competent with the scanning system employed at their study site. In addition, the material in this manual will be read and understood before beginning to scan subjects for this study. The MQIR will certify that each DXA technologist is qualified by performing Expert Review of 5 DXA whole body scans acquired and analyzed prior to the study by each technologist. These scans can be from volunteers or from recent patients with patient identifiers removed.

Other requirements for DXA in this study are as follows:

1) No scanner hardware changes - without prior notification of MQIR
2) No scanner software upgrades - without prior notification of MQIR
3) No scanner relocation – without prior notification of MQIR

Notification of the above can be made by e-mail to MQIR. Procedures, if required before changes, will be described using MQIR specific forms.

Any questions or comments concerning the DXA procedures of this study will be directed to the UCSF, Musculoskeletal and Quantitative Imaging Research Ctr. (MQIR):

Mary Sherman, RT
UCSF / MQIR
Attn: PEDS-C
185 Berry Street, Suite 350, Box 0946
San Francisco, CA 94143-0946

Fed Ex 94107

Tel: (415) 353-9457
Fax: (415) 353-9425

e-mail: msherman@radiology.ucsf.edu

Other questions regarding the study protocol will be directed to the site Study Coordinator.

Lunar Prodigy DXA Operator's Log

Dear DXA Technologist and Study Coordinator,

UCSF/MQIR and PEDS-C require that all DXA technologists using the GE Lunar Prodigy densitometer read and fully understand the GE Lunar Prodigy DXA Operator's Guide for PEDS-C.

Please print your name, sign and date this form to confirm completion of this requirement. For MQIR's documentation, please send a copy of this information including the 5 DXA certification scans as described in section E, to Mary Sherman at MQIR. Please keep the original at your site to document any future changes in personnel.

Lead Site Investigator: _____

Study Coordinator: _____

Site: _____

DXA Technologists:

Printed Name	Signature	DD/MMM/YY	Initials

INTRODUCTION TO THE PEDS-C PROTOCOL

DXA Procedures Introduction:

The primary objective of the PEDS-C trial is to assess the safety and efficacy of PEDS-Cinterferon alfa-2a (PEDS-C) for treatment of chronic hepatitis C virus (CHC) infection in 112 children, ages 5 to 18 years of age, at 11 Clinical Centers. Recruitment is for 1 year with continued follow-up for 5 years. The subjects' body composition will be tracked with the use of Dual X-Ray Absorptiometry (DXA) Whole Body scans at baseline, 24 weeks, 48 weeks, and 72 or 100 weeks or at discontinuation. There will also be a one year and two year follow up scan. This section describes the DXA procedures to be followed for the duration of the study.

Please read this manual carefully before scanning subjects. These instructions assume you are familiar with correct scanning procedures.

Schedule of DXA Scans - Please be sure to enter the codes exactly as presented in the table.

Exams	**Baseline Visit Code**	**24 week Visit Code**	**48 week Visit Code**	**72/100 week visit or Discontinuation**	**1 Year follow up**	**2 year follow up**
DXA Whole Body	**000**	**024**	**048**	**072/100 or correlating #of weeks**	**1 year**	**2 year**

Figure 1. Schedule of DXA scans and visit codes

Creation of New Database

Create a PEDS-C database, which will allow you to easily locate and compare all future, scans of the same subject to their original scans. Please note the name of the Working Directory for future reference. This will be different for each site.

Subject Registration

Select the PEDS-C Database and New (patient). The Mandatory Information screen appears. Enter the following data in the information fields. At the end of each field press Tab to move the cursor to the next field.

Enter **the Subject's 3 letter code** in the *First Name* field. Enter the subject's 6 digit **ID number** in the *Last Name* field **exactly** as it is entered on the PEDS-C DXA Form. For this reason, you will always obtain the subject's number from the Program Coordinator to ensure accuracy. In the *Patient ID* field, also enter the subject's 6 digit ID number. In the Physician field, enter PEDS-C followed by the 3-letter reference for your site.

Enter the DOB, sex, ethnicity, weight and height in the appropriate fields. The visit code entered into the Exam ID field, on the secondary page, and updated on the follow-up visits.

First Name:	MES
Middle Initial:	None
Last Name:	Subject's ID Number (123450 example)
Patient ID:	Subject's ID number (123450 example)
Physician:	PEDS-C-UOW
Birth Date:	Subject's BD
Height:	Subject's height
Weight:	Subject's weight
Sex:	Male/Female
Ethnic Group:	Asian
Exam ID:	Enter appropriate visit number (000, 048, etc)
Comments:	Operator's Initials

Note from this example that all leading zeroes must be included. Be sure to use zeroes and not the letter "O" when entering the Subject information into any of the fields.

B. DXA SCAN ACQUISITION

The following sections describe in detail the MQIR's requirements for acquiring subject scans for the PEDS-C study, above and beyond those mentioned in the GE Lunar Prodigy operator's manual.

In order to get the most consistent subject results it is important to follow consistent procedures in acquiring all scans. These include the following:

Use the "Standard" scan mode throughout the study. If the scanner recommends the "Thick" mode, that may be used. However, all follow-up scans on those subjects must be acquired using the "Thick" scan mode. Never use the "Thin" scan mode.

Remove all radio-opaque objects from the scan areas.(underwire bras, jewelry, belts, etc.)

Ensure correct positioning of the subject on the baseline exam.

Ensure that no movement occurs during scanning.

Keep a printout of the baseline scan to use as a reference for follow up scans.

Monitor the scan during acquisition. If positioning is not correct, or the subject moves, etc., abort the scan, reposition the subject if necessary and restart the scan.

The subject will be dressed in a hospital gown or scrubs wearing only underpants and, if necessary, thin socks. A thin sheet may be placed over the subject for warmth.

NOTE: when scanning subjects it is important to keep in mind that it is much less time consuming to rescan the subject immediately if a problem is detected, rather than having to recall the subject for a repeat of the scan on another day. Please note any problems with scan acquisition in the comment field of the DXA log sheet.

When performing follow-up scans refer to a printout of the baseline scan to assure duplicate positioning and scan parameters.

B.1 WHOLE BODY SCANS

Details specific to the PEDS-C Study are noted below.

Keep the scan width and length set to the default settings –Smart Scan on.

Position the subject in the center of the table aligned with the long axis of the scanner, head near the head end of table. The subject's head will face straight up, not turned to the left or right. If required for subject comfort, use only radiolucent pillows. If pillows are used however, make a note to use the same pillow again during follow-up measurements.

The legs and feet **must** be positioned together with a Velcro strap around the ankles to help avoid movement. **Please keep the feet relaxed with the toes pointed upwards.** (Figure 2)

Position hands with palms flat against the scan table. **Please maintain space between the arms and the torso when possible**. If necessary, with larger or heavier subjects, the hands may be placed in a lateral position next to the hips. **Do not** tuck the hands under the hips to keep them in the scan field. If necessary, tape the subject's hands to the scan table. For patients who are too tall to fit within the scanning limits, it is acceptable for the feet to extend beyond the lower scan limit line. Do not bend the knees to keep the feet within the scan field.

Monitor the scan during acquisition for patient movement so the scan may be stopped and restarted. Do not engage the patient in conversation because it may cause motion, but give them encouragement and updates on the scan's progress.

No analysis.

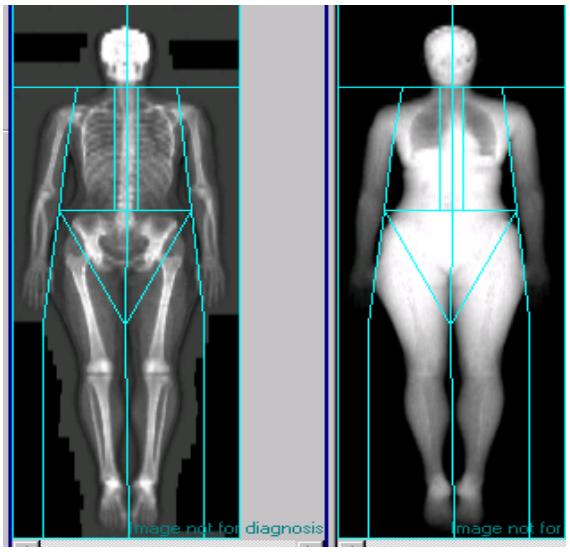


Figure 2: Properly acquired whole body scans.

C. DATA SECURITY

When preparing to send subject scan files to MQIR, use the below procedure to transfer subject scan files to diskette, superdisk, or Zip. Do not use the Archive command. Archive the scans to the system archive disk only after they have been copied to the disks for shipping.

C.1. To Copy Scan Images to the SuperDisk or Zip

Within the PEDS-C Database, choose the subjects you want to copy.

Click on the 1st scan in the series. Hold down the Shift key and click on the last scan.

All scans for a selected subject will then be highlighted. Right click on the shaded area. A small command box will appear.

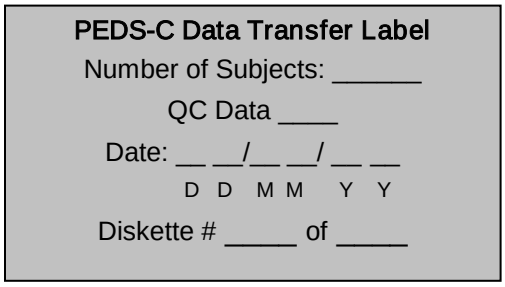
Select “Send Image File To Disk”

At “My Computer,” select A:\ (3 ½ Floppy A): to send scans to the SuperDisk/Zip. Repeat until all scans for all desired subjects have been copied to the SuperDisk/Zip.

Do **not** use the ARCHVE command.

Labeling copy diskettes

Each diskette/superdisk must be labeled using the labels addressed in the following manner: Unfortunately, subject scans and the QC MDB have to copied to separate disks.



Data label

IMPORTANT: ALWAYS USE COPIES OF THE FORMS PROVIDED IN THE APPENDIX FOR ALL DXA DATA TRANSFERS

D. QUALITY CONTROL DATA (LONGITUDINAL AND CROSS-CALIBRATION)

Scanner Quality Control (QC) procedures are used to monitor scanner performance throughout the course of the study. Longitudinal QC procedures consist of daily procedures used to monitor the performance of a single scanner over time. Cross–calibration procedures are used to monitor scanner variation from machine to machine. An additional QC measure is the use of the "DXA Bone Densitometer Report" (see D.3 and appendix). The DXA technologist completes and sends this report monthly to UCSF in addition to a copy of the QC mdb (master database) on site-specific transfer modality. Both longitudinal Quality Control and cross–calibration will be discussed in this section.

D.1. 1. Normal Longitudinal QC Procedures

The Lunar Aluminum Spine Phantom is scanned every day a subject is scanned but at least 3 times per week.

A copy of the Master Database (MDB) is made to diskette and collected from the technologist by the Program Coordinator. This disk is sent to MQIR monthly. Please do not send copies of scans.

The Bone Densitometer Report (BDR) (Sec.D3)(I) is completed at the end of each month by the technologist and submitted to the Study Coordinator. It provides a record of additional information about each study scanner. The BDR tracks scanner maintenance and repairs as well as technologist changes, which are then reviewed by the MQIR. Two critical pieces of identifying information are the scanner serial number and the Lunar Prodigy spine phantom serial number.

D.1.2 To Copy MDB (Master Data Base Files) To Floppy Disk

At the Main Menu, click on the database containing the QA scans. Note in the "Active Database" field, the "Working Path"; ie: C:\data2\ . This will appear as a folder when you open the "C" drive.
Exit from Prodigy to Windows.
Place diskette or superdisk in the "A" drive.(3 ½ diskette is sufficient)
Go to "My Computer" – double click to open.
Select C: Drive – double click to open – several folders will appear.
Highlight the appropriate Data set folder i.e. data2 – double click to open.
The Lunar.mdb document will appear.
Right click on document (do not open document). A menu will appear.
Scroll down to "Send." Choose "3 ½ inch Floppy (A)" – files will be sent to the diskette/superdisk in the "A" drive.
When the send procedure is complete, remove diskette/superdisk from "A" drive.
End procedure by going to "File" menu and selecting "Close."

D.1.3 ARCHIVE

The **Archive** function on Prodigy scanners is used to store scan files on Zip or superdisks or other electronic storage. Archive your scan files on a regular basis. See your Prodigy Operator's

manual for instructions. **Do not** use the archive command to transfer subject scan files to disk**.** If you do, you may not be able to find your scans in the future. The system remembers only the last place the scans were archived to and if that is to our disk, you won't be able to retrieve the scans.

D.2 SCANNER CROSS-CALIBRATION PLAN

In order to accurately assess differences in scanner performance among investigator sites, cross-calibration phantoms will be sent to each site at least once during the course of the study. Coordination will be made in advance between the QA Center and each site for delivery of the cross-calibration phantoms. Phantoms used will be the: Hologic Block Phantom, European Spine Phantom, and Hologic Whole Body Phantom. Detailed scanning and analysis procedures will accompany the phantoms.

D.3 DXA Bone Densitometer Report (BDR)

The BDR is completed at the end of each month by the site technologist and submitted to the Study Coordinator. It provides a record of additional information about each study scanner. The BDR tracks scanner maintenance and repairs as well as technologist changes, which are then reviewed by the MQIR. The scanner serial number and the Lunar spine phantom serial number are critical identification numbers.

For reference purposes, an original blank BDR form (Section I) is supplied with this DXA Operator's Guide. Copies of the form are included in your supply packet.

IMPORTANT: Changes in scanners, software, or location of scanners can have a large impact on the integrity of study data. For this reason, such changes are NOT ALLOWED for the duration of this study without prior notification of MQIR and NIDDK. Requests for changes may be made by telephone or e-mail to MQIR (Mary Sherman at 415-353-9457, msherman@radiology.ucsf.edu).

E. Operator Qualification

All technologists must be qualified by the QA Center prior to scanning any study subjects. Qualification consists of on-site training by a QA Center staff person and the QA Center's evaluation of print-outs of 5 total body scans acquired and analyzed by each technologist. Each study technologist will provide a copy, if available, of their manufacturer's training certificate and license to the QA Center. Please forward with a copy of the GE Lunar Operator's Form (page 3) as soon as possible after receiving and reviewing this Procedures Manual. As technologists are added, please follow the above instructions.

F. Data Export Procedures / Timelines

This section details the data export items and delivery schedules.

F.1 Subject Data

All subject scans for all visits are to be sent on labeled diskettes, CDs, or superdiscs with a copy of DXA Examination Form to UCSF for analysis by the MQIR on a monthly basis.

F.2 Instrument Quality Control Data

Instrument Quality Control data will be sent to UCSF once monthly. QC data transfers will consist of the following:

1) Completed DXA Bone Densitometer Report (BDR) (page 17).

2) Labeled diskette, or superdisc containing a copy of the mdb of the Lunar Al. Spine Phantom for the past month.

Address:

Mary E. Sherman, RT
MQIR, University of California, San Francisco
Attn: PEDS-C
185 Berry Street, Suite 350, Box 0946
San Francisco, CA 94143-0946
(Fed-Ex zip code: 94107)

Telephone: (415) 353-9457
FAX: (415) 353-9425
E-Mail: msherman@radiology.ucsf.edu

G. SITE CODES AND NUMBERS

SITE CODE	**SITE NUMBER**	**SITE**
CIN	01	University of Cincinnati
FLO	02	University of Florida
PHI	03	Children's Hospital of Philadelphia
HAR	04	Children's Hospital, Boston
GWU	05	George Washington University
IND	06	Indiana University
UOW	07	University of Washington
DEN	08	University of Colorado
SFO	09	University of San Francisco
JHU	10	John Hopkins University
COL	11	Columbia University

H. FORMS

Fed Ex Transfer Log

Complete this form and place it on top of the contents in the FedEx package. Send an email to mary.sherman@radiology.ucsf.edu with the expected delivery date and tracking # for the package.

SITE ID__ __ __	**SITE CODE__ __ __**
PATIENT ID	**SUBJECT CODE**
☐☐☐☐☐☐	☐☐☐
☐☐☐☐☐☐	☐☐☐
☐☐☐☐☐☐	☐☐☐
☐☐☐☐☐☐	☐☐☐
☐☐☐☐☐☐	☐☐☐

Note: For each patient ID listed above, an updated, patient-specific, DXA Form must be included in this shipment:

☐ Subject Data
☐ DXA Form
☐ Longitudinal QC Data
☐ DXA Bone Densitometer Report

PC SIGNATURE: _____ *DATE: / /*

(MM/DD/YYYY)

PEDS-C DEXA FORM

Subject ID Code	☐☐☐
Subject ID Number	☐☐☐☐☐☐
Date DEXA performed (mm/dd/yy)	☐☐/☐☐/☐☐
Visit number	☐☐☐
Staff ID (? NEEDED)	☐☐☐

Instructions: Complete this form for every DEXA recorded.

DEXA information	
Was the whole body DEXA scan performed?	Yes ☐ No ☐
Were there any problems associated with obtaining the whole body scan?	Yes ☐ No ☐
If YES, check all that apply	
Child uncooperative	☐
Child had difficulty remaining still	☐
Equipment problem	☐
Problems positioning child	☐
Participant weighs over 300 lbs	☐
Other (Specify, _____)	☐
Date DEXA transmitted (mm/dd/yy)	☐☐/☐☐/☐☐

Bone Densitometer Report

USE ONE FORM FOR EACH SCANNER IN THIS STUDY

THIS FORM ONLY PERTAINS TO STUDIES IN WHICH DXA DATA ARE SENT TO UCSF. OPERATORS WILL SEND THIS FORM ALONG WITH COPIES OF QC DATA ACCORDING TO INSTRUCTIONS FOR EACH MAKE OF SCANNER

DXA Bone Densitometer Report • PEDS-C

Site number and code _____

Scanner Serial Number _____ Lunar Spine Phantom Number _____

1) Has a new / different scanner been used for any study patients? ☐☐ Yes ☐No
If so, what make of scanner was used? _____
Was scanner change approved in advance by UCSF? ☐☐ Yes ☐No By whom?_____

2) Have there been any software changes? ☐☐ Yes ☐No If yes, indicate:
Old software version: _____New software version: _____Date installed: _____
Was software change approved in advance by UCSF? ☐☐ Yes ☐No By Whom? _____

3) Were there any technologist changes? ☐☐ Yes ☐No If yes, indicate:

Technologist	Add/Departed	Date of Change	Date of Manufacturer's Training

4) Were there any maintenance/recalibration/repair problems? ☐☐ Yes ☐No If yes, indicate:

Service performed	**Date of Service**

Please attach a copy of service report if available.

5) Additional comments (Use reverse side if necessary) :

Main Technologist: _____ Date: _____ Telephone:_____

Please make copies of this blank form. Complete this form each reporting period and send the original to the UCSF Quality Assurance Center and keep a copy for your records.

CHAPTER 12

BIOLOGICAL SAMPLE COLLECTION AND HANDLING

All routine biological samples will be analyzed at Covance (see the Covance Lab Manual on the PEDS-C web site secure page for details). Redrawn and rush hematology tests may be analyzed at local laboratories (the investigator's site or a geographically close laboratory). When possible the Covance Laboratory should be used. Anytime a local laboratory is used the Clinical Center Coordinator is responsible for returning the local lab results to the DCC/CRO promptly; obtaining the laboratory's CLIA certificate and the license and CV of the director; putting a copy of these documents in the patient's chart, and faxing a copy to the DCC/CRO.

When collecting samples for PEDS-C all tubes should be filed.

Johns Hopkins School of Medicine
PEG-2a, Pediatric HCV

Stephen Lambert, Project Manager
Baltimore, MD 17-18 June 2004

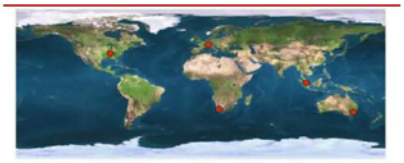
COVANCE

Agenda

- Supplies, Kits and Requisition
- Specimen collection procedures
- Packaging and Shipment
- Laboratory Reporting

COVANCE

COVANCE Central Laboratory Services



COVANCE CLS - Indianapolis (US), Geneva (CH), Singapore (SG)
DSP GLOBAL CLINICAL TRIALS - Cape Town (ZA) / SONIC CLINICAL TRIALS - Sydney (AU)

- Devoted exclusively to clinical trials
- Combinable data

COVANCE

CCLS, Indianapolis, Indiana, USA

COVANCE

Start-up Supplies

- Visit-specific kits

VISIT:	Screen	Baseline	Week 2	Week 4	Week 6	Week 8	Retest
US Sites:	3 kits	3 kits	3 kits	3 kits	3 kits	3 kits	2 kits

COVANCE

Start-up Supplies, will also include

- Shipping material (boxes and pre-printed shipping documents)
- Investigator manual
  - English
- Bulk supplies
  - A standard bag, containing the tubes, vials and items most frequently used in clinical trials
  - Urine pregnancy test kits
  - Training video (upon request)

COVANCE

1

Urine Pregnancy Kits (EU-US-CA-ZA)

- Check expiration date
- Remove the test device from the pouch and place it on a flat surface
- Pipette 4 drops of urine into the round window
- After 4 minutes (and no later than 30 minutes), the result can be read:
  - Negative result: a colored line in the C (control) window and no line in the T (test) window
  - **Positive result: a colored line in the Control and Test window**
  - Invalid result: no colored line in the Control window
    - Add 1 or 2 additional drops of urine and wait 4 additional minutes. If a colored line still does not appear, the test is invalid and should be repeated using a new kit

7

Resupply

- Visit kits are resupplied based upon patient enrollment and visit schedule.
- Sites should check kit inventories routinely in preparation for patient visit(s).
- Keep us informed of lost or damaged kits; it is important for Covance to update our database with your current inventory.

Visits	Minimum	Maximum
Screen	3	5
Scheduled visits	Shipped automatically prior to patient's next scheduled visit	
Retest (unscheduled)	2	3
Early Termination (unscheduled)	3	3 supplied upon receipt of first kit

- **Kit Inventory Center telephone number: 800-327-7270, ext. 7603**

8

Upon Request Resupply

- Resupply request is necessary for:
  - The shipping boxes and documentation
  - Damaged, lost or expired kits
  - Extra tubes
- The order form is in your investigator manual
- Fax completed form to Covance or place your order by phone,
  - Fax: 317-616-2352
  - Phone: 800-327-7270, x7603
- Please allow for the delivery of your resupply order:
  - 7 working days in the USA

9

Investigator Manual

- Contents:
  - Specimen collection instructions
  - Packaging and shipping instructions
  - Protocol-specific reference ranges
  - Protocol-specific laboratory requisitions
  - Laboratory certifications (also found at www.covance.com)
  - Resupply forms

10

Accession Number and Bar Code

- A unique accession number is assigned to each kit (example: K879630)
- Located on kit box, tubes, vials and laboratory requisition form
- 1 accession number per visit and per patient. Protocol, site number and visit name are encoded
- Key to Covance's pre-defined database
- Provides audit trail
- Becomes patient specific when kit is used
- Demographic information on laboratory requisition form will link the patient with the individual accession number

11

Collection Kits

Kits are protocol and visit specific before use.

Kits become patient specific when used.

Do not interchange kits between investigators, or other protocols !
Do not collect specimens in expired containers !

12

Kit Contents

- Pre-labeled tubes and vials (all w/same accn #)
- Laboratory requisitions
- Safety needles / needle holder
- Diff-Safe device for hematology slides
- Microscope slides
- Specimen collection bag(s)
- Zip lock bag(s)
- Gel Pak to insulate specimens during shipment
- 2 extra barcoded labels

12 COVANCE

Collection Tubes

- All tubes are pre-labeled
  - Test name(s)
  - Accession number
- Write the patient's identifier (initials or pt #) on each label
  - Incorrect patient's identifier could cause cancellation of testing

Please do not interchange tubes or requisition forms between kits !

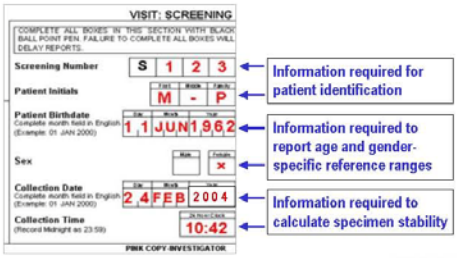
14 COVANCE

Laboratory Requisition Form

- Complete with a black ballpoint pen
- Patient demographic section
- Administrative questions
- Completion of all information is mandatory for reporting of laboratory results
- Collection instructions
- Ship white copy to Covance with samples
- Retain pink copy for your records

15 COVANCE

Demographic Section



16 COVANCE

Administrative Information

- Is patient fasting ?
  - Fasting sample is required for Ceruloplasmin and Alpha-1-Antitrypsin, which are collected at the Screening Visit only.
  - Check 'Yes' or 'No' box on the requisition.

17 COVANCE

Report Holds

- Covance will hold your laboratory reports for data clarification when:
  - Patient data are missing, incomplete or inconsistent with previous records
  - Additional data requested on requisition are missing
  - Incorrect kit was used
  - Patient initials incorrect or missing
  - Subject / Patient number incorrect or missing
  - Birthdate incorrect or missing
  - Inverted dates (correct dates in the wrong places)
  - Collection date or time incorrect or missing
  - Administrative question not answered
- The samples will be analyzed upon receipt
- When the issue has been clarified, the laboratory report will be released
- In case of clinically important alert in reports held back, Covance will immediately contact the investigator

18 COVANCE

DNA Extraction

- DNA extracted from whole blood for HCV genotyping and quantitation may also contain a small amount of patient genomic DNA.
- Isolated patient genomic DNA, even when it is not going to be analyzed as such, comes under special protection, and additional informed consent documents may be required.
- It is the responsibility of the investigator to ensure that the patient has signed the appropriate informed consent, and that it is duly filed prior to collection and shipment of samples for any sort of genetic testing.
- Covance has no responsibility for, nor liability to control this very important function and must rely on the investigator to secure patient consent.
- It is assumed that the investigator has the appropriately executed documents on file when we receive a sample for such testing.

19 COVANCE

Return Specimen Types

	Ambient	Frozen
Whole Blood	Hematology Hemoglobin A1c	--
Serum	Chemistry beta-hCG Thyroid Panel HIV Ab Hepatitis Panel Ceruloplasmin Alpha-1-Antitrypsin	Archive Serum Anti-Mitochondrial Ab Anti-Nuclear Ab Anti-Smooth Muscle Ab Thyroperoxidase Ab
Plasma	--	Coagulation Panel HCV Genotyping HCV RNA PCR
Urine	Urinalysis	--

20 COVANCE

Whole Blood Collection

Hematology & Hemoglobin A1c

- **Draw whole blood samples last** (except when collecting coagulation group at the same visit)
- Fill EDTA tube completely and mix immediately by gently inverting tube at least 8 to 10 times
- Smears are made with blood using the Diff-safe device
- Remove the Diff-safe after use and ship the tube with the hematology slides
- Ship to Covance at ambient temperature on day of collection

21 COVANCE

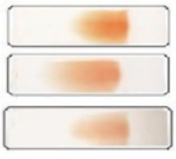
Hematology Slide Preparation

- Label frosted end with pencil
- After mixing the hematology tube, insert the Diff-safe
- Turn tube upside down and press until drop of blood appears
- Holding the second spreader slide at a 30° angle, pull the slide towards the drop of blood
- Allow droplet to spread completely across the edge of the slide and gently push the spreader slide forward
- Repeat the process for the other slide and allow slides to air dry
- Remove the Diff-safe from the hematology tube prior to shipment and dispose of in a bio-hazard (sharps) container

22 COVANCE

Example of a Good Slide

- Use rapid, even motions to make slides
- The weight of the slide should be the only pressure applied
- Good slides should be thick at one end, and thin at the opposite end



Good quality, fresh peripheral smears are necessary for optimal patient results

23 COVANCE

Examples of Bad Slides

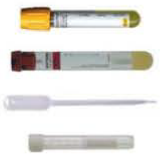
- Made with jerks and ridges
- Small voids of blood due to a large droplet, causing excess thickness
- Not wide enough

24 COVANCE

Serum Collection (Serum Separator Tube, SST)

Chemistry, beta-hCG, Thyroid Panel, HIV Ab, Hepatitis Panel, Ceruloplasmin, Alpha-1-Antitrypsin, Archive Serum, Anti-Mitochondrial Ab, Anti-Nuclear Ab, Anti-Smooth Muscle Ab, Thyroperoxidase Ab

- Fill Serum Separator Tube completely
- Allow blood to clot for 30 minutes at ambient temperature with tube standing upright
- Centrifuge at a minimum of 1500 x g for 15 minutes; clot and serum must be well separated
- Carefully pipette all the serum into labeled plastic vial
- Discard collection tube and pipette
- For ambient specimens: secure screw cap vial with adhesive tape
- Store and ship to Covance as instructed



25

COVANCE

Citrate Plasma Collection

Coagulation

- Fill Sodium Citrate tube completely and mix immediately by gently inverting tube at least 8 to 10 times
- Centrifuge at a minimum of 1500 x g for 15 minutes; cells and plasma must be well separated
- Carefully pipette only the plasma into labeled plastic vial
- Discard collection tube
- Freeze immediately at –20°C until shipment
- Ship to Covance frozen on dry ice as instructed

26

COVANCE

EDTA Plasma Collection

HCV Genotyping & PCR

- Fill EDTA tube completely and mix immediately by gently inverting tube at least 8 to 10 times
- Centrifuge immediately at 1500 x g for 15 minutes; cells and plasma must be well separated
- Carefully pipette only the plasma into labeled plastic vial
- Discard collection tube and pipette
- For ambient specimens: secure screw cap vial with adhesive tape
- Freeze immediately at –20°C until shipment
- Ship to Covance on dry ice as instructed

27

COVANCE

Urine Collection

Urinalysis

- Have patient void into a standard urine collection cup
- Transfer specimen into labelled transport tube
- Do not fill above the 13 ml mark on tube
- Screw cap on tightly
- DO NOT SHAKE – tablet is not intended to dissolve completely
- Secure screw cap tube with adhesive tape
- Store and ship to Covance at ambient temperature on day of collection

28

COVANCE

Dangerous Goods & IATA Requirements

IATA Training is required for all persons handling and shipping Dangerous Goods

Including:
Dry Ice

Training provided by Covance CLS is this presentation, does not qualify as official training as outlined by the IATA regulations.

www.iata.org/atdi/endorsed_schools.htm

Additional information can be found in your investigator manual

29

COVANCE

Diagnostic Ambient Packaging

- Secure all screw cap vials with adhesive tape
- Insert tube(s) into Specimen Collection Bag with white copy of Requisition in outside pouc (make bar code visible)
- Prepare Gel Pak, fill to indicator line with cool tap water
- Lightly press the absorbent pack to expel its content
- Massage bag until the gel material is formed
- Expel air out of bag and seal
- Wrap around Specimen Collection Bag
- Do not place vials directly inside Gel Pak
- Then place into white kit box and into Zip B
- Place into cardboard shipping box
- Fill empty spaces with newspaper and close box securely
- Consolidate shipments when possible

30

COVANCE

5

US - Ambient Shipping, Clinical Specimens: **Airway Bill**

- Documents are pre-printed
- Data to be entered:
  - **Sender's signature**
  - **Date**
  - **Mark Saturday Delivery (if sent on Friday)**

31

COVANCE

Diagnostic Frozen Packaging

- **Insert tube(s) into Specimen collection Bag, with white copy of Requisition (if not already sent with ambient samples) in the outside pouch (make bar code visible)**
- **Place Specimen Collection Bag(s) within 2 Kgs / 5 Lbs of dry ice**
- **Replace lid and close box securely**

32

COVANCE

Diagnostic Combined Ambient & Frozen Packaging

- **Frozen samples**
  - **Insert tube(s) into Specimen Collection Bag**
  - **Place Specimen Collection Bag(s) completely surrounded by dry ice**
  - **Replace lid and cardboard spacer**
- **Ambient samples**
  - **Package as previously instructed**
  - **Place kit box in top portion of shipping box**
- **Shipping Box**
  - **Pre-printed with the Class 9 miscellaneous label**
  - **Confirm amount of dry ice is pre-recorded on the UN1845 label on the shipping box and on the appropriate air waybill**

33

COVANCE

US - Frozen Shipping, Clinical Specimens: **Airway Bill**

- Documents are pre-printed
- Data to be entered:
  - **Sender's signature**
  - **Date**
  - **Total weight in Kgs**
    - **Record/verify amount of dry ice (2 Kgs) on air waybill and shipping box**
    - **Air waybill and UN1845 label on shipping box must match**
    - **Record in whole numbers only**
  - **Mark Saturday Delivery (if sent on Friday)**

34

COVANCE

Shipping Summary

- USA
  - **Inquire about local courier service schedule**
  - **Attach to the outer sleeve of the shipping box:**
    - **Air waybill**
  - **Keep your copy of air waybill at site**
  - **Friday shipments must have air waybill marked for "Saturday Delivery"**
  - **When calling to schedule pick-up, inform dispatcher that your package is an "Urgent Covance Medical Shipment"**
  - **With Airborne Express:**
    - **Telephone: 888-708-8825**

35

COVANCE

Courier Pick-up

- **If you miss the cut-off time or have a late afternoon patient, proceed as follows:**
  - **AMBIENT samples should remain at room temperature until the next available shipment**
    - **The Hematocrit has a stability of 60 hours**
    - **Do not refrigerate**
  - **FROZEN samples should remain frozen at the appropriate temperature**

Do not hesitate to call Covance, if you need assistance.
Investigator Call Center: 800-327-7270

36

COVANCE

Laboratory Reports

- Automatically faxed to the site by test group (i.e., Chemistry, Hematology etc.) as completed
  - To ensure fax delivery, sites must have a reliable fax service
- A hardcopy will be sent weekly to the site
- Results out of reference range will be marked CS or NCS, and a line will appear for comments
- Date and signature line
  - The investigator must date and sign each report
  - Do not send reports back to Covance; they must be filed at site
- Any missing data on the requisition form will delay reporting

27

COVANCE

Reporting Flags and Alerts

- -d, +d no notification
- L, H no notification
- LT, HT faxed, phoned
- LP, HP faxed, phoned
- EX faxed, phoned

LP	LT	L	Normal	H	HT	HP
Low Panic	Low Telephone	Low Flag	Reference Range	High Flag	High Telephone	High Panic

-d ◄——— ———► +d

28

COVANCE

Site Support Services

- Covance will call you:
  - To obtain missing patient's demographics
  - When incorrect visit kits are used
  - To report abnormal values
- Contact Covance for questions about:
  - Kits
  - Collections instructions
  - Resupply
  - Results
  - Comments

29

COVANCE

Covance CLS
Site Support Services Contact Numbers

(800) 327-7270

Investigator Call Center:	Questions concerning laboratory reports	Ext. 7420
Investigator Training Center:	Questions concerning specimen collection or processing	Ext. 7455
Kit Inventory Center:	Investigator Supplies	Ext. 7603
Transportation:	Courier Issues	Ext. 7404

40

COVANCE

Summary

- Refer to your investigator manual
- Check your inventory weekly
- Kits must not be interchanged between investigators or other protocols
- Collection tubes must not be interchanged between kits
- Select appropriate kit, always check expiration date
- Do not place samples inside Gel Pak bag
- Order the dry ice for your frozen shipments in advance
- Remove Diff-safe device from hematology collection tube prior to shipment
- Do not refrigerate hematology specimens

41

COVANCE

Summary

- Complete Requisition form in black ink
- Laboratory reports cannot be generated if data are missing or inconsistent on laboratory requisition
- Verify amount of dry ice recorded on shipping box (2Kgs / 5Lbs) and on air waybill
- Please allow a minimum of 7 working days for delivery of resupply orders
- Mark "Saturday Delivery" if shipping on Friday

Do not hesitate to call us if you have any questions
Investigator Call Center: 800-327-7270

42

COVANCE

CHAPTER 13

PREGNANCY TESTING

13.1 Pregnancy Testing Requirements

Extreme care must be taken to avoid pregnancy during the study in female patients, and female partners of male patients. During any visit where pregnancy tests are not done or for telephone assessments, females over the age of 10 years will be asked for the first day of their last menstrual period. If they show secondary amenorrhea of 1 week or more, a serum pregnancy test will be performed. Sexually active males will also be asked if their sexual partners are pregnant. If the male answers "Yes", he will be moved to untreated follow-up.

Serum or urine pregnancy tests are to be performed in fertile or potentially fertile females only (age 10 years and older) within 24 hours prior to first tablet (RV/placebo) or at any time of a secondary amenorrhea of more than 1 week. Pregnancy tests are to be performed every 4 weeks during treatment and for the 6 months following completion of treatment.

All records regarding pregnancy testing are to remain confidential.

All pregnancies will be reported to the Ribavirin Pregnancy Registry (1-800-593-2214).

13.2 Pregnancy Test Kits

Covance will supply urine pregnancy test kits to the clinical sites. The Fisher Sure-Vue test will be the kit supplied by Covance. The tests are simple to do and take about 15 minutes. See the Appendix for instructions on using the Sure-Vue kit (University of Texas, Medical Branch Point of Care Testing Procedures). Some clinical sites will be using other means of urine testing due to restrictions regarding point of care testing and lab requirements.

13.3 Occurrence of Pregnancy

A female subject must be instructed to stop taking the test drug and immediately inform the investigator if she becomes pregnant during the study. Pregnancies occurring

up to 6 months after the completion of the test drug must also be reported to the investigator. The Clinical Center investigators will report all pregnancies within 24 hours to MMRI and the PI. The investigator will counsel the subject; discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Untreated follow-up of the patient will continue until conclusion of the pregnancy.

The patient must immediately report to the investigator (who will inform the MMRI safety monitor and the PI) any pregnancy occurring in a partner during the duration of the trial. Such patients may not continue to receive RV.

For reasons of safety, breast-feeding and pregnant females are excluded as are sexually active females of child-bearing potential who do not use two methods of contraception during and up to 6 months after cessation of therapy. Males whose female partners are pregnant are also excluded from the study.

13.4 Schedule for Collecting Information

Serum pregnancy tests will be obtained at the site and sent to the Central Lab, Covance, for analysis. Serum tests will be obtained at the following visits: Screening, weeks 3, 8, 12, 20, 24, and regularly during the study treatment period after weeks 24. (See Tables 1, 1a and 1b.). Serum tests will also be obtained during untreated follow-up visits at follow-up weeks 4, 8, 12 and 24.

Urine pregnancy tests will be obtained at the following visits: Baseline, weeks 16 and at the time of untreated follow-up telephone assessments.

Urine pregnancy tests will be obtained and analyzed at the site. All positive urine tests must be confirmed by a serum pregnancy test. Serum confirmation of positive urine tests is required. However, patients will be considered pregnant if either the urine or serum tests are positive. The serum samples will be sent to Covance for analysis. At telephone assessments urine pregnancy tests must be done in the home. Two study test kits will be sent home with the family at the week 60 visit. Prior to home pregnancy kit use, the patient or guardian will be taught how to perform the test. Results of the tests will be reported to the Clinical Center staff at the time of the phone contact. The date of the patient's last menstrual period will also be obtained to check for amenorrhea of one week or more.

13.5 The Ribavirin Pregnancy Registry

13.5.1 What is the Registry?

The Ribavirin Pregnancy Registry (Registry) is a program to monitor pregnancy exposures to Ribavirin. The development of the Registry was mandated by the FDA. The Registry was implemented in January 2004. A Scientific Advisory Board oversees the Registry data, analyses, and presentation of results. A Registry Interim Report, published semi-annually, summarizes the aggregate data and is available to interested health care providers.

The Ribavirin Pregnancy Registry is a voluntary, largely prospective registry designed to collect observational data on pregnancies and their outcomes following a pregnancy exposure to Ribavirin. The Registry also collects "retrospective" information, i.e., reports after the outcome of the pregnancy is known for additional analysis. Ribavirin exposures may be direct through the pregnant female, or indirect through her male sexual partner. Registry data are used to supplement other sources of data and, as data accrue, may assist clinicians and patients in weighing the risks of Ribavirin exposure in pregnancy. The lack of data on Ribavirin pregnancy exposures and their outcomes makes such a Registry an essential component of the ongoing risk management program and epidemiological studies on the safety of this product.

13.5.2 How to Participate in the Registry

The Registry will accept reports of pregnancy exposures to Ribavirin from health care providers, pregnant patients, or pregnant patient's male sexual partners. The data collected are minimal and targeted. Data are collected at each trimester and at the outcome of the pregnancy through the obstetric health care provider and for a live birth for 12 months after birth through the pediatric health care provider. Patient identity is kept confidential. The Registry assigns ID numbers to follow the pregnant female until a signed authorization for release of medical information is obtained.

The data are collected through the Registry Coordinating Center. Contact information is as follows:

Ribavirin Pregnancy Registry
1011 Ashes Drive
Wilmington NC 28405
Phone: 1-800-593-2214
1-910-509-4991
Fax: 1-800-800-1052
1-910-256-0637
Web Site: www.ribavirinpregnancyregistry.com

13.6 Birth Control Requirements- Instructions for Patients

Female patients over the age of 10 years who are sexually active and males who are sexually active must use two forms of birth control, one of which is a barrier method. The following instructions should be used. [To be added.]

CHAPTER 14

DEPRESSION SCREENING AND MANAGEMENT

14.1 Screening and Management for Depression

All children undergoing screening for enrollment will be screened for depression using the Childhood Depression Inventory (CDI), published by Multi-Health Systems, Inc (see copy of the questionnaire in the Appendix.) This is a 10 minute questionnaire. The questionnaire will be completed by the parent for children under age 10. Patients who are 18 years of age or older will be screened using the 20-item Center for Epidemiological Studies Depression Scale (CES-D). Any child meeting the criteria for severe depression will not be entered into the study and will be referred to a child psychiatrist for management.

In addition, each investigator will screen children at entry for a Major Depressive Episode - criteria from the American Psychiatric Association. See Table 14-1.

Table 14-1: CRITERIA FOR MAJOR DEPRESSIVE EPISODE *

A major depressive episode is indicated by the presence of five or more of the following symptoms nearly every day during the same two-week period, representing a change from the previous level of functioning:

Depressed mood most of the day

Markedly diminished interest or pleasure in all or almost all activities

Clinically significant weight loss in the absence of dieting or weight gain (e.g., a change of more than 5 percent of body weight in a month) or a decrease in appetite †

Insomnia or hypersomnia

Observable psychomotor agitation or retardation

Fatigue or loss of energy

Feelings of worthlessness or excessive or inappropriate guilt

Diminished ability to think or concentrate or indecisiveness

Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

---

* Criteria are from the American Psychiatric Association. (58)

† In children, this criterion includes the failure to make the expected growth-related weight gains.

The CDI or CES-D will be used to screen children for depression at screening, the baseline visit, 12 weeks, 24 weeks, at the last study treatment period visit, and at the last untreated follow-up visit (follow-up week 24). They will also be administered at both long-term annual follow-up visits. If depression develops as defined by the CDI Manual (score >19), or the CES-D Manual (score >15), then the investigator will perform a more thorough evaluation to determine the validity of the test results. If the participant meets the criteria listed above for Major Depressive Episodes, and fits the criteria listed under A in Table 14-2, then he/she will be referred to a mental health professional and the PEG-2a or PEG-2a plus RV will be continued. If the management of the depression is not successful after eight weeks or if the participant develops criteria under B in Table 14-2 for referral to a specialty physician during that eight week period, the PEG-2a or PEG-2a plus RV will be stopped and the participant will be referred to a specialty physician. The participant will be moved to the first untreated follow-up visit.

Table 14-2: Indications for Mental Health Professional Care and Specialty Physician Care in Pediatric Patients with Depression

A. Indications for mental health professional care:

Initial episode of depression

Recent onset of depression

Absence of coexisting conditions

Ability to make no-suicide contract

High level of family discord

Chronic, recurrent depression

B. Indications for specialty physician care and immediate withdrawal of study drugs:

Lack of response to initial course of treatment*

Coexisting substance abuse*

Recent suicide attempt, current suicidal ideation with plan, or both*

Psychosis*

Bipolar disorder*

Inability of family to monitor patient's safety*

* The presence of this factor indicates the need for more urgent or more intensive care.

14.2 Measurement of Psychosocial Functioning

In addition to the CDI psychosocial functioning will be assessed. The assessment protocol for this is designed to evaluate the child's health-related QOL, cognitive and developmental and psychological functioning. Some of the constructs will be measured from multiple sources (e.g., child and parent) depending on child age. All assessment tools have been selected on the basis of their demonstrated reliability and validity. All measures will be completed at the time of scheduled clinic visits. There are versions in Spanish for the CBCL, CHQ, and SF-36 but not for the BRIEF or LEC.

Health-related QOL. QOL will be measured using the Child Health Questionnaire (CHQ), which is one the best-validated measures of children's QOL and is completed by both children (at least 10 years old) and parents. For children under 10, parental information on the same constructs will be collected. Information is gathered on several QOL domains, including physical functioning, role/social limitations, general health, bodily pain/discomfort, parent impact, self-esteem, mental health, general behavior, and family impact.

Cognitive functioning. Cognitive functioning will be measured using the Behavior Rating Inventory of Executive Function (BRIEF) at all assessment points. There is a preschool version and a version normed for older children and adolescents. It contains 86 items in 8 non-overlapping clinical scales and 2 validity scales. These theoretically and statistically derived scales form two broader Indexes: Behavioral Regulation (3 scales) and Metacognition (5 scales), as well as a Global Executive Composite score. The BRIEF measures emotional and behavioral dysregulation, difficulties with response inhibition, working memory and the ability to quickly transition into new situations or tasks. It has demonstrated high internal consistency, test-retest reliability, and validity.

Psychosocial functioning. In addition to the CHQ, which has a mental health component, parents will complete the Child Behavior Checklist (CBCL) at all assessment points. This well-validated measure permits an assessment of child adaptation across both internalizing (e.g., depression, anxiety) and externalizing (e.g., conduct problems, aggression) domains.

In addition to the foregoing, the assessment protocol will include a measure of life stress and a measure of parental QOL. Specifically, parents will complete the Life Events Checklist (LEC), which measures their perception of 46 life events and the degree to which

they represent positive or negative stressors. Also, parents will complete the MOS 36-Item Short-Form Health Survey (SF-36) to assess their physical and mental health status, including physical function, social function, pain, psychological well being, energy, impairment due to emotional problems, and general health perceptions. The results of cognitive, psychosocial and behavioral measures will be available to those interested within 4 weeks after discontinuation of treatment, and within 4 weeks after testing for long-term annual visits.

QOL/Health Outcomes Assessment Protocol and Timeline:

Assessment	Baseline		Week 24		Week 48		24 weeks after End of Treatment Week 72 or 100 ^		2 annual visits (Long-term Follow-up)	
	C	P	C	P	C	P	C	P	C	P
CHQ	X*	X	X*	X	X*	X	X*	X	X*	X
BRIEF		X		X		X		X		X
CBCL/ABCL		X		X		X		X		X
SF - 36		X		X		X		X		X
LEC		X		X		X		X		X

^For those subjects who fail PEG –2a monotherapy at 24 weeks and go on to another 48 weeks of combination therapy (76 weeks total treatment)
* Not completed by children <10 years of age
[C = Child completes or administered to child; P = Parent completes]

CHAPTER 15

PATIENT WITHDRAWAL

15.1 Criteria for Premature Withdrawal

Patients have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study if it is in the best interest of the patient. An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients will be avoided. When a patient decides to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible.

The investigator will contact the parent/legal guardian either by telephone or through a personal visit, or a responsible relative must be contacted to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal will be made with an explanation of why the patient is withdrawing from the study.

The informed consent will include procedures for withdrawal from and termination of the study.

Participating patients will complete treatment, unless study drug is discontinued because of intolerance, investigator withdrawal of the patient or consent is withdrawn.

15.2 Follow-Up Schedule for Patients Prematurely Withdrawn

Investigators will make every attempt to follow patients who discontinue study drug permanently for whatever reason (e.g. AEs) for at least 24 weeks by the post treatment follow up schedule.

15.3 Replacement Policy

No patient prematurely discontinued from the study for any reason will be replaced.

A center may be replaced for the following administrative reasons:

Excessively slow recruitment

Poor protocol adherence

CHAPTER 16

COMPLIANCE MEASURES

16.1 Drug Recording in Patient's Medication Diary (PMD)

It is mandatory that each PEG-2a injection and RV dose be recorded. The PMD will be labeled with the patient ID and letter code and the visit weeks covered before giving it to the parent. The parent/guardian will be instructed to record the date and exact time of PEG-2a and RV. The person giving the PEG-2a injection must initial the diary. The date and exact time of PEG-2a and RV administration as well as the amount in mL of PEG-2a that was injected and number of tablets of RV will be recorded. In addition, the BL study treatment prescription will be faxed to the DCC/CRO.

The PMD will be reviewed with the parent at each clinic visit. The interview will be carried out in a private place away from excessive noise. The reviewer will be familiar with the patient's current dosages and his/her history of compliance before the start of the interview. Review drug compliance one week at a time for both drugs. The first week reviewed will be the week after the last clinic visit. At clinic visits at weeks 1, 3, 5 and 8 this may not be the first week in the Diary because the booklet contains six weeks (one month with two extra pages for partial weeks or to cover special situations like holidays).

During the review pay special attention to missing doses, changes in dose, and drug stops and re-starts. These may differ for each drug taken. Ask the parent if the patient has experienced any side-effects or illnesses during that week and complete the information on each illness or side-effect on the right hand side of the weekly record. Probe the "Reasons not given" for missed doses and discuss how problems may be resolved with the parent. It may be necessary to re-instruct the parent in how to give an injection or when to change the injection site. When appropriate, complete the Therapy Missed Dose Form to report missed doses, the Therapy Stop/Restart Form to report therapy stops and restarts, and the Therapy Dose Adjustment Report to report changes in dosage. If a reason not given for a dose not taken in the Patient's Medication Diary is coded 2 or "dose held or stopped", complete a Therapy Stop/Restart Form. The dose was not "missed" since only prescribed doses can be missed.

The Patient's Medication Diary will be collected once a month. It will not be collected by DCC/CRO or data entered, but will be filed by patient ID at the Clinical Center in a secure location.

16.2 Drug Accountability for Compliance Assessment

The date(s) and quantity of the drug returned by the parent/guardian will be recorded by the research pharmacist to assess compliance.

Accountability and subject compliance will be assessed by maintaining adequate drug dispensing logs and study drug return records.

A drug dispensing log must be kept current and will contain the following information:

The identification of the patient to whom the drug was dispensed

The date(s) and quantity of the drug dispensed to the parent/guardian

The date(s) and quantity of the drug returned by the parent/guardian

In addition, the Study Drug Count Form 34 must be completed at each study visit during the study drug treatment period in order to report the counts of pills and vials returned by the patient, given to the patient for the next study period, and unaccounted for. If the patient does not report taking drug in the PMD, does not return the correct amount to the clinic, and says that the drug is lost, it should be considered "unaccounted for".

The drug inventory (empty study drug vials/bottles, as well as partly used and unused study drug vials/bottles) must be available for inspection at every monitoring visit. All unused study drug must be returned by the parent/guardian to the investigator at each visit. Drug supplies, including unused, partially used or empty vials/bottles and the drug dispensing logs, must be returned to Roche at the end of the study.

16.3 Protocol Adherence Aids from Data Management System

The DCC/CRO staff will prepare and distribute protocol adherence aids from the data management system, including: 1. data collection schedules for children based on date of randomization; and 2) a list of forms delinquent based on the data collection schedule. The data collection schedule is available to Clinical Centers in the form of an on-line visit

calculator distributed by the DCC/CRO. The resulting schedule, generated to reflect the schedule of visits in the protocol, will be customized to show the time window for each visit for that child and the data to be collected. A list of expected visits to be scheduled for the next month will be a reminder for the Clinical Centers to schedule the visits and/or to verify that the children will be returning for their visit. The list of delinquent forms will also be sent as a reminder to the clinical sites to submit required forms for visits that have already been completed. This list will also be given to the CRA to resolve during the monthly site visit.

CHAPTER 17

ADVERSE (AE) AND SERIOUS ADVERSE EVENT REPORTING

17.1 Adverse Events and Laboratory Abnormalities

17.1.1 Clinical Adverse Events

An adverse event is any expected or unexpected medical occurrence in a PEDS-C patient. It does not necessarily have to have a causal relationship with the PEDS-C study drug therapy. An adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the study drug therapy, whether or not considered related to the therapy. Pre-existing conditions, which worsen during the study, are to be reported as adverse events.

All clinical adverse events (AEs) encountered during PEDS-C will be reported on the Expected Non-Serious Adverse Event, Unexpected Non-Serious Adverse Event, or Serious Adverse Event Forms. Intensity of adverse events will be graded on a scale (mild, moderate, severe, life threatening) and reported in detail as indicated on the CRF.

Mild: discomfort noticed but no disruption of normal daily activity

Moderate: discomfort sufficient to reduce or affect daily activity

Severe: inability to work or perform normal daily activity

Life threatening: represents an immediate threat to life

Relationship of the adverse event to the treatment will be assessed.

17.1.2 Laboratory Test Abnormalities

In the event of unexplained abnormal laboratory test values, the clinically significant laboratory values will be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

If a laboratory abnormality has only triggered a dose reduction or a held dose, this should be handled and recorded as a laboratory abnormality and should NOT be recorded as an adverse event.

If a laboratory abnormality has received a specific treatment (e.g. elevated BUN and treatment of dehydration) this should be handled and recorded as an adverse event.

If a laboratory abnormality is serious, constituting a serious adverse event, this should be handled and recorded as an SAE.

If a laboratory abnormality has resulted in drug discontinuation, this should be handled and recorded as an adverse event.

Please see Appendix "Toxicity Table for Grading Severity of Pediatric (>3 months to 18 years of age) Adverse Experiences".

17.2 Serious Adverse Events (Immediately Reportable to Roche, Dr. Schwarz, the DCC/CRO, FDA and NIDDK Project Scientist)

Any clinical adverse event or abnormal laboratory test value that is serious and occurs during the course of the study, irrespective of the treatment received by the patient, must be reported by the individual investigator via telephone to Dr. Schwarz and the PEDS-C Safety Committee (contact is through the DCC/CRO) within one working day of knowledge of the occurrence by the investigator. The individual investigator will also fax the completed SAE form to the DCC/CRO within one working day of occurrence. The DCC/CRO will automatically notify the Roche Drug Safety Group, the FDA and NIDDK electronically via a completed SAE form within one working day of knowledge of the occurrence by the investigator. The DCC/CRO will be responsible for submitting the follow-up SAE reports to FDA. The Roche Drug Safety group will submit IND safety reporting (MedWatch) to the individual sites.

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. With respect to human clinical experience, this includes any experience which:

Is fatal or life-threatening (NOTE: death is an outcome, not an event);

Requires inpatient hospitalization or prolongation of an existing hospitalization;

Results in persistent or significant disability/incapacity;

Is a congenital anomaly/birth defect;

Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not

be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

For serious and all other adverse events, the following must be assessed and recorded on the adverse event page of the Case Report Form: intensity, relationship to test substance, body system, action taken regarding test substance, and outcome to date.

In accordance with international and local laws and regulations, the investigator must promptly notify the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) of a serious adverse event.

CHAPTER 18

REGULATIONS

18.1 Food and Drug Administration

FDA regulations are promulgated in the Federal Register under Sec. 10.40 or Sec. 10.50 and codified in the Code of Federal Regulations. Regulations may contain provisions that will be enforced as legal requirements, or which are intended only as guidelines and recommendations, or both.

FDA guidelines are included in the public file of guidelines established by the Dockets Managements Branch. Guidelines establish principles or practices of general applicability and do not include decisions or advice on particular situations. Guidelines relate to the performance characteristics, preclinical and clinical test procedures, manufacturing practices, product standards, scientific protocols, compliance criteria, ingredient specifications, labeling, or other technical or policy criteria.

Guidelines state procedures or standards of general applicability that are nor legal requirements but are acceptable to FDA for a subject matter which falls within the law administered.

18.2 Protection of Human Subjects

Subjects participating in this trial will be protected under 45 CFR 46 HHS Protection of Human Subjects

The FDA published a guideline entitled “Good Clinical Practice”. The guideline was prepared under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guideline is intended to define “Good Clinical Practice” and to provide a unified standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. The guideline also describes the minimum information that will be included in an investigator’s Brochure (IB) and provides a suggested format. In addition, the guideline describes the essential documents that individually and collectively permit evaluation of the conduct of a clinical study and the quality of the data produced.

The GCP guidelines were generated to be applied to all investigations involving human subjects that may have any impact on the safety and well-being of the subjects. These guidelines were followed when generating the documents for the PEDS-C Trial, including all documents that will be forwarded to the regulatory authorities.

18.3 Guidance for Investigators Concerning the Health Insurance Portability and Accountability Act of 1996 (HIPPA) Privacy Rule

18.3.1 Introduction

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) is a multifaceted Federal law which covers three areas: insurance portability, fraud enforcement (accountability) and administrative simplification. The administrative simplification part of the legislation includes rules for privacy and security. The Privacy Rule is intended to protect individuals= right to control access to and disclosure of their protected health information. The Security Rule complements the Privacy Rule and requires organizations to control the means by which protected health information remains confidential. The Privacy Rule, which was issued August 14, 2002, takes effect on April 14, 2003.

The Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. It changes the rules regarding how Aprotected health information@ may be handled and creates equal standards of privacy protection for research governed by the existing Federal human subjects regulations and research that is not. The Privacy Rule also insures that researchers continue to have access to medical information necessary to conduct vital research. A covered entity may also use or disclose for research purposes health information which has been de-identified [in accordance with 45 CFR 164.502(d) and 164.514(a)-(c) of the Rule] without regard to the provisions outlined as follows.

In the course of conducting research, investigators may obtain, create, use and/or disclose individually identifiable health information. Under the Privacy Rule, covered entities are permitted to use and disclose protected health information for research with individual authorization or without individual authorization under the limited circumstances set forth in the Privacy Rule. The Authorization for research must be for a

specific research project. The Authorization must contain core elements and required statements as outlined in the Privacy Rule; this information is different from, but may be combined with, the informed consent form for the study. The Privacy Rule does not replace or modify the Common Rule or Food and Drug Administration (FDA) regulations, but the Privacy Rule does extend privacy protections of the Common Rule and FDA regulations.

In order to comply with the law, each Principal Investigator of a Clinical Site will have to obtain authorization or a waiver to use and disclose protected health information from each patient enrolled in a clinical study on or after April 14, 2003; the authorization document or a request for a waiver of authorization must be approved by the Clinical Site Institutional Review Board (IRB) or Privacy Board. The investigator must also obtain informed consent using the consent form(s) for the study approved by the investigator=s local IRB and, if appropriate, by study leadership. The authorization may be merged with the text of an existing informed consent form(s) for the study, or it may be a stand-alone addition to the informed consent form.

Participants enrolled in a research study prior to April 14, 2003 and who have given informed consent do not have to be recontacted to obtain authorization concerning release of protected health information; however, study investigators may decide to obtain authorization at a subsequent visit.

Non-compliance or violation of this law can lead to serious sanctions. Inadvertent violations can result in fines of up to $100 for each violation of a requirement per individual. Criminal penalties for wrongful disclosure can include, not only larger fines, but may also involve incarceration.

18.3.2 Definitions

A. Research

Research is defined in the Privacy Rule as, Aa systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledgeable.@ Creation of a repository is considered a research activity. HIPAA covers all research activities that use individually identifiable health information about humans, as long as the information is collected in a setting related to the patient care process.

B. Covered Entities

HIPAA states that covered entities include most providers, clearinghouses and health plans. Thus, the definition of a covered entity includes most clinical research sites that examine and treat patients.

C. Identifiable Information

Individually identifiable information is anything that can be used to identify a subject. Releasing this information for reasons other than treatment, payment or operations, such as research, without obtaining an authorization or a waiver is a violation of the privacy regulations. The elements that make information individually identifiable are listed in Table 18-1.

D. Use or Disclosure

There is a difference between the terms Ause@ and Adisclosure.@
HIPAA regulations use these terms to refer to ways in which information is shared. A Ause@ happens within a health care organization or other covered entity and is under the direct control of that organization. ADisclosure@ occurs when information is given to someone who is not part of the organization=s workforce.

E. De-identified Health Information

To completely de-identify protected health information (PHI) requires the removal of the 18 types of identifiers listed in Table 10-2. Statistically Ade-identified@ information applies when a statistician certifies that there is a Avery small risk@ that the information could be used to identify the individual.

F. Limited Data Set

Under the HIPAA Privacy Rule, limited types of identifiers may be released with health information. Direct identifiers must be removed, but useful information such as complete dates, geographic information other than street addresses; and a link field as an encrypted identifier may be included in the data set. This information is then referred to as a Limited Data Set. The identifiers that must be removed are listed in Table 10-3.

G. Data Use Agreements

The Data Use Agreement between the covered entity collecting the data and the recipient organization receiving the data must: (1) describe the permitted uses and disclosures (recipient cannot use or disclose PHI in a way that the covered entity cannot), (2) identify who can use and disclose the PHI, (3) require the recipient to use or disclose information for specified purposes only, (4) apply safeguards to protect the information, (5) report known violations to the covered entity, (6) hold subcontractors to the same standards as in the agreement and (7) not re-identify the information or contact the individuals.

H. Link Fields

A Alink field@ is a code that allows you to go back to the original, identified PHI. This code is a list of random (or haphazardly selected) letters and/or numbers that match up the stripped data with its original form. As long as the link field is totally unrelated to any identifier of the subject, it is allowed under HIPAA.

18.3.3 Authorization Document

In general, the Privacy Rule requires an individual=s written authorization be obtained before the use and/or disclosure of PHI. The Authorization for research must be for a specific research study. The Authorization Document must contain the core elements and the required statements specified in the rule.

The written Authorization Document to use or disclose PHI must include the following core elements:

1. Description of PHI to be used or disclosed (a complete list is required);
2. Persons authorized to use or disclose the information;

3. Purpose for the use or disclosure; and
4. Expiration date or event (for example, end of research study or ANone@).

The required statements must include:

1. Right to revoke authorization plus exceptions and process;
2. Ability or inability to condition treatment, payment or enrollment/eligibility for benefits on authorization; and
3. PHI may no longer be protected by Privacy Rule once it is disclosed by the covered entity.

18.3.4 Research Use and Disclosure of PHI Without Authorization

The Privacy Rule also specifies that not all research uses and disclosures of protected health information require a research participant to give authorization. The different circumstances which are allowed are: (1) if the protected health information is de-identified as defined above; (2) the information is contained in a Limited Data Set with a Data Use Agreement between the data collection group and the recipient; (3) local Institutional Review Board grants a waiver of the authorization requirement for activity preparatory to research; (4) research is on decedents= information; (5) research qualifies for the transition provisions; and (6) disclosure to a public health authority or is required by law.

The Privacy Rule assumes authorization will be obtained; therefore, to use any of the above exceptions, the following documentation must be prepared to confirm that the criteria for each of any one of the above exceptions are met.

A. De-identified Protected Health Information
   It will be documented that the 18 types of direct identifiers that must be excluded as listed in Table 2 will not be available.
B. Limited Data Set with Data Use Agreement
   There will be documentation that the information meets the criteria for a Limited Data Set (see Table 3) and that there is a written Data Use Agreement between the covered entity and the recipient.
C. Local Institutional Review Board or Privacy Board Grant Waiver of Authorization

In order for the Institutional Review Board to issue a waiver, the following criteria must be met:

1. Use or disclosure involves no more than minimal risk because of an adequate plan/ assurance (a) to protect PHI from improper use and disclosure, (b) to destroy the identifiers at the earliest opportunity and (c) that PHI will not be inappropriately re-used or disclosed.
2. The research could not practicably be conducted without the waiver.
3. The research could not practicably be conducted without access to, and use of, PHI.

The researcher is also obliged to obtain documentation of all of the following if a waiver is granted:

1. Identification of the IRB or Privacy Board and the date on which the alteration or waiver of authorization was approved;
2. A statement that the IRB or Privacy Board has determined that the alteration or waiver of authorization in whole or in part satisfies the three criteria in the rule described previously in point C;
3. A brief description of the protected health information for which use or access has been determined to be necessary by the IRB or Privacy Board;
4. A statement that the alteration or waiver of authorization has been reviewed and approved under either normal or expedited review procedures; and
5. The signature of the Chair or other member as designated by the Chair of the IRB or Privacy Board, as applicable.

D. Preparatory to Research

1. A researcher must document that PHI is to be used solely to prepare a Protocol or for a similar purpose;
2. PHI will not be removed from the covered entity, and PHI is necessary for research.

E. Research on Decedents= PHI

Researchers must provide documentation that:

1. Use or disclosure is solely for research;
2. PHI is necessary for research; and
3. Individuals are decedent, and provide documentation upon covered entity=s request.

F. Transition Provisions

Authorization is also not required if a researcher had obtained before April 14, 2003 signed informed consent, waiver of informed consent, or express legal permission to use or disclose PHI for research.

G. Disclosure to a Public Health Authority or Required by Law

Disclosure without authorization is permitted if required by law or for public health activities; for example, adverse event reporting to a sponsor or the Food and Drug Administration.

H. Covered entity may disclose PHI related to an adverse event to NIH if required to do so by NIH regulations. Even if not required to do so, the researcher may disclose an adverse event to the NIH Public Health Authority.

18.3.5 Contents of Report for the Institutional Review Board

Each Principal Investigator will summarize the approach that each of the Clinical Sites in a given research study have elected with respect to obtaining authorization for release of protected health information. If an Authorization form is to be used and the required elements are not merged with the text of the existing informed consent form, a copy of the Authorization Document will be collected from each of the Clinical Sites to confirm that the required elements have been covered.

Exhibit A is a sample Authorization Document. This sample includes the following sections:

1. An overview or introduction;
2. A statement concerning the right of the individual not to participate or to withdraw or to decide, after having given authorization indicating a willingness to participate, to withdraw; this requires contacting the appropriate investigator in writing;

3. A statement that the individual has the right to refuse to sign Authorization;
4. A statement concerning the confidentiality of the records and that the recipients of the information will be in compliance with the Federal privacy regulations and that the individual will not be identified by name, social security number, address, telephone number or other direct personal identifiers;
5. A designation of the groups that will be recipients of the information and exactly what information these groups will receive;
6. If appropriate, a description of the other reviewers or groups that may have access to the information and that they may also review the entire medical record but they are obliged to maintain confidentiality;
7. That the study results will be retained for a period of at least six years or until the study is completed; and
8. A statement of understanding that the staff members and physicians who are performing the research will use and disclose the information only as described in the document; however, once it is disclosed to others for research purposes, these individuals cannot directly control future uses or disclosures. For this reason, the individuals at the site have requested that the research sponsor and its agent use the participant's information only for this research and not for other purposes.

If a Clinical Site requires a Data Set Agreement, the attached template in Exhibit 10-B could be used for that purpose. Each Principal Investigator will request that (1) the IRB approve a Data Set Agreement or (2) grant a waiver to receive a Limited Data Set (See Exhibit 10-C for sample request for a waiver).

HIPAA regulations also require that investigators follow acceptable approaches for screening participants for a research study. Study staff may approach patients regarding a research study if they are part of the patient=s treatment team. The patient=s physician, if not part of the study team, may not give permission for study staff to speak to the patient. However, the physician may ask the patient or individual to contact the study staff.

The study Protocol which has or will be approved by an Institutional Review Board will include a description of the process of screening for study eligibility. To comply with the Privacy Rule, it may be necessary to submit a request for a waiver to collect information prepatory to research. The appropriate Institutional Review Board or Privacy Board must approve this request prior to initiating the screening process.

TABLE 10-1

INDIVIDUAL DIRECT IDENTIFIERS

Names

Addresses

Employers= names or addresses

Relatives= names or addresses

Dates (e.g. birth date, dates of clinical events)

Telephone and fax numbers

E-mail addresses

Social Security numbers

Medical record numbers

Certificate numbers (including device serial numbers for implants)

Member or account numbers

Voiceprints

Fingerprints

Full face photos and comparable images

Any other characteristics that may be used, individually or in combination, to identify the individual

TABLE 10-2

18 DIRECT IDENTIFIERS DEFINED IN THE PRIVACY RULE

Names	Certificate/license Numbers
Geographic Info (including city, state, zip)	VIN and Serial Numbers, License Plate Numbers
Elements of Dates	Device Identifiers, Serial Numbers
Telephone Numbers	WEB URLs
Fax Numbers	IP Address Numbers
E-mail Address	Biometric Identifiers (Fingerprints)
Social Security Number	Full Face, Comparable Photo Images
Medical Record, Prescription Numbers	Unique Identifying Numbers
Health Plan Beneficiary Numbers	Account Numbers

TABLE 10-3

LIMITED DATA SET

A data set that excludes all of the following direct identifiers can be considered a Limited Data Set.

Names	Certificate/license Numbers
Postal Address Info (if other than city, state, zip)	VIN and Serial Numbers, License Plate Numbers
Telephone and Fax Numbers	Device Identifiers, Serial Numbers
E-mail Address	WEB URLs
Social Security Number	IP Address Numbers
Medical Record, Prescription Numbers	Biometric Identifiers (Fingerprints)
Health Plan Beneficiary Numbers	Full Face, Comparable Photo Images
Account Numbers	

EXHIBIT 10-A
SAMPLE AUTHORIZATION DOCUMENT

SAMPLE AUTHORIZATION DOCUMENT

Authorization for Release of Private Health Information for the Occluded Artery Trial (OAT)

INTRODUCTION/OVERVIEW

You have already signed an informed consent form for your participation in the Occluded Artery Trial. In that consent form, it was explained to you that you are invited to join the occluded artery research study because you had a heart attack within the past 28 days. Heart attacks are caused by a blockage in vessels (arteries) that bring blood to the heart. Your doctors have already checked or will check to see if the artery of your heart attack is still blocked. If the artery causing the heart attack is totally blocked, you will be eligible to participate in this study. If the artery is already open, you can not join this study and further care will depend on your doctor's advice. Doctors have used heart balloons and stents (as described below) to treat blocked arteries in cases where severe angina (chest pain) is present. However it is not known whether it is beneficial for your condition. This study is designed to find out whether opening blocked arteries is beneficial for patients like you. Doctors are working on this study in about 320 hospitals. The study will involve 3,200 patients. You may join the study if you agree with the research rules that apply to patients in this study. Taking part in this study is your choice. You may refuse to join or leave the study at any time without affecting your health care.

This authorization form will explain exactly what information is collected for this research study and who will see this private information about your health. If you have any questions, please ask Dr. [PI] or [study coordinator].

This study is sponsored by a grant from the National Institutes of Health. Portions of Dr. [PI]'s and [his/her] research team's salaries may be paid by this grant.

RIGHT NOT TO PARTICIPATE OR TO WITHDRAW

You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor and the Clinical and Data Coordinating Centers.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at [site name]. If you do decide to withdraw, we ask that you contact Dr. [PI] in writing and let [him/her] know that you are withdrawing from the study. [His/her] mailing address is [address].

RIGHT TO REFUSE TO SIGN AUTHORIZATION

You may refuse to sign this authorization. If you do not sign this form, you will continue to receive appropriate medical care, but not as a part of this study.

CONFIDENTIALITY

Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except as addressed in this authorization form, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of [site name]. For records disclosed outside of [site name], you will be assigned a unique code number. The key to the code will be kept in a locked file in Dr. [PI]'s office. These groups will also be in compliance with the Federal Privacy Regulations.

As part of the study, Dr. [PI] and [his/her] study team will report the results of your study-related laboratory tests, history, exam, electrocardiograms, procedures and x-rays, as necessary, to some or all of the following:

- The Clinical Coordinating Centers at St. Luke's-Roosevelt Hospital (NY) and Mount Sinai Medical Center (Miami, FL)
- The Angiographic Core Laboratory at Vancouver General Hospital
- The Data Coordinating Center at Maryland Medical Research Institute
- The Economics and Quality of Life Coordinating Center at Duke University
- The Electrophysiology Coordinating Center at the University of Maryland

Version date February 5, 2003

EXHIBIT 10-B
SAMPLE
DATA USE AGREEMENT

Letter of Agreement for Clinical Trials & Surveys Corp. (C-TASC) or Maryland Medical Research Institute (MMRI) to receive Limited Data Sets from Clinical Sites participating in the _____ Study.

The Coordinating Center for study _____ funded by _____ serves as the Data Management and Analysis Center for this study. To fulfill these responsibilities, the designated Coordinating Center will receive Limited Data Sets from the Clinical Centers that enroll, treat and follow patients. The Health Insurance Portability and Accountability Privacy Rule specifies that prior to submission to the Coordinating Center of data for the individual patients enrolled in the study, 18 types of individual identifiers must be excluded. The direct identifiers that must be excluded are listed in the attached table. The investigators of the Coordinating Center at Clinical Trials & Surveys Corp. and Maryland Medical Research Institute also agree to be in compliance with the Federal privacy regulations. That includes assurance that all of the following steps will be taken:

1. The Limited Data Set will not be used or disclosed other than as permitted by the Data Use Agreement or as otherwise required by law;
2. Appropriate safeguards will be taken to prevent the use or disclosure of the information other than as provided for in the Data Use Agreement;
3. Covered entity releasing this information will be notified if any use or disclosure of the information not provided for by the Data Use Agreement will occur;
4. Investigators agree to insure that any agents, including a subcontractor, to whom the recipient provides the Limited Data Set agree to the same restrictions and conditions that apply to the recipient with respect to the Limited Data Set; and
5. Investigators confirm that there will be no attempt to identify the information or contact the enrolled individuals.

EXHIBIT 10-B
SAMPLE
DATA USE AGREEMENT (cont.)

To further assure the privacy of the participants in the study and to comply with existing regulations as stipulated by the NHLBI (or other sponsor), a more limited Public Use Data Set will be prepared for delivery to the NHLBI (or other sponsor). The data will be modified as follows:

A. Identification of the Clinical Site of enrollment will not be provided;
B. All dates will be converted to dates from entry into the study. Any follow-up information will be coded as time after enrollment;
C. Variables that might lead to the identification of the study participants or variables that are sensitive, inaccurate or of limited scientific utility will be deleted;
D. All data for study participants who refused to have the data shared with other researchers will be deleted; and
E. Variables with low frequency which might be used to identify enrolled participants will be recoded or omitted.

To assure that all of the above steps are taken to maintain the privacy of the individuals enrolled in the study, all Coordinating Center staff receive regular training in all the required procedures for protecting all study records in the Coordinating Center. That includes maintaining all of the study patient files in locked cabinets and assuring that, after each use of patient records, the records are filed in the locked files and in computer files that are protected in several ways to protect access except by authorized users.

TABLE FOR EXHIBIT 10-B

LIMITED DATA SET

A data set that excludes all of the following direct identifiers can be considered a Limited Data Set.

Names	Certificate/license Numbers
Postal Address Info (if other than city, state, zip)	VIN and Serial Numbers, License Plate Numbers
Telephone and Fax Numbers	Device Identifiers, Serial Numbers
E-mail Address	WEB URLs
Social Security Number	IP Address Numbers
Medical Record, Prescription Numbers	Biometric Identifiers (Fingerprints)
Health Plan Beneficiary Numbers	Full Face, Comparable Photo Images
Account Numbers	

SAMPLE REQUEST FOR WAIVER OF CONSENT AUTHORIZATION

PI: [redacted]
TITLE: [redacted]
Date: February 24, 2003

Dear Dr. [redacted]

Pursuant to 45 CFR 46.116(d) and 45 CFR 164.512(i)(2), ~~W~~we are writing to request that the St. Luke's-Roosevelt Hospital Center IRB grant a waiver of consent authorization to the Occluded [redacted] Clinical Coordinating Center (CCC). We will indicate below how the [redacted] intends to fulfill the requirements of such a waiver. For your convenience, the requirements for such a waiver, used in preparation of this document, are provided as an attachment.

Statement of Protected Health Information (PHI) Needed

As the Clinical Coordinating Center for the [redacted] we serve many functions. Three of our functions are impacted by the HIPAA Privacy Rule:

1) Assisting sites with the daily conduct of the study, including providing 24 hour/day, 7 day/week assistance with eligibility and protocol questions
2) First case reviews
3) Evaluating adverse events

All OAT-participating centers in the U.S. will obtain authorization from each patient enrolled in OAT, as required by the HIPAA Privacy Rule. This request for waiver of authorization is specific to participating centers that are located outside the U.S. Approximately half of the 236 centers enrolling (as of February 24, 2003) are located outside the United States.

The PHI used by the CCC include dates: dates of service, dates of procedures, dates of events and dates of birth. In section 1(a) and section 5, below, we outline why it is necessary for the CCC to use this protected health information.

We outline below how we plan to protect the PHI against improper use or disclosure.

1(a) The staff at the CCC will not use or disclose the protected health information except as necessary to perform each of the following tasks:

- Answer eligibility questions. As the CCC it is our responsibility to respond to questions we receive from enrolling centers. We are available in our office or by pager 24 hours/day, 7 days/week to answer questions. Questions asked by site staff may include dates of service, as the following example illustrates: One of the inclusion criteria for OAT is a totally occluded infarct related artery, confirmed by coronary angiography, 3-28 days after myocardial infarction (MI). Day 1 is the (calendar) date of MI. Day 3 is the first day that a qualifying angiogram may be performed, for inclusion into OAT. Site staff often call the CCC and ask questions about this important, protocol-related timing issue. In order to adequately advise them, we need to know dates of service and MI. Many questions are asked by phone. We record in a database a brief summary of each phone conversation, but will not after April 14 include ~~in such a summary any PHI~~any PHI in this summary after April 14, 2003.

  Without a waiver of authorization, we will be unable to answer the inquiries of international enrolling centers. Preventing us from answering protocol and eligibility questions would significantly deter enrollment from these sites. Failure to complete the study due to reduced international enrollment does a disservice to patients already enrolled.

- Perform first case reviews. In our capacity as the Clinical Coordinating Center, we confirm the accuracy of the Case Report Forms (CRFs) for the first patient and randomly selected

patients thereafter, enrolled at every site. As an NIH-funded study we do not have the funds to pay for on-site monitoring, so these first-case reviews are an important quality control function performed by the CCC. To this end, we request that the site send us the following: a copy of the baseline CRFs and copies of all supporting source documentation, including but not limited to the history and physical, laboratory reports, progress notes, and discharge summary. Site staff are instructed to black out the patient name throughout these materials prior to sending this information to the CCC. Revised instructions will be provided to ensure that unnecessary PHI, such as medical record number, address, phone number, device serial number (where applicable), and health insurance plan number are also blacked out.

PHI that are included in these materials and which are necessary for review of the case are dates, in particular, dates of service.

Quality of data is a primary concern for any study. If data gathered for the first case enrolled cannot be confirmed to be correct, then we cannot rely on the quality of subsequent data collected by those sites. Data analyses performed using unverified data may lead to erroneous conclusions.

- Evaluate adverse events. When a patient experiences an adverse event at the site, the study coordinator notifies the Clinical Coordinating Center, the Data Coordinating Center, and records the event on the CRFs. Supporting documentation is requested as necessary, and evaluated to determine whether the event is in fact an adverse event. The Study Chair then completes a form, which is filed in the CCC files and is sent to the Data Coordinating Center. Please be advised that the Data Coordinating Center, which is at Maryland Medical Research Institute, is not a "covered entity" and is not bound by the Privacy Rule.

  Without a waiver of authorization, international sites would be unable to advise the CCC of such events. Preventing the evaluation of events occurring at international centers compromises patient safety.

1(b) The PHI used in the above three functions will be kept for the duration of the study and destroyed three years after the end of the study, as per NIH guidelines. The study is expected to be completed in December 2006. Three years after that time, all PHI collected at the CCC in accordance with the above three functions can and will be destroyed.
1(c) The PHI will not be reused or disclosed by the CCC except as described in this document. If any data from this study are disclosed to or used by any other research organization, steps will be taken first to de-identify the data.

(2) Granting this waiver of authorization will not adversely affect the rights and welfare of the subjects. The PHI disclosed to and used by the CCC will not affect the individual subjects.

(3) The research could not be practicably carried out without this waiver. We are obtaining authorization from patients enrolled in the United States, as required by law. However, the logistics of bringing international centers to compliance with this federal law are complex and would overwhelm the conduct of the study. We are in the fourth year of this research study and do not have any funds allocated in the current grant to cover additional costs. In order to bring international centers into compliance, the authorization form would have to be translated into each local language, then the accuracy of the translation would have to be verified. This translation, back-translation, and review process, for each language, is extremely expensive and time-consuming. In addition, it is our experience that each country prefers slightly different translations; for example, our Canadian, Belgian, and French sites have all prepared different versions of the French-language informed consent form. After each translation is verified, each center would then be required to submit the authorization to their local IRB or Ethics Committee. Most non-US IRBs or ECs grant IRB approval for the duration of the study; as an NIH-funded study we already substantially increase the workload of these centers by requiring annual IRB or EC review. Adding an additional review, of an authorization form based on a U.S. federal law

solely for the purpose of CCC use of certain PHI would cause an unfair and enormous burden on these centers. HIPPA regulations are not applicable at these international sites. The regulatory demands on them are already overwhelming, not remunerated and an extra burden would likely lead to their withdrawal from the study.

(4) If any pertinent information should become available, solely based on the CCC's use of the PHI as described above, every effort would be made to notify the affected research subject(s) immediately.

(5) The research could not practicably be conducted without access to and use of the protected health information. The functions of the CCC as described above are critical to the successful conduct of the research study and to our role as the Clinical Coordinating Center. Without use of the PHI we would be unable to:

answer questions asked by our enrolling centers, thereby jeopardizing enrollment and possibly completion of the study;

verify the accuracy of the data collected, which casts suspicions on the accuracy of any conclusions drawn from analyses of these data; and

obtain accurate information on whether an adverse event has occurred, which jeopardizes patient safety.

Both the success of the trial and the safety of all enrolled patients depend upon the ability of the CCC to perform its duties as outlined in the original grant proposal.

If you have any questions, please feel free to contact me by phone at [redacted] or by email at [redacted] or you may contact [redacted] the [redacted] Project Manager, at [redacted] or by email at [redacted] Thank you for your consideration.

Sincerely,

[redacted]

[redacted] Study Chair

JUSTIFICATION FOR WAIVER OF CONSENT AUTHORIZATION PROCEDURE
Combined for Common Rule and HIPAA

"An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section [see 45 CFR 46.116(a), or waive the requirements to informed consent provided the IRB finds and documents that:

(1) the research involves no more than minimal risk to the privacy of the subjects, based on at least the presence of the following elements:
- *(a) an adequate plan to protect the identifiers from improper use and disclosure*
- *(b) an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and*
- *(c) adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;*

(2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;
(3) the research could not be practicably carried out without the waiver or alteration; and
(4) whenever appropriate, the subjects will be provided with additional pertinent information after participation; and
(5) the research could not practicably be conducted without access to and use of the protected health information."

In addition, HIPAA requires a statement of: *Protected health information needed. A brief description of the protected health information for which use or access has been determined to be necessary by the IRB ore privacy board has determined, pursuant to paragraph (i)(2)(ii)(c) [item (5), above] of this section.*

CHAPTER 19

QUALITY CONTROL OF DATA COLLECTION

19.1 Training and Certification for Data Collection

In a collaborative study with multiple Clinical Centers collecting data, it is important to strive for uniformity in data collection among the centers. For certain data collection tasks in PEDS-C, standardized knowledge of the task being documented as well as knowledge of the PEDS-C protocol is necessary. For some tasks, MMRI or their designee will provide standardized teaching. For other tasks, previous training will be sufficient as long as these tasks are within the standard scope of practice for this individual. Training or competence will be required in the following areas:

1. Growth and Body Composition Measures
2. Physical Exam Procedures
3. Pregnancy Testing
4. Compliance Procedures
5. Biological Sample Handling and Shipping
6. Randomization and Drug Assignment
7. Study Drug Management
8. Diet and Physical Activity Data Collection
9. Monitoring Requirements and Regulations
10. Psychosocial/Quality of Life Data Collection
11. Depression Screening and Management
12. Adverse Event Reporting and Safety Monitoring
13. Forms Completion and Edits

Persons attending centralized training sessions will be certified to collect data and to train other personnel in standard data collection techniques. Personnel who join PEDS-C after the centralized training sessions will be trained in the Clinical Center by someone who has already been certified. A certification number will be assigned at the Clinical Center. (See Chapter 20)

The first two digits of the certification number will consist of the Clinical Center ID (01-11 see the PEDS-C Address Directory) and the last three digits will be assigned consecutively beginning with 001 at each Clinical Center. The certification number will be reported to the DCC/CRO on the Certification Number Report form. The certification number must appear on each data collection form completed. The DCC/CRO will carry out quality control checks by certification number in order to ensure that data collectors are trained and certified, and to detect routine mistakes as well as data manipulation.

When unacceptable error rates are detected, the DCC/CRO will contact the Clinical Center PI to discuss the problem and possible solutions.

19.2 In-Clinic Training Checklist

New personnel who have not had the opportunity to attend a centralized PEDS-C training session may be trained in-clinic by a certified data collector or the visiting CRA monitor. They should become familiar with the PEDS-C Protocol, the Manual of Procedures (MOP), and the study data collection forms. All in-clinic personnel who will collect study data should be certified, including the site Principal Investigator.

The following general design and methods detailed in the Manual of Procedures will be covered during in-clinic training for all data collectors:

Subject	MOP Section
Introduction to PEDS-C	Chapter 1
Data Collection Schedule Summary	2.1
Screening , Recruitment, Randomization	Sec. 2.2.12, Chapters 3, 5.
Informed Consent	Chapter 4
Data Collection Procedures	Chapter 7
Monitoring Requirements	Chapter 10
Pregnancy Testing	Chapter 13
Patient Withdrawal/Close-Out	Chapter 15
Adverse and Serious Adverse Events Reporting	Chapter 17
Regulations	Chapter 18
Quality Control of Data Collection	Chapter 19

In addition, personnel in each of the following areas of expertise will review the following MOP chapters or sections:

Vital Signs and Physical Exam: Sections 2.2.1- 2.2.2, 11.1- 11.2.
Blood Drawing and Sample Handling: Sections 2.2.3-2.2.9; 6.4; and Chapter 12.
Drug Distribution, Handling, and Patient Compliance: Section 2.2.15, and Chapters 5, 6, and 16.
Ophthalmology Exam: Section 2.2.10
Growth Measures: Section 2.2.13, Chap. 8, and Section 11.3
Depression and QL Measures: Section 2.2.14, and Chapters 9 and 14.

The attached In-Clinic Training Checklist should be completed, signed by the Clinical Center Principal Investigator, and kept on file at the Clinical Center.

When data collectors leave the Clinical Center or are no longer collecting data, they will return a De-Certification From to the DCC/CRO.

12/1/04

PEDS-C

IN-CLINIC TRAINING CHECKLIST

Clinical Center Number: __ __

Name of Data Collector Trained: _____

Complete area(s) below in which the above data collector has received in-clinic training. Record the name of the certified trainer or CRA and the date trained in each area:

Area	**Certified Trainer or CRA**	**Date of Training**
General Design and Methods		
Vital Signs and Physical Exam		
Blood Drawing and Sample Handling		
Drug Distribution, Handling, and Patient Compliance		
Ophthalmologic Exam		
Growth Measures		
Depression and QL Measures		
Other Area		
Other Area		

Principal Investigator's Signature: _____ **Date**: _____

CHAPTER 20

Question by Question Instructions for Data Collection Forms

20.1 Certification Number Report (Form 01)

The purpose of the Certification Number Report (Form 01) is to report to the DCC/CRO certification numbers assigned to data collectors at the Clinical Centers. The Study Coordinator at each site will keep a log of previously assigned certification numbers and assign new numbers as new data collectors are trained.

Questions on the **Form 01** should be completed as follows:

Ques. 1- Enter your Clinical Center's two-digit identification number from the PEDS-C Address Directory :

01= Children's Hospital Medical Center- Cincinnati, Ohio
02= University of Florida- Gainesville, Florida
03= Children's Hospital of Philadelphia- Philadelphia, Pennsylvania
04= Children's Hospital Boston- Boston, Massachusetts
05= George Washington University- Washington, D.C.
06= Indiana University- Indianapolis, Indiana
07= Children's Hospital and Regional Medical Center- Seattle, Washington
08= The Children's Hospital- Denver, Colorado
09= University of California- San Francisco, California
10= Johns Hopkins University- Baltimore, Maryland
11= Columbia College of Physicians and Surgeons- New York, New York

Ques. 2- Enter your name in block letters: **A**. First name, **B**. Middle initial, and **C**. Last name. If you have no middle initial, leave the box blank. Do not use an initial for your first name.

Ques. 3- If you have attended a centralized training session organized for all PEDS-C sites, such as the session held in Baltimore on June 17-18, 2004, answer this question "yes". Sessions held at your Clinical Center for your center's personnel only are not considered "centralized".

Ques. 4- Enter the dates that the centralized session was held in months, days, and years. If the session was one day only, enter that date for both the starting and ending dates. Remember to zero fill from the left for single digit months or days. For example, January

2, 2005 will be recorded as 01/02/2005.

Ques. 5- Enter the five-digit certification number assigned by your clinic's Study Director. The first two digits of the certification number will always be the Clinical Center ID number (01-11) as found in the PEDS-C Address Directory (see above list). The second three digits will represent the data collector and will be consecutive numbers starting with 001 at each Clinical Center. For example, the first data collector certified at the Baltimore Clinical Center will be 10-001 and the fifth data collector certified at Children's Hospital Boston will be 04-005, and so forth.

Ques. 6- Enter the date that the certification number was assigned in months, days, and years. Then skip to Item 12, the Informed Consent statement. It is not necessary for you to report additional in-clinic training if you attended a centralized training session.

Ques. 7- If you did not attend a centralized training session and were trained in your clinic by a certified person or the PEDS-C site monitor, answer ques. 7 "yes". In-clinic certification requires a guarantee from the site Principal Investigator that the data collector is familiar with the PEDS-C Manual of Procedures (MOP). See MOP Section 19.2 for the In-Clinic Training Checklist which will be used to document in-clinic training. This checklist should be completed and filed in the clinic with a copy of the data collector's Form 01.

Ques. 8- Complete the date of the training as instructed above in Ques. 4.

Ques. 9- Enter the name of the certified trainer. If you had more than one trainer, enter the name of the principal trainer.

Ques. 10-11- Enter the certification number and date assigned as in Ques. 5-6 above.

Ques. 12 - Informed Consent- You are being asked to agree in writing to basic standards of ethical conduct associated with your position as a data collector in PEDS-C. Sign on line **A**. to indicate that you agree to abide by these standards. If you feel that you cannot agree to any one of these guidelines, please discuss the issue with your Principal Investigator. Your Principal Investigator will sign on line **B**. to indicate that he/she has reviewed the Form 01 and that your training for certification as a PEDS-C data collector has been successfully completed.

The Certification Number Report (Form 01) will be faxed to the DCC/CRO at 410-323-4729. Clinical Centers have the option of holding the Form 01 for pick-up by the

CRA Monitor at his/her monthly visits. However, Clinical Centers should keep in mind that the Form 01 must be received at the DCC/CRO at least four days in advance of receiving data collection forms containing the certification numbers being reported. If the Form 01 has not been received at the DCC/CRO, the data system will not accept the any data form containing that certification number and a query will be sent to the Clinical Center.

20.2 De-Certification Report

Study personnel who no longer collect data should complete a De-Certification Report Form 09. After the receipt of that report forms containing their certification number will no longer be accepted by the fax data entry system at the DCC/CRO.

20.3 Screening Visit 1 (Rev 3) and Screening Visit 2 Forms

The purpose of the Screening Visit 1 (Form 02) and Screening Visit 2 (Form 03) Forms is to record information needed for the evaluation of eligibility on the Eligibility Summary Form. All screening assessments will be obtained from 1 to 35 days before the baseline visit. The liver biopsy must be performed within 24 months of screening visit 1.

Before starting the Screening Visit 1 Form 02, call the DCC/CRO to get a Patient ID number. Assign the patient a three letter code from the list supplied by the DCC/CRO. Record them in the header of the form. Since the Form 02 can only be used during screening, the "ELG" code has been pre-printed in the Week # boxes. The "Date of Assessment" is the date that the form is completed.

Demographic Information

Ques. 1: Begin by obtaining demographic information from the patient or parent/guardian. Record the patient's birth date in months, days, and years. Don't forget to zero fill left hand boxes for single digit responses.

Ques. 2: Code the patient's gender by observation.

Both parts of question 3 conform to 1997 OMB Directive 15 guide lines which specify two ethnic categories and five racial categories. The categories are socio-political constructs and should not be considered anthropological in nature.

Ques. 3 A.: Ask for the patient's self-identified ethnic group. Choose one answer. The

term “Hispanic or Latino” refers to a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.

Ques. 3 B.: Ask for the patient’s self-identified racial group. Answer “yes” or “no” for parts 1-6 of the question. Definitions of each racial category are as follows:

American Indian or Alaska Native- A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian- A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

Black or African American: A person having origins in any of the black racial groups of Africa.

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Vital Signs and Physical Measurements

Ques. 4-8: Vital signs and physical measurements will be obtained from the patient.

Informed Consent

Ques. 9-10: Make sure that informed consent has been obtained from the parent/guardian and that assent has been obtained from the patient. Both the patient and the parent/guardian must consent for the patient to participate in the study.

Medical History

Ques. 11: Indicate PAST medical conditions (not within normal limits) in each of the organ systems or conditions listed (A. through S.) If the system or condition was not within normal limits, # 1= “No”, specify or comment in the space provided below #2. Try to keep comments within the area provided for each organ system or condition. If the condition is still a problem, the answer to #3 should be “Yes”.

Ques. 12: Indicate the date of the patient's initial Hepatitis C (HCV) diagnosis. It may help to ask the parent/guardian how old the patient was at initial diagnosis. A best guess at a month and year is an acceptable answer. If a day cannot be specified, leave the field blank.

Ques. 13: Indicate the probable route of HCV transmission to the patient.

Ques. 14: Record information on the patient's CURRENT medications. Include over-the-counter as well as prescribed medications. Route of administration abbreviations are: PO= By mouth, PR= Per Rectum, SC= Subcutaneous, IM= Intramuscular, and IV= Intravenous.

Ques. 15: Ask the patient to swallow a 100 mg placebo tablet (supplied by Hoffmann-La Roche) in your presence. Supply the patient with a drink and suggest that he/she take a sip before trying to swallow the tablet. A practice session with candy about the size of the 100 mg tablet may help. If the patient is unable to swallow the tablet on the first try, suggest trying again later.

Ques. 16: If the patient is a sexually active female at least 10 years old or a sexually active male, answer questions 17 and 18; otherwise skip to question 19. Indicate all types of contraception used by answering each part of the question (A through G) "Yes" or "No". If the patient is sexually active male or a sexually active female older than 10 who does not use two forms of contraception (one of them a barrier method), the case will be brought to the attention of the Clinical Center Principal Investigator and a decision on the risk of enrolling the patient will be requested.

Ques. 17: If the patient is a sexually active male whose current partner is pregnant, he should not be enrolled in the study.

Physical Exam

Ques. 19: Physical exams of PEDS-C patients should be conducted according to each Clinical Center's standard medical practices. Indicate whether each body area (A. through G.) is within normal limits. If the answer is "No" (# 1), specify or comment in the space provided under # 2. Try to keep comments for each area within the space provided.

Ques. 20: Indicate if the listed organ systems (A. through G.) are within normal limits. If the answer is "No", specify or comment under # 2. Try to keep comments within the space provided.

Ques. 21: Indicate whether enough blood was drawn to perform all laboratory tests required at screening visit 1. If sample could not be obtained for a test, record "Unable to Obtain" and schedule an additional screening visit to draw another sample for the remaining tests.
Use the Screening Visit 2 Form 03 to report the test samples obtained at the second screening visit.

Depression Screen

Ques. 22-24: Since all patients are required to be younger than 18 years at screening visit 1, they will be screened for depression using the Children's Depression Inventory (CDI Form). See MOP section 20.4 for detailed instructions on administration and scoring the CDI.

Ophthalmologic Exam

Ques. 25: See MOP Section 20.6 for detailed instructions on forms used to document the ophthalmologic exam. Record the date of the Baseline Ophthalmology Summary form. Answer "Yes" if the examining ophthalmologist reported that the patient has severe retinopathy.

Liver Biopsy

Ques 26A: Based upon protocol requirements, the liver biopsy must be within 24 months of the screening date. If it is not within 24 months of the screening visit, the patient is ineligible unless an exemption is granted.
Ques 26A: If yes, record the date of the patient's liver biopsy .

20.4 Eligibility Summary Form 04 Revision 1 (Rev 1)

The revision 1 (Rev 1) version of the Form 04, including changes to questions 4, 14E and 32 required by the DSMB and the addition of question 42 on exemptions for ineligible patients, should be used. The revision number is printed in the upper right-hand corner of the form. Do not use the Rev 0 version of this form. The Eligibility Summary Form 04 will be used as a checklist of inclusion and exclusion criteria to make sure that all eligibility criteria have been covered during the screening process. Criteria which are

reversible and could change on a subsequent re-screening are marked with a "*" below. When re-screening keep in mind that time-dependent criteria, such as having a liver biopsy within 24 months of screening, must also be satisfied. When patients have been assigned patient IDs and letter codes, are reported ineligible on the Form 04, and are subsequently re-screened, they must be assigned new patient IDs and letter codes. After the assignment of the new codes, both the new and the old codes must be reported to the DCC/CRO on the Re-Enrollment Report Form. See MOP Sections 3.3 and 20.6 for details on re-screening.

The Eligibility Summary Form 04 is divided into four sections as follows:

Inclusion Criteria

Ques. 1* The lower age limit is 5 years old at the patient's last birthday on the day of the first screening visit. The upper age limit is 18 years at the patient's last birthday on the day of the randomization phone call. The patient must not have reached his/her18th birthday on the day of the first screening visit. If the patient has not yet reached his/her fifth birthday on the day of the first screening visit, they may be re-screened later.

Ques. 2* See instructions for Ques. 15 on the Screening Visit 1 Form 02. A patient who is otherwise eligible can be re-screened later if he/she could not swallow the tablet at the first visit.

Ques. 3*: The Protocol requires that the eligible patients demonstrate evidence of HCV viremia by any test on two occasions separated by at least six months. If the patient has had at least one positive HCV test 6 months prior to the date of the first screening visit, the HCV-RNA clinical test done at screening will constitute the second required test. If the patient has a positive HCV-RNA test that is not at least six months old, they may be re-screened at a later date.

Ques. 4: A liver biopsy, performed as a part of the patient's normal care, within 24 months of the first screening visit is required for eligibility.

Ques. 5-7: In general, test results performed by PEDS-C are non-reversible eligibility criteria.

Ques. 8: See instructions for questions 9-10 on the Screening Visit 1 Form. If the parent/guardian or the patient refuses initial consent and later consents, they may not be re-screened.

Ques. 9: This question is designed to summarize the answers to questions 1-8. In order to satisfy all inclusion criteria, all of the questions must be answered "Yes". If one or more questions are answered "No", put a check in the box provided. Make sure that the check is inside the box and does not touch the sides of the box.

Exclusion Criteria

Ques. 10: Patients with any prior treatment with interferon or Ribavirin.

Ques. 11*: Patients who have received any investigational drug less than six weeks prior to the first dose of PEDS-C study drug at baseline will be excluded. If a patient has taken any investigational drug within six weeks of baseline and agrees to stop, they may be re-screened later.

Ques.12*: Patients who have received any systematic antiviral therapy less than six weeks prior to the first dose of PEDS-C study drug at baseline will be excluded. An exception will be patients who have taken or are expected to require acyclovir for herpetic lesions. If the patient has taken systematic antiviral therapy six weeks prior to the first dose of study drug at baseline and stops the therapy, they may be re-screened later.

Ques. 13-18: These positive tests and medical conditions at screening are not reversible eligibility criteria.

Ques. 20: See MOP Section 14.1 for a detailed discussion of depression screening and management. Major depression according to study criteria or a history of a severe psychiatric disorder are not reversible eligibility criteria.

Ques. 21-29: These positive tests and medical conditions at screening are not reversible eligibility criteria.

Ques. 30: The Principal Investigator (PI) at the Clinical Center has the option of considering any patient unsuitable for participation in the study.

Ques. 31: The patient is engaged in active substance abuse. The assessment of this condition will depend on the judgment of the Clinical Center PI. The patient will not be re-screened at a later date.

Ques. 32: Patients with a sibling already enrolled in the PEDS-C will be excluded.

Ques. 33: Sexually active females of child bearing potential (age 10 or older) and sexually active males who do not indicate on Screening Visit Form 02 question 17 that they are

using two forms of effective birth control will be excluded. They will not be re-screened.

Ques. 34: Females with a positive serum pregnancy test within 7 days of the initiation of study drug treatment or females who are breast feeding will be excluded from the study. The will not be re-screened at a later date.

Ques. 35: Males whose sexual partners are pregnant will be excluded from the study. They will not be re-screened.

Ques. 36: This question is designed to summarize the answers to questions 10-35. In order to satisfy all inclusion criteria, all of the questions must be answered "No". If one or more questions are answered "Yes", put a "1" (not a check) in the box provided. Make sure that the "1" is inside the box and does not touch the sides of the box.

Concomitant Medication and Treatment

Ques. 37*: Patients currently taking anti-neoplastic and/or immunomodulatory treatments, including steroids and radiation, are excluded from the study. If treatment is discontinued, they may be re-screened at a later date.

Ques. 38*: Patients currently taking any investigational drugs, herbals, and/or other remedies for possible or perceived effects against HCV will be excluded from the study. If these drugs or remedies are discontinued, patients may be re-screened later.

Ques. 39*: Patients currently taking a total dose of acetaminophen that exceeds one gram per day will be excluded from the study. Patients may be re-screened if they eliminate or reduce their daily dose.

Ques. 40: This question is designed to summarize the answers to questions 37-39. In order to satisfy all inclusion criteria, all of the questions must be answered "No". If one or more questions are answered "Yes", put a "1" in the box provided (not a check). Make sure that the "1" is inside the box and does not touch the sides of the box.

Eligibility Summary

Ques. 41-42: This section is designed to summarize the answers to questions 9, 36, and 40. If <u>none of the boxes</u> contain a "1", the patient is eligible to participate in the study. Obtain a copy of the ATRS Voice Response Worksheet C (Randomization) and complete the questions on the sheet before calling the DCC to randomize the patient. You will need

your personal PIN, your Hospital Password, the patient's ID number and letter code, the patient's HCV genotype number (1-6), and the patient's body weight in kg and height in cm to record on Worksheet B. Next, call the DCC ATRS number (1-800-731-3103) at any time and follow instructions. If you are unable to connect with the ATRS System, please call cell phone number 410-299-6879 or beeper number 410-416-3935. Enter your area code, telephone number, and # after the beep. After you have received medication package numbers for the patient, record them on Worksheet D, and key them back for verification.

If one or more of the boxes for questions 9, 36, and 40 contain a "1", the patient is not eligible. Indicate in question 42 if the patient has received an exemption from the PEDS-C Exemptions Committee. An Eligibility Criteria Exemption Form 07 should be completed. If the patient has received an exemption, he/she may be randomized. If the patient is ineligible and has not received an exemption, do not call the DCC/CRO to randomize the patient.

20.5 Children's Depression Inventory (CDI Form 06)

The CDI Form 06 will be used detect depression in patients at screening and at subsequent follow-up visits. It will be self-administered to patients aged 7 to 17 years. For patients aged 5 and 6 years, the parent will be asked to respond for the patient. The form can be read to patients by an interviewer if they are unable to read and understand it for themselves. If the patient is aged 18 or more, the CES-D Form 26 should be used to detect depression instead of the CDI Form 06.

Instructions- If the Form 06 is self-administered, tell the patient to begin by reading the instructions and completing the test item. Emphasize that they should respond about how they have felt in the LAST TWO WEEKS and that only one item should be selected in each group of three. Check the test item before leaving the patient alone to complete the rest of the form. If he/she has filled more than one bubble, repeat the instruction. Do not allow the parent or patient to write their name on the form.

If the form is being read to the patient, begin by reading the instructions and completing the sample question. Ask if the patient has any questions before asking the rest of the questions.

Questions 1 through 27- If the child or parent comment that none of the three choices provided in questions 1-27 really apply, instruct them to make the choice that fits them BEST. For younger children or those with reading difficulties, it may be necessary to read the instructions and/or questions aloud while the patient follows along on his/her own copy of the form. If the form is self-administered, do not allow the patient to erase mistaken responses. Rather, the patient should draw and X through the incorrect response and fill in the correct bubble.

All CDI Forms should be checked for omissions, multiple responses, and Xed out responses before the patient leaves the Clinical Center. If questions were skipped, the data collector should point out the omission and ask the patient to complete the question. If responses were Xed out, the data collector should initial the change to the Xed response and check the correct response. All questions must be answered to score the CDI.

Sensitive Questions- Parents or patients may question the personal nature of the questions being asked. It sometimes helps to explain that the Form 06 is a screening tool that all PEDS-C patients answer and that many questions will not apply to them.

Form 06 Scoring- The CDI Form will be scored in the clinic before the patient leaves. The DCC/CRO has provided each site with scoring materials (three templates and a worksheet) for the PEDS-C Teleform version of the CDI. Scoring materials from Multi-Health Systems cannot be used for the PEDS-C form. Transparent scoring templates have been provided for each page of the CDI Form. The templates provide the correct codes for the responses marked. Place the scoring template over the CDI Form page and make sure that the form cornerstones (black boxes in each corner) line up. Record the code for the bubble darkened for each question on the CDI Scoring Worksheet. After the codes for each page are recorded, add up the totals for each page (a calculator may help to improve accuracy), and add up the total of the three pages to get the Total CDI Score. Check your addition after the first totals have been made. If the Total CDI Score is greater than 19 at screening, the patient will be considered depressed and will not be enrolled in the study. If the Total CDI Score is greater than 19 at baseline, do not begin the study drug and begin a

Depression Management Tracking Form. If the Total CDI Score is greater than 19 after baseline, a Depression Management Tracking Form will be started.

20.6 Ophthalmology Exam Forms

The Baseline Ophthalmology Summary Form 05 and the Follow-up Ophthalmology Summary Form 61 will be used along with two worksheets: 1) the Ophthalmology Exam form and the 2) Ophthalmology Exam Worksheet. The Ophthalmology Exam form was adapted from the Johns Hopkins Hospital Wilmer Eye Institute exam form for use in PEDS-C . The Ophthalmology Exam Worksheet is intended to summarize the results recorded on the much more complicated Ophthalmology Exam form. Both of the worksheets will be completed by the examining ophthalmologist and returned to the PEDS-C Clinical Center. Clinical Center staff will use them to complete the Forms 05 and 61 which are designed for data entry at the DCC/CRO.

Baseline Ophthalmology Summary Form 05

The Form 05 will be used during the screening period only and "ELG" will be recorded in the Week # header boxes.

Ques. 1: Record the date that the ophthalmologist performed the patient's baseline exam from question #2 of the Ophthalmology Exam Worksheet (OEW).

Ques. 2: Record the name of the examining ophthalmologist from question 3 of the OEW.

Ques. 3: If the patient has severe retinopathy (question # 4 on the OEW) do not enroll the patient in the study.

Ques. 4: If the patient was referred to another ophthalmologist, record the date of the referral in B. and the name of the ophthalmologist referred to in C.

Ques.5: If the patient withdrew from PEDS-C, record the date of the Withdrawal/Close-Out Form.

Follow-up Ophthalmology Summary Form 61

The Form 61 is designed to be completed for <u>regularly scheduled</u> ophthalmology follow-up exams at weeks 24 and 48 and also for <u>unscheduled</u> ophthalmology exams. The sequence number box in the header of the form should always be filled out with 01 for the

only visit performed during that week. If a second unscheduled visit occurs during the same week, the sequence number should be 02. For example, when the regular 24 week follow-up visit takes place the Week # should be 024 and the sequence number should be 01. If a second unscheduled visit takes place during week 24, the Week # should be 024 and the sequence number should be 02. In another possible scenario, an unscheduled visit takes place at week 30. The Week # will be 030 and the sequence number will be 01. If a second unscheduled visit takes place that same week, the Week # will be 030 and the sequence number will be 02.

The Form 61 was designed to identify and track the management of new or worsening ocular disorders during the study drug treatment period or the untreated follow-up.

Ques. 1-2: Record the date of the ophthalmologic exam and the name of the examining ophthalmologist from questions 2 and 3A of the OEW.

Ques. 3: Answer "Yes" if, in the opinion of the examining ophthalmologist, the patient had new or worsening ocular symptoms (question 5 OEW).

Ques. 4 A-C: If the patient was referred to an ophthalmologist other than the PEDS-C examining ophthalmologist, record the date of the referral and the name of the ophthalmologist.

Ques. 5: Describe the nature of the new or worsening ocular symptoms briefly. Summarize question #6 on the OEW completed by the examining ophthalmologist.

Ques. 6: Indicate if the problem was resolved and if "Yes" give the date. If the problem was not resolved, the date of future exams and possible resolution can be reported on a later Form 61s.

Ques. 7: Indicate if the study drug was stopped and the patient was placed on untreated follow-up as a result of the new or worsening ocular symptoms detected.

Ques. 8: If the patient withdrew from the study, record the date of the Withdrawal/Close-Out Form.

20.7 Baseline Assessment (Form 10 Rev 1)

The Baseline Assessment form should be used at the baseline examination on patients who are eligible and have been randomized. It is intended to serve as a check list

for all measures and forms required at the visit. The Week # code will always be 000 and has been pre-printed on the form. Regarding the order of the baseline visit, the quality of life battery should be administered early in the day before patients or parent/guardians become fatigued or upset.

Ques. 1A: If the patient is not willing to continue in the study (will not attend any further visits) after being randomized, they will be withdrawn from the study. Complete the Withdraw/Close-Out Form, record the date of the Withdrawal/Close-Out Form on the Baseline Assessment Form, **Ques. 1B**, and sign and date page 1 of the form. Do not complete the remaining pages of the form, including headers and signatures.

Ques. 2A: The Vital Signs and Symptom Directed Physical is a separate 3 page form required for the Baseline Assessment. Record the date the form was completed in **Ques. 2B**.

Ques. 3-9: These 7 anthropometry measures are to be performed and recorded on the Baseline Assessment Form. Each measure should be taken two times by the same measurer. Measurers should be taken with shoes removed and clothing reduced to a practical minimum. See Manual section 11.2 for further details. If you are not able to take the measure after repeated attempts, fill in the "Unable to Measure" bubble under column C.

Ques. 10 A-B: The date of the DXA scan will be recorded. For further details on measurement procedures see Manual section 11.4.

Ques. 11 A-B: The date of the Bio-electrical Impedance Analysis will be recorded. For further details on measurement procedures see Manual section 11.3.

Ques. 12 A-B: The Three Day Food Diary has been provided in the form of a booklet with blue covers. It will be given to the patient or parent/guardian at the baseline assessment and they will be instructed on how to use it. Record the patient's ID, the Week #, and the Diary Start Date (first day of food intake data collection) on the cover of the booklet before giving it to the patient or parent/guardian. Record the days assigned for the patient to keep the diary on the front cover. They will be instructed to keep the diary <u>during the week following the baseline visit</u> and to record food intake on <u>two week days and one weekend day</u>. Ideally, food intake should be recorded as it is eaten. If the patient is not feeling well, the diary should still be kept. Please review the patient instructions in the front of the

diary, “10 Reminders” and the “Food Description Guide” before instructing the patient. Patients will need to use cup and spoon measures and a ruler to estimate portion sizes. In addition to food intake, vitamin and mineral supplements will also be recorded. Patients are asked to indicate if the days of food intake data collection were typical. If a day was not typical, they will be asked to give a reason. After the patient has completed the Three Day Food Record, it will be analyzed with the nutrition analysis software from ESHA Research. Hard copies of food coding results should be kept with the patient’s records and electronic copies should be sent to the DCC/CRO.

Ques. 13A-B: The Physical Activity Assessment Form is a one-page form required at the time of the baseline assessment. It should be administered by the PEDS-C interviewer sitting with the patient and parent/guardian. Estimates of activity level will be made separately for week days and weekend days. Estimate all hours for weekdays first and then estimate all hours for weekend days. If the patient mentions an activity that is not listed in definitions given for B. through E, choose the category that is the best fit. Note that the difference between “Moderate” and “Intense” activities is that intense activities are sustained for the entire time recorded. Make sure that the hours for each type of day total to 24.0. See Manual section 8.2 for further details.

Ques. 14 A-D: Question 14 records the use of forms recording information on medical events that may have taken place since the patient’s first screening visit. If the patient has not had any problems with serious adverse events or non-serious adverse events, skip to question 15. If more than one AE form was completed, record the dat of the first AE form. The Concurrent Medical Conditions Form has been dropped and should not be completed. Answer question 14B. “No”.

Ques. 15 A-B: Question 15 records the use of any new medicines since the first screening visit. If the patient has not taken any new medicines since the first screening visit, skip to question 16.

Ques. 16 A-B: If the patient is a female 10 years of age or older, a urine pregnancy test will be performed. Record the date of the test and the result. If the urine pregnancy test is positive, confirm the result with a serum pregnancy test. If either the urine or serum results are positive, DO NOT BEGIN DRUG THERAPY and withdraw the patient from the study. Record the date of the Withdrawal/Close-Out Form in Ques. 16 B. 5.

Ques. 17 A-C: If the patient is a sexually active male, ask if his sexual partner is pregnant. If the answer is "Yes", DO NOT BEGIN DRUG THERAPY and withdraw the patient from the study. Record the date of the Withdrawal/Close-Out Form in question 17C.

Ques. 18 A-B: Screening for depression is required at the baseline visit. Administer the Children's Depression Inventory (CDI) if the patient is 17 years old or younger. Administer the CES-D Form if the patient is 18 years old or older. If the patient scores higher than 19 on the CDI or higher than 15 on the CES-D, DO NOT BEGIN DRUG THERAPY and use a Depression Management Tracking Form to collect information on subsequent screening or referrals and whether the patient is withdrawn from the study. If the patient is not withdrawn from the study, he/she may continue with the baseline assessment and receive study drug therapy. If necessary, forms may be held and the patient's baseline assessment may be rescheduled to another day within the 1 to 35 days from screening visit window.

Ques. 19-21: Questions 19 to 21 deal with patient study drug therapy. The first Peg2a injection and RV placebo tablets will be administered in the Clinical Center. Record the time of the first drug administration in clock time (hours, minutes, and AM or PM) and the dose given on the Baseline Assessment. When recording the dose of Peg2a in 19D, zero fill single digit responses after the decimal to the right. Record the first dose of RV in 20D and the number of tablets. Fax the BL prescriptions for Peg2a and RV to the DCC/CRO.

Instruct the patient or the parent/ guardian in the correct method of administering medications. Give the patient or parent/guardian a copy of the Patient's Medication Diary. Record the date of the first scheduled administration by the parent (diary start date) at the top of the booklet cover. Record the three digit codes for the weeks contained in the Diary on the front cover. Since each booklet is collected roughly every month, the codes for the first Diary will be Week 000 to Week 005. They could be Week 000 to Week 003 if the Clinical Center wishes to collect finished diaries more often. In addition, label inside pages with the patient ID, letter code, and the correct codes for Week 1 (000 to 001), Week 2 (001 to 002), Week 3 (002 to 003), Week 4 (003 to 004), Week 5 (004 to 005, and Week 6 (005 to 006). Each week in the dairy contains three pages: one page for recording drug administration information and two pages for recording a maximum of four side effects or illnesses experienced during that week. Space has been provided for recording three

medications taken for each illness. If a study medication was not given, the key on the first page of the booklet will be used to record the reason that the medication was not given. When a reason for not giving the medication does not fit the categories in the key, patients or parent/guardians will be instructed to choose the best answer category. If the reason the dose was not given is #2, dose held or stopped, the dose is not "missed" and a Therapy Stop/Restart Form should be completed. Missed doses are those which are prescribed by the study, but not taken by the patient.

Ques. 22A-E: Question 22 is a checklist of the laboratory tests required at the baseline assessment. All tests should be performed. If you were unable to obtain a sample for the test, mark "Unable to obtain".

Ques. 23 A-G: Question 23 is a checklist of all quality of life tests required at the baseline assessment. Record the date that the test was administered in column 2. Record whether the test was completed by the patient or the parent/guardian in column 3.

Don't forget to sign and complete the certification number on each page of the form. When the form is finished, check the header information on each page to make sure that patient ID, letter code, and date of assessment are the same.

20.8 Treatment Period Assessment Summary – Week 1 Visit

The Treatment Period Assessment Form 21 will be used as a checklist for all forms and measures to be collected at the first treatment period assessment visit. The Week # in the header is pre-printed with 001. Please make sure that the patient ID number and letter code assigned at patient registration are recorded in the header of each page. Check to make sure that the header information on each page of the form is identical.

Ques. 1: If the patient says that they are unwilling to attend further PEDS-C data collection visits, complete a Withdrawal/Close-Out Form and record the date the form was completed in 1B.

Ques. 2: The Vital Signs and Symptom Directed Physical Form 11 is a separate form. Record the date that the form was completed in 2B. Vital signs and physical measurement must be taken for all patients. If the examiner feels that a symptom directed physical is not indicated at the Week 1 visit, he/she may skip to question 9 on the Form 11. If the organ system or body area was not examined, fill in the NA bubble.

Ques. 3: Ask the parent or patient the question printed in Form 21 question 3A: *"Has your child (have you) had any other problems since the last visit?"* In this context "Last visit" means the baseline visit. Adjust the wording according to whether the patient or parent is answering. If the parent or patient answers that they have experienced a concurrent medical condition, a serious adverse event, or a non-serious adverse event, complete the appropriate separate form and record the date the form(s) was completed in the date boxes provided. If more than one AE form was completed, record the date of the first form. The Concurrent Medical Condition Form was deleted 3/15/05. The question should always be answered "No".

Ques. 4: Ask the parent or patient the question in Form 21 question 4A: "Has your child (have you) taken any new medicines, other than those given to you within this study, since the last visit?" Adjust the wording according to whether the patient or parent answers. If the answer is "Yes", complete a separate Concurrent Medications Form 41 Rev 1. The Form 41 Rev 1 contains a check-off question for routine medications and space for three other medications. To report more than three other medications, use multiple Form 41s with the same patient ID number, letter code, week #, and date of assessment in the headers. Only the sequence number in the header of the multiple Form 41s will differ. The first form will be labeled sequence # 01, the second form sequence # 02, and so on. If only one Form 41 is used, the sequence number will still be 01. Do not leave the sequence # boxes in the Form 41 header blank. Concurrent medications taken routinely will be reported at each visit. For other medications lacking a stopped date, the stopped date may be added later by submitting a form correction. In general, other medications should be closed-out after one month.

Ques. 5: If the patient is a female 10 years of age or older, ask her for the first day of her last menstrual period. If she cannot remember the day, ask for her best estimate. If she is at least 10 years old but has not reached menarche, darken the NA bubble after the date boxes. If the girl has reached menarche and shows secondary amenorrhea of one week or more, a serum pregnancy test will be done. If the serum pregnancy test result is positive, stop study drug therapy and move the patient to her first untreated follow-up visit. Complete a Therapy Stop/Restart Form and record the date the form was completed in Form 21 question 5G. At the subsequent untreated follow-up visit use the Untreated

Follow-Up Assessment – Follow-Up Week 4 Form 62. See MOP Table 2-1 for a description of subsequent untreated follow-up visits. Do not forget to report all positive pregnancy tests to your Principal Investigator (PI), the DCC/CRO, and the Ribavirin Registry within 24 hours of obtaining the information. See MOP section 13.5 for more details on the Ribavirin Registry.

Ques. 6: If the patient is a sexually active male, ask if his sexual partner is pregnant. If the answer is "yes", stop study drug therapy and begin untreated follow-up at the next regular visit as described for females above. Complete a Therapy Stop/Restart Form and record the date the form was completed in Form 21 question 6C. Report the pregnancy of the male's sexual partner to your PI, the DCC/CRO, and the Ribavirin Registry within 24 hours of obtaining the information.

Ques. 7-10: During the treatment period assessment visit at Week 1, the Patient's Medication Diary given to the patient or parent at Baseline will be reviewed. The first Baseline dose of Peg2a and the first Baseline RV/placebo pills were given at the Baseline visit. The dates of subsequent doses given between the Baseline visit and the Week 1 visit or at the Week 1 clinic visit will be recorded on the first three pages of the Diary provided for Week 1. Study drug doses given between the Week 1 visit and the Week 3 visit will be recorded on Diary pages provided for Week 2 and Week 3. The person giving the doses will initial the spaces provided. The person may be the patient, a parent, a physician, or PEDS-C clinic personnel. If a dose was not given, choose a reason from the key on the first page of the diary and record the number of the reason in the space provided on the week page. If the patient takes only one dose of RV/placebo a day (Dose 1), leave the space for a second dose (Dose 2) blank. A space is provided for PEDS-C staff notes at the end of each week. The Patient's Medication Diary contains pages for six weeks of study drug administration. Clinical Center personnel will use their own discretion in deciding how often to collect the Diary. It may be collected as early as Week 1 or as late as Week 5. Collected Diaries will be filed with the patient's records in a secure location. They will not be returned to the DCC/CRO unless requested.

Three therapy tracking forms are used in conjunction with the Diary review. If the patient's therapy dose has been changed, the Therapy Dose Adjustment Form will be completed. Record the date the form was completed in Form 21 question 8B. If the

patient's therapy has been stopped or restarted for any reason, the Therapy Stop/Restart Form will be completed. Record the date that the form was completed in Form 21 question 9B. If the patient has missed any doses since the Baseline visit, complete the Therapy Missed Dose Form. Record the date that the form was completed in Form 21 question 10B. Stopped or held doses are not "missed". Missed doses are those prescribed by the Clinical Center but not taken by the patient.

Ques. 11: Question 11 is a check-off list for laboratory samples required at the Week 1 visit. If a sample was collected, fill the "Done" bubble for that test. If the sample could not be obtained, fill the bubble for "Unable to obtain" for that sample.

20.9 Treatment Period Assessment Summaries- Weeks 3 to 8

The Treatment Period Assessment Summaries for Weeks 3 through 8 will be used as checklists for all forms and measures to be collected at these visits. The Week # in the header of all forms is pre-printed with the correct week number. Please make sure that the patient ID and letter code assigned at registration is recorded in the header of each page. Check to make sure that the header information on each page of a form is identical. The date of assessment is the date that the form is completed (or started if the form is held).

Ques. 1: In each of these forms if the patient is not willing to attend further PEDS-C data collection visits, complete a Withdrawal/Close-Out Form and record the date the form was completed in 1B. Do not complete the rest of the Treatment Period Assessment Summary. Instead, sign your name and record your certification number at the bottom of page 1. Do not complete or sign subsequent pages.

Ques. 2: Vital Signs and Symptom Directed Physical Form 11 is a separate form required at each visit. Record the date that the form was completed in 2B. Vital signs and physical measurements must be taken for all patients. If the examiner feels that a symptom directed physical is not required at any of these visits, he/she may skip to question 9 on the Form 11. If an organ system or body area was not examined, fill in the NA bubble.

Ques. 3: Ask the parent or patient the question printed in 3A: "*Has your child (have you) had any other problems since the last visit*". The "last visit" for the week 3 treatment assessment means the week 1 treatment assessment. The "last visit" for the week 5 treatment assessment means the week 3 treatment assessment. The "last visit" for the

week 8 treatment assessment means the week 5 treatment assessment. Adjust the wording according to whether the patient or parent is answering. If the patient or parent answers that they have experienced a serious adverse event, or a non-serious adverse event, complete the appropriate separate form(s) and record the date the first form was completed in the date boxes provided on the Treatment Assessment. The concurrent Medical Conditions Form was deleted 3/17/05. All concurrent conditions are either an AE (expected or unexpected) or an SAE. The expected adverse event form is a check-off list of general categories. The unexpected event form contains space for three diagnoses or symptoms. To report more than three unexpected diagnoses or symptoms, use multiple copies of the form with the same patient ID number, letter code, week # , and date of assessment in the headers. Only the sequence number in the header of each form will differ. The first form will be labeled sequence #01, the second form sequence #02, and so on. If only one form is used, the sequence number will still be 01. The sequence numbers on the pages of each individual form must be identical. Do not leave the sequence number boxes in the unexpected AE form headers blank.

Ques. 4: Ask the parent or patient the question printed in 4A.: "*Has your child (have you) taken any new medicines, other than those given to your in this study, since the last visit?*" Adjust the wording according to whether the parent or the patient answers. If the answer is "yes", complete a separate Concurrent Medications Form 41 Rev 1. The Form 41 contains space for three medications. To report more than three medications, use multiple Form 41s with the same patient ID number, letter code, week # , and date of assessment in the header. Only the sequence numbers in the headers of the multiple Form 41s will differ. The first form will be labeled sequence #01, the second form sequence #02, and so on. If only one Form 41 is used, the sequence number will still be 01. Do not leave the sequence number boxes in the Form 41 header blank.

Ques. 5: Question 5 on pregnancy will be asked of female patients 10 years of age or older. At weeks 3 and 8 a serum pregnancy test is required. At week 5 a serum pregnancy test is not required unless the girl shows secondary amenorrhea of 1 week or more. Ask the girl to recall the date of the first day of her last menstrual period. If the girl has not reached menarche, fill the NA bubbles in question 5B and C. If the girl cannot recall the first day of her last menstrual period, encourage her to give her best estimate. If she still

cannot recall a day, fill the NA bubble beside the date boxes and ask if she thinks her period is a week or more late. Under these circumstances, consult your PI about whether a pregnancy test should be performed. If the serum pregnancy test is positive, stop study drug therapy and move the patient to her first untreated follow-up visit. Complete a Therapy Stop/Restart Form and record the date the form was completed in the Treatment Assessment Summary question 5. At the subsequent untreated follow-up visit use the Untreated Follow-Up Assessment- Follow-Up Week 4 Form 62. See MOP Table 2-1 for a description of subsequent untreated follow-up visits. Do not forget to report all positive pregnancy tests to your PI, the DCC/CRO, and the Ribavirin Registry within 24 hours of obtaining the information. See MOP Section 13.5 for more information on the Ribavirin Registry.

Ques. 6: If the patient is a sexually active male, ask if his sexual partner is pregnant. If the answer is "yes", stop study drug therapy and begin untreated follow-up at the next regular visit as described for females above. Complete a Therapy Stop/Restart Form and record the date the form was completed on the Treatment Assessment Summary. Report the pregnancy of the male's sexual partner to your PI, the DCC/CRO, and the Ribavirin Registry within 24 hours of receiving the information.

Ques. 7-10: During the treatment period assessments visits at Weeks 3 to 8, the Patient's Medication Diary will be reviewed. The Diary given out at the Baseline visit contains pages for six weeks and should last until it is collected at the Week 5 visit. Check the patient's schedule to make sure that the interval between BL and Week 5 visits is not more than six weeks. Another Patient's Medication Diary will be distributed to patient's at Week 5. This copy should be reviewed and collected at Week 8. Diaries may be distributed and collected more frequently if necessary. The dates of doses of Peg2a and RV/placebo administered between Weeks 3 and 5 should be recorded on the pages for Weeks 3 to 4 and Weeks 4 to 5. Doses given between Weeks 5 and 8 should be recorded on pages labeled for Weeks 5 to 6, Weeks 6 to 7 and Weeks 7 to 8. The person giving the doses will initial the spaces provided. It may be a parent, a physician, or PEDS-C clinic personnel. If a dose was not given, choose a reason from the key on the first page of the Diary and record the number of the reason in the space provided on the week page. If the patient takes only one dose of RV/placebo a day (Dose 1), leave the space for the second

dose (Dose 2) blank. A space is provided for PEDS-C staff notes at the end of each week. Collected Diaries will be filed with the patient's records in a secure location. They will not be returned to the DCC/CRO unless requested. The patient will be given a new Patient's Medication Diary at Week 8 which will be collected at Week 12.

Three study drug therapy tracking forms are used in conjunction with the Diary review. If the patient's therapy dose has been changed, the Therapy Dose Adjustment Form will be completed. Record the date the form was completed on the Treatment Period Assessment Week 3, 5, and 8 question 8B. If the patient's therapy has been stopped for any reason or restarted, the Therapy Stop/Restart Form will be completed. Record the date that the form was completed on the Treatment Period Assessment Week 3, 5, and 8 question 9B. If the patient has missed any doses, complete the Therapy Missed Dose Form(s). Use one of the latter forms for each week that a dose was missed. Record the date the Missed Doses Form(s) were completed on the Treatment Period Assessment Week 3, 5, and 8 question 10B. Missed doses are those which were prescribed by the study but not taken by the patient. Held or stopped doses are not "missed" doses.

Ques. 11: Question 11 is a check-off list for laboratory samples required at Weeks 3, 5, and 8. If a sample was collected, fill the "Done" bubble for the test. If the sample could not be obtained, fill in the bubble for "Unable to Obtain" for that sample.

Ques. 12: (Treatment Period Assessment -Week 8 only) Two liver biopsy slides will be sent to the PEDS-C Central Pathology Laboratory (Dr. Goodman) by the time of the week 8 treatment assessment. See Manual section 3.2.2 for details on slide preparation and sending. The cost of sending liver biopsy slides will be paid by the Clinical Centers.

20.10 Treatment Period Assessment Summaries- Week 12 to 24 Visits

Treatment Period Assessment Summaries for week three to eight visits are similar in content to those of earlier visits. Beginning with Week 8, visits will take place monthly. Information on hematology, chemistry, pregnancy testing, adverse events, concurrent medications, the Patient Medication Diary review, and the Vital Signs and Symptom Directed Physical form will be collected at all visits. Other content of visits will vary. Please note that more information will be collected at weeks 12 and 24 visits. In particular, a follow-up ophthalmology exam will be conducted at week 24. Study drug

treatment will be stopped for any patient who develops worsening ocular symptoms and they will be moved to untreated follow-up at their next visit.

The results of the HCV-RNA test for viral disappearance at week 24 will have important implications for the future treatment of PEDS-C patients. For patients who show no viral disappearance at week 24 (treatment failure), their response will be unblinded to Clinical Center personnel and some patients will have study drug therapy either discontinued or changed. Information on viral response will become available to Clinical Centers and the DCC/CRO at about the same time. The DCC/CRO will send an official unblinding message to the Clinical Center reporting the treatment group assignment. The DCC/CRO will enter the Form 31 (Treatment Failure/Reassignment Report) into the database. The Form 31 will trigger the system to print out a new visit schedule for patients who show no viral disappearance (treatment failure). The new schedules will be sent to the Clinical Centers. Therapy Stop/Restart Forms should be completed at the Clinical Center reporting that therapy was permanently stopped for reason P. Other and specify "Tx failure at 24 weeks". The method of making therapy drug bottle assignments will be unchanged.

20.11 Concurrent Medical Conditions Form 40

The Concurrent Medical Conditions form was deleted as of 3/17/2005. All concurrent medical conditions should be reported as non-serious or serious adverse events.

20.12 Adverse Events (AE)

Clinically significant non-serious or serious adverse events (new conditions, worsening pre-existing conditions, or unexplained laboratory values) should be reported to the DCC/CRO.

20.12.1 Expected Non-Serious Adverse Events Form 77 (Rev 1)

Clinically non-significant events may be expected side-effects of study drug therapy (unless drug therapy has been discontinued) or common childhood conditions. Complete the header of the Form 77 with patient identifying information as for other forms. Expected adverse events that have occurred since the last clinic visit may be reported at

each treatment assessment. If there are no unexpected AEs at the visit, the form need not be completed The "Week # "will be the same as the week number of the treatment assessment form. The "Date of Assessment" is the date that the form was completed. Expected AEs have been categorized in 14 categories related to study treatment (1-14) and 8 categories of common childhood conditions. Each category is defined by a number of expected symptoms. If the patient shows at least one of the symptoms, the condition has occurred. Category definitions are not limited to the symptoms listed. Choose the category that best fits the expected event(s) you are reporting and darken the "Yes" bubble. Then enter the severity grade of the AE (1-3) in the "Severity" box. A severity grade of 4 is considered a serious adverse event.

20.12.2 Unexpected Adverse Events Form 78 Rev 0

Unexpected adverse events are events that are not usually related to study drug therapy or are not common childhood conditions. They may be reported at any time.

The Form 78 contains spaces for reporting three unexpected adverse events. For reporting more than three events at one time, use multiple forms.

Part A, Event #: Each AE will be identified by an event number unique for the patient. Each Clinical Center should keep a log of the event numbers used for each patient.

Part B, Report #: Each report on each event # will be also be numbered. A log of the report numbers used by event number for each patient should be kept. For example, Johnny may have an unexpected AE event number 001 and reports on that event numbered 01 to 05. He may also have an event number 002 with one report (01) on that event. For Johnny, subsequent events must never be numbered 001 or 002. In this way the DCC/CRO will be able to track multiple reports on a patient's AEs over time.

Part C, Adverse Event: Print the name of the event's diagnosis or symptom, one letter to a box. Leave blanks between words. If the name is longer than 24 characters, standard abbreviations may be used. It is best to specify events in general terms rather than specific terms. For example, "rash" rather than "rash on face". In this way duplicate AE's will be avoided.

Part D, Body System: Choose a code for the body system affected by the AE from the

categories in the key at the top of the form and record the number in the box provided.

Part E, Onset Date: Record the date of the event onset or the date that the event was first observed. If the exact onset date is not known, record the date that the condition was first detected by the patient, parents, or other caretakers. If the respondent cannot remember the day, ask for their best guess. Do not leave the day boxes in the date field blank.

Part F, Ending Date: Record the date that the event ended or was resolved. If the condition has not been resolved, leave the ending date boxes blank As a general guide, AE's should be closed-out after 4 weeks. Subsequent reports on the event number may report an ending date. Do not report an ending date by using a form correction.

Part G, Severity: Grade the severity of the AE at this report. Report a number from the severity key at the top of the form. Severity grades of 4 are serious adverse events. In subsequent reports on this event #, the severity may change.

Parts H and I, Study Drug Related: Indicate whether the adverse event may have been caused by the Peg2a or RV/placebo study drug therapy. If the answer is unclear, consult with your PI. Choose a response from the key at the top of the form and record the number in the proper box. In subsequent reports on this event number, this response may change.

Part J, Action: Indicate actions taken as a result of the non-serious AE. Choose an action taken from the key at the top of the form and record the number in the box. If the response is #6, Other, specify the action taken on the comments line. In subsequent reports on this event number, this response may change.

Part K, Current Status: Summarize the current status of the unexpected AE by choosing a response from the key at the top of the form and record the number in the proper box. In subsequent reports on this event number, this response my change.

Here are some examples of correct usage of the Unexpected Adverse Events Form 78. Patient Amy appears at Clinical Center X with a broken arm as a result of a fall on 12/11/2006. She was taken to a hospital to have the arm set. It is her first unexpected AE. The event # is 001 and the report number is 01. C. is recorded as " broken arm", D. is 09, E. is 12/11/2006, F. is blank, G. is 2 (hypothetical), H. and I are 0, J. is 3, K. is 4. Amy comes back to the clinic for a follow-up visit two weeks later. Her arm is still in a cast. Another Unexpected AE Form is completed as follows: A. is 001, B. is 02, C. is "broken

arm", D. is 09, E. is 12/11/2006, F. is blank, G. is 1 (her arm has improved), H and I are 0, J. is still 3, and K is still 4. Amy comes back to the clinic for a visit 6 weeks later on Feb. 11, 2007. Her cast is off and she has recovered with no sequelae. Now A. is 001, B. is 03, C. is "broken arm" , D. is 09, E. is 12/11/2006, F. is 02/11/2007 (or whenever she said she recovered), G. is blank, H and I are still 0, J. is still 3, and K. is 1. For Amy's next unexpected AE the event # will be 002 and the report # 01, and so on. In the same Clinical Center, Johnny's first unexpected AE will be event # 001 and report # 01. In a different Clinical Center, Sarah's first unexpected AE will be event # 001 and report # 01. Her next report of event 001 will be report # 02.

20.12.3 Serious Adverse Events

20.13 Child Behavior Checklist Ages 6-18 (CBCL/6-18)

Parts of the following instructions for the administration of the CBCL/6-18 have been abstracted from the *Manual for the ASEBA School Age Forms and Profiles* (T.M. Achenbach and L.A. Rescorla, 2001).

Since the copyright owner will not permit the reformatting of the CBCL form, it must be used as a blue, three page folding document. The form must not be punched to put into a binder because question responses on page 3 may be lost. The patient ID number, letter code, and week # should be written clearly in black pen on the top margin of the form. In the first 24 weeks of PEDS-C the form will be administered at baseline (week # 000) and week 24 (024). Later it will be administered at Week 48, Week 72 or 76, and at both long-term annual follow-up visits.

The CBCL/6-18 is completed by parents, parent-surrogates, and others who see children in family-like contexts. The first page of the CBCL requests demographic information about the child and asks respondents to indicate their name and relationship to the child. PEDS-C data collectors need not record the name or occupation of parent/guardians, but their gender and relationship to the child should be collected. The respondent then completes the competence items on pages 1 and 2. Some items on page 2 are more open-ended descriptions of the patient's illnesses and disabilities. CBCL pages 3 and 4 request ratings of behavioral, emotional, and social problems. The respondent rates each problem item as 0= not true, 1 = somewhat or sometimes true, and 2= very true or

often true based on the preceding six months. Several items ask parent/guardians to describe the patient's problems. Item 56h on page 3 requests that parent/guardians describe and rate any additional physical problems. Item 113 on page 4 requests that they describe and rate problems of any kind that were not previously listed.

For parent/guardians whose reading skills are poor or who may be unable to complete the CBCL for other reasons, the test makers recommend the following procedure: An interviewer hands the respondent a copy of the form while retaining a second copy. The interviewer says: "I'll read you the questions on this form and I'll write down your answers." Respondents who can read well enough will typically start answering questions without waiting for each one to be read. However, for respondents who cannot read well, this procedure avoids embarrassment and inaccuracies, while maintaining standardization like that for respondents who complete the form independently.

Data collectors should be sure to review the CBCL before the respondent leaves the clinic to make sure that all items have been answered. The original CBCL form should be sent by FedEx to the DCC/CRO and a copy retained at the Clinical Center. The form will be scored by a licensed Clinical Psychologist and the summary scores entered into the database at the DCC/CRO.

20.14 Child Health Questionnaire (CHQ- PF50)- Parent about Patient/ Child Health Questionnaire (CHQ-CF87) Patient Self-Report

In PEDS-C the CHQ-PF-50 is administered to the parent. In addition, if the patient is 10 years of age or older, he/she will complete the CHQ-CF87. In pediatric studies, information about young children is often collected from an adult proxy respondent because of concerns about the reliability of information from young respondents. The following instructions for administration of both questionnaires have been abstracted from the *Child Health Questionnaire (CHQ), A User's Manual*, by J.M. Landgraf, L. Abetz, and J.E. Ware Jr., 1999.

The CHQ is designed to be self-completed without the use of a trained interviewer. It can be administered in many settings (homes, schools, and clinics), but should be completed in a quiet and private place by a single respondent without consultation from others. The forms should be completed separately by parent/guardians and patients. Spouses or other family members <u>should not</u> assist patients or parents.

The parent or patient should not self-administer the CHQ if they are non-English speaking and cannot read English or if they are unable to understand the questionnaire due

to limited reading ability. If they are unable to read English, record on the form that it was not administered due to a language barrier. If they are unable to read, record on the form that it was not completed due to limited reading ability.

The CHQ should be administered early in the day before the patient is examined, has blood drawn, or is asked about adverse experiences or illnesses so that discussions of health problems will not influence responses. A respondent is more likely to complete the CHQ honestly and completely if they have a positive relationship with the questionnaire administrator. The administrator can emphasize the importance of their responses to the completion of the study. The administrator can also address concerns about the CHQ and confidentiality.

The following script may be used to introduce the CHQ to respondents:
"The CHQ was designed to provide reliable information about the everyday functioning and well-being of children in ways that matter most to them and their families. The CHQ asks questions about your child's physical wellness, his/her feelings, behavior, and activities at school and with family and friends. The parent completed CHQ also asks a few questions about you.
The CHQ is simple to complete. Be sure to read the instructions [point to them]. The CHQ contains questions that ask how you ***feel.*** *Remember, there are no right or wrong answers. This is not a test. Choose the response that best represents the way you* ***feel****. Please do not share or compare responses with your child or other family members.*"

If the parent/patient asks about the meaning of specific items, assist them by re-reading the question verbatim. Do not try to explain the item, but suggest that they should use their own interpretation of the question. When the parent/patient returns the CHQ, check the questionnaire for completeness by scanning the pages. Bring missing questions to the respondent's attention. If they chose not to answer questions, gently encourage them to do so. If more than half the items for a scale (CHQ contains 14 scales) are missing, it will not be possible to calculate scale summary scores. If the parent/patient has an objection or difficulty completing any items, simply record their reason(s) for non-completion. Never force someone to answer if they do not feel comfortable doing so on their own.

Sometimes parent/patients may have trouble with the response choices. They may say "I don't know." or suggest a new response categories. It is important to gently guide the respondent to chose one of the pre-set categories by saying something like: " *I know that it may be hard for you to think this way, but which of these categories most closely expresses what you are thinking and feeling?*" If the respondent does not like a question or

thinks it is unnecessary or inappropriate, emphasize that all questions in the CHQ are very important and included for different reasons. Respondents should try to answer all questions.

The following is a summary list of CHQ administration suggested do's and do not's:

DO'S	**DO NOT'S**
Do check to make sure that you are using the correct CHQ- the Parent about Patient form for parents and the CHQ-Patient Self Report for patients age 10 or older.	**Do not** confuse the two CHQ forms. **Do not** reorder items, response choices, or scales in the questionnaire.
Do have the parent/patient answer the CHQ before physical exams, AE or SAE reports, or blood draws.	**Do not** discuss the patient's health, health data, or emotions with the patient or patient before they complete the CHQ.
Do be warm, friendly, and helpful.	**Do not** minimize the importance of the CHQ.
Do request and encourage the parent/ patient to complete the CHQ.	**Do not** force or command the parent/patient to complete the CHQ.
Do read and repeat a question verbatim for the parent/patient.	**Do not** interpret or explain a question.
Do tell the parent/patient to answer a question based on what they think the question means.	**Do not** accept an incomplete questionnaire without first encouraging the parent/patient to fill out unanswered questions.
Do have the parent/patient fill out the CHQ by themselves.	**Do not** allow spouses or family members to help the parent/patient fill out the CHQ.
Do encourage the parent/patient to complete	**Do not** force or command the parent/patient

all questions. to complete a particular question.

Do thank the parent/patient for completing the CHQ.

Do inform the parent/patient that they will be asked to complete the CHQ again at future visits.

Appendix A
List of Abbreviations

Ab	Antibody
ABCL	Adult Behavior Checklist
AE	Adverse Event
ALT	Alanin aminotransferase
AST	Alanine transaminase
Atg	Antigen
ATRS	Automated Telephone Response System
BIA	Bioelectrical Impedance analysis
BMI	Body Mass Index
BRIEF	Behavior Rating Inventory of Executive Function
BUN	Blood Urea Nitrogen
CBCL	Child Behavior Checklist
CDC	Center for Disease Control
CDI	Children's Depression Inventory
CES-D	Center for Epidemiologic Studies – Depression Scale
CHC	Chronic Hepatitis C Virus
CHQ	Child Health Questionnaire
CRA	Contract Research Assistant
CRF	Case Report Form
DCC/CRO	Data Coordinating Center/Contract Research Organization
DRR	Drug Return Record
DSMB	Data and Safety Monitoring Board
DXA	Dual-energy X-ray absorptiometry
ESF	Eligibility Summary Form
FDA	Food and Drug Administration
g/dL	Grams per deciliter
GEE	Generalized estimating equations
GLP	Good Clinical Practice
GMP	Good Medical Practice
HCV	Hepatitis C Virus
HIPPA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB/IEC	Institutional Review Board
L	Liter
LEC	Life Events Checklist
m	Meter
mcg	Micrograms
mg/dL	Milligrams per deciliter
mL	Milliliters
NA	Not Applicable or Not Assessed
ND	Not Done
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases

Appendix A
List of Abbreviations

NR	Non-responders
PEDS-C	Pegylated Interferon +/- Ribavirin for Children with HCV
PEG-2a	Peginterferon Alfa-2a
PHI	Protected health information
PI	Principal Investigator
PIN	Personal Identification Number
PMD	Patient's Medication Diary
PT/PTT	Partial Prothombin Time
QL or QOL	Quality of Life
RNA	Ribonucleic Acid
RV	Ribavirin
SAE	Serious Adverse Events
SDV	Source Documentation Verification
SF 36	Short Form 36 Health Survey
SOP	Standard Operating Procedure
SS#	Social Security Number
SVR	Sustained Viral Response
TSH	Thyroid stimulating hormone

>	greater than
≥	greater than or equal to
<	less than
≤	less than or equal to

Appendix B

PEDS-C FORMS LIST

Certification Number Report- reports data collector certification # to DCC/CRO.

De-Certification Report- reports that a data collector is no longer collecting data.

Eligibility Summary Form- checklist to determine eligibility.

Eligibility Criteria Exemption Form (for DCC/CRO use only.)

Screening Visit Form 1

Screening Visit Form 2

Patient Re-Registration Form

Liver Biopsy Scoring Report- for pathology lab to report Knodell, Ishak, and Metavir scores.

Vital Signs and Symptom Directed Physical

Registration Worksheet A- ATRS call in instructions, registration and ID number.*

Re-registration Worksheet B- ATRS worksheet for re-registering a patient *.

Randomization Worksheet C- ATRS worksheet for randomization. *

Study Drug Re-Supply Worksheet D- ATRS worksheet used to request study drug re-supply.*

24 Week Tx Re-Assignment Worksheet E - ATRS worksheet used to report therapy re-assignments to the DCC/CRO.*

Unblinding Worksheet F- ATRS worksheet used to obtain emergency unblinding.*

Baseline Assessment

Ophthalmology Exam Form*

Baseline Ophthalmology Summary

Follow-Up Ophthalmology Summary (for scheduled and unscheduled exams)

Ophthalmology Exam Worksheet*

Bio-Electrical Impedance Report Form

Appendix B

PEDS-C FORMS LIST

Treatment Period Assessment Summaries (1, 3 , 5, 8, 12, 16, 20, 24, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76 wks)

Untreated Follow-Up Assessment Summaries (Follow-Up Weeks 4, 8, 12, 16, 20, 24)

Long-Term Follow-Up Annual Assessment (Annual Visit 1 and Annual Visit 2)

Unscheduled Assessment Summary- extra assessment if child is ill, etc.

Treatment Failure/Reassignment Form Week 24 (For DCC/CRO use only.)

Treatment Failure/Reassignment Form Week 52 (For DCC/CRO use only.)

Three Day Food Record (booklet)*

Physical Activity Assessment

QL Battery: Child Behavior Check List (CBCL) - standardized forms purchased (blue)
Adult Behavior Checklist (ABCL)- for kids 19 years old or more (blue)
Life Events Checklist (LEC- Patient)- Patient QL completed by parent
Child Health Questionnaire (CHQ)- Patient self-report
Child Health Questionnaire (CHQ)- Parent report on patient
Behavior Rating Inventory of Executive Functioning (BRIEF)- Parent
Child Depression Inventory (CDI)- for patients 5-17 years old
Center for Epid. Studies-Depression Scale (CES-D) Form- for patients 18 or more
Your Health and Well-Being- Parent (SF-36)

Concurrent Medications Form- drug, start and stop dates, conditions treated, pre or post study.

Therapy Missed Dose Form

Therapy Stop/Restart Form- reason for stopping drug and date, restart date.

Therapy Dose Adjustment Report

Patient's Medications Diary - 6 week record of drug administration (booklet)*.

Expected Non-Serious Adverse Events

Unexpected Non-Serious Adverse Events

Serious Adverse Events Report

Appendix B

PEDS-C FORMS LIST

Withdrawal/ Close Out Form- final evaluation and reason for withdraw or close-out of follow-up.

Depression Management Tracking Form - used when CDI score > 19 (age 5-17) or CES-D score >15 (age 18 or older).

Death Report

Missed Forms Report

Patient Transfer Report

Protocol Deviation Report

* Worksheets or booklets not for data entry.

The Johns Hopkins Medical Institutions
(The Johns Hopkins Hospital
The Johns Hopkins Bayview Medical Center, etc.)

Subject I.D. Plate

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: PEGYLATED INTERFERON +/- RIBAVIRIN FOR CHILDREN WITH HCV (PEDS-C)

PROTOCOL NO.: WIRB® Protocol #20040045

SPONSORS: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Bethesda, Maryland
United States

Hoffmann-La Roche Inc.
Nutley, New Jersey
United States

INVESTIGATOR: Kathleen B. Schwarz, M.D.
Johns Hopkins University
Johns Hopkins Children's Center
Pediatric GI/Nutrition, Brady 320
600 North Wolfe Street
Baltimore, Maryland 21287
United States
410-955-8769
410-955-6070 (24-hour pager)

SITE(S): Johns Hopkins University
Johns Hopkins Children's Center
Pediatric GI/Nutrition, Brady 320
600 North Wolfe Street
Baltimore, Maryland 21287
United States

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

The Johns Hopkins Medical Institutions
(The Johns Hopkins Hospital
The Johns Hopkins Bayview Medical Center, etc.)

What you should know about research studies:

- Your child is being asked to be in a research study.
- This consent form explains the research study.
- Please read it carefully and ask questions about anything you do not understand.
- If you do not have questions now, you may ask later.
- If this study relates to a health problem your child has, we will explain what other treatment could be given outside the research. You should understand those options before you sign this consent form.

Why is this research being done?

Your child has an infection with a virus called hepatitis C. The virus infects the liver and if it does not go away on its own after a short time, it may stay in your child's body and cause serious liver damage. In this study your child will be given a study medication called Pegylated interferon alfa-2a. You may also hear this drug called PEG-2a, Peg, or Pegasys. It is an investigational drug for treatment of hepatitis C in children, which means that it has not been approved by, the U.S. Food and Drug Administration (FDA) for use with children.

The study medication is given as a shot once a week for 48 weeks. The second drug your child may receive is called ribavirin. It is a new type of the drug that has been used to treat adult patients with chronic hepatitis C. It was recently approved for use with children when used with a type of interferon, which is given three times a week. It is a tablet that your child will take by mouth once or twice a day. This tablet must not be crushed; therefore, to be in this study your child must be able to swallow the tablet.

The main purpose of this study is to compare the "effectiveness" (how well the study medicines work) and how safe the study medicines are when given in the combination of PEG-2a and ribavirin and PEG-2a alone for the treatment of chronic hepatitis C in children. The second purpose is to see whether PEG-2a in combination with ribavirin or PEG-2a alone results in a better long-term response in children with hepatitis C.

To be able to enter this study, your child must be 5 to 18 years of age (up until their 18th birthday) at the time of enrollment in the study. Test results must show your child has chronic hepatitis C. Your child must never have been treated with interferon or ribavirin.

Your child's study doctor will monitor your child's growth during treatment and during follow-up time periods. It has been noted that weight loss, slow weight gain and changes in height occur in some children treated with interferon. However, little is known about these side effects in children.

Your child's quality of life, thinking ability and psychological well-being will also be monitored. Studies in adults have shown that interferon and ribavirin can cause psychological problems, including depression, and changes in quality of life. Little is known about these side effects in children treated with these study medications.

There will be approximately 112 subjects enrolled in this study nationwide.

Study Medications:

Interferons

- Interferons are natural substances produced by your body in response to infection by viruses. Interferon may reduce or eliminate hepatitis C virus from the blood and liver.

Interferon given three times per week by subcutaneous (under the skin) injection for 6 to 12 months was the first approved treatment for chronic hepatitis C in the United States. There have been several small studies of interferon in children for the treatment of hepatitis C. These studies suggest that interferon is as safe in children as adults and children are more likely to respond to interferon than adults.

In order to have better effectiveness and more convenient treatment, the interferon made by Hoffmann-La Roche Inc., Roferon®A, has been changed to make PEG-2a. It is approved for subjects 18 years of age and older. Studies in healthy subjects indicate that single doses of PEG-2a are as safe as single doses of Roferon®A. A small group of children with hepatitis C have received PEG-2a. The PEG-2a comes as an injectable liquid. Your child will have one injection each week.

Ribavirvin

- Ribavirin treatment may normalize liver enzymes and improve the condition of the liver. Although scientists believe subjects will get more benefit from PEG-IFN and ribavirin when they are used together, this has not been proven for children. Studies to determine this are ongoing and approximately 850 adult subjects are already receiving the combination of PEG-IFN and ribavirin. A form of ribavirin called Rebtrol used with interferon (also called Intron A) has recently been approved for treating hepatitis C in children at least three years of age and older. The new form of ribavirin comes as a tablet. Your child will take the tablet/s by mouth once or twice a day.

What will happen if your child joins this study?

If your child is eligible and chooses to participate in the study, your child will be randomly assigned (by chance, like flipping a coin) to one of following two groups:

- Group A: your child will receive PEG-2a + ribavirin
- Group B: your child will receive PEG-2a + placebo.

The placebo tablet will not contain the medication ribavirin, but it will look and taste, exactly like the ribavirin tablets. Placebo is something that is not expected to produce drug effects.

Your child will have an equal chance at being assigned to either group. Neither you nor your child will know which treatment group your child is in until week 24 of treatment.

If your child is in Group A and does not get rid of the hepatitis C by week 24 of treatment, your child will have both PEG-2a and ribavirin stopped. This is because the study medicines do not get rid of the hepatitis C by week 24, it is not likely they will work after that point.

If your child is in Group B and does not get rid of the hepatitis C by week 24 of treatment, your child will begin taking ribavirin tablets along with the PEG-2a. After your child has been on the combination of PEG-2a and ribavirin for 24 weeks, their blood will be checked again. If your child is still positive for hepatitis C, both study medicines will be stopped. This is because the study medicines do not get rid of the hepatitis C by week 24, it is not likely they will work after that point. If your child does respond by 24 weeks and the hepatitis C is negative, your child will continue on both study medicines for 24 more weeks. This means your child will be on the combination of study medicines for a total of 48 weeks.

All children will have measurements done during the study to follow their growth.

All children will be followed for changes in their quality of life, thinking ability and psychological well-being.

Both groups of subjects will be followed for 24 weeks of a treatment free observation period. Following the 24 weeks of close follow-up, all subjects will come to the clinic for 2 yearly visits for long-term follow-up.

Your child will need to have a liver biopsy within 24 months before starting the study. You will need to sign an additional consent form for this procedure. If your child has already had this liver biopsy and the results are available, they will not have to have another one.

All other procedures are considered standard clinical treatments.

The study will have three parts:

- **<u>The first part</u> is a screening process.**

This screening process will determine whether your child qualifies for the study. It will allow your child's study doctor to carefully describe your child's hepatitis and overall state of health. This screening will also include tests to determine what form of hepatitis C virus is present and also how much virus. Your child may require a repeat test to accurately determine the amount of virus.

Note: Your child will be tested for presence of HIV (Human Immunodeficiency Virus) in their blood before your child can enter this study. HIV is the organism that causes AIDS. Your child's study doctor will ask you to sign a separate consent form to ask for your permission to check your child's blood for HIV. Your child will not be able to participate in this study if infected with HIV or if you refuse to have your child tested for HIV. Your state law requires that the results of positive tests for HIV be reported to a local health agency. This is the legal obligation of the medical personnel.

Your child will be interviewed and given a physical examination.

Your child will complete a questionnaire that will help us know if your child has any signs of depression.

Your child will have blood drawn (up to 2 tablespoons), and be asked to give a urine sample.

Your child will have a pregnancy blood test if your child is a girl of childbearing age (10 years of age and older).

- **<u>The second part</u> is treatment.**

Your child will receive PEG-2a as a shot subcutaneously (under the skin) once a week, and ribavirin or placebo tablets given by mouth daily. The exact dose will be determined by your child's body size.

Blood tests will be performed on your child at all visits during treatment. Blood will be taken from your child's arm with a small needle. Between 2 to 6 teaspoons of blood will be taken at each visit. In the process of testing for hepatitis C virus, a small amount of DNA might be obtained. This will be discarded without any genetic testing.

The Johns Hopkins Medical Institutions
(The Johns Hopkins Hospital
The Johns Hopkins Bayview Medical Center, etc.)

During this part of the study, your child's growth will be measured in several ways:

- weight and height will be done at each visit
- the following tests will be done at the baseline visit and at weeks 24 and 48:

1) DXA scan is an x-ray like test that is used to measure body composition and bone density. The DXA looks at different body compartments (fat, lean tissue, fat free mass, and bone mineral content). The test will take about 15 minutes and will not be painful for your child.
2) BIA is another test to measure body composition. This test measures body electricity by using electrodes similar to an electrocardiogram.
3) Anthropometry measures weight, height, and fatness in skinfolds.
4) Your child's diet will be evaluated using a questionnaire that you will fill out for three days during the week after the study appointment
5) You will fill out a questionnaire about your child's activity.

Your child's quality of life, thinking ability and psychological well-being will be measured by having you and your child fill in questionnaires. These questionnaires will be done at the baseline visit, and at weeks 24 and 48. The results of these measures will be given to you within 4 weeks after stopping treatment.

Your child is expected to visit the study doctor once a week for the first 2 weeks, then every 2 weeks for the next 6 weeks, then less frequently for the rest of the treatment period.

At all study visits, the study doctor will check your child's hepatitis and look for side effects. Your child will be asked if any problems have occurred since the last visit. You/your child should report any new problems.

Study personnel will teach you to give the injections of PEG-2a to your child. If your child is old enough they may give their own injection with your supervision. Each shot must be given with a standard needle and syringe. It is preferred that injections be given in the child's leg.

It is important to record each dose of study medication your child takes. You will be provided with a diary (a record sheet) in which you are to record the date and time each dose of PEG-2a and ribavirin/placebo is taken. You need to bring the diary to each visit.

Your child will not be allowed to take other medications for hepatitis C during their participation in this study. You should inform your study doctor of any medications your child is taking or any changes in medications. Your study doctor or study staff will discuss with you the results of all your child's blood tests.

Procedures that will take place at some or all of your child's checkups:

- an interview
- a physical examination
- an eye examination by an ophthalmologist (eye doctor)
- blood drawing
- collection of a urine sample
- pregnancy test if your child is 10 years and older
- complete a questionnaire to see if your child has any signs of depression

You must return all used, partially used or unused study medication to the study doctor/site at each visit during the treatment period.

- **<u>The third part</u> is close follow-up during a 24-week treatment-free observation period followed by 2 yearly visits for long-term follow-up.**

Your child will continue to be evaluated for the long-term effects of the study drugs during this time period.

Your child is expected to have checkups and laboratory tests during the follow-up time.

Twice during the 24-week close follow-up time, study personnel will telephone you to see how your child is doing.

If your child is of childbearing age she will be required to take a urine pregnancy test at home 2 times during the 24-week close follow-up period and report the result to the study personnel. An additional checkup may be required if your study doctor thinks it necessary.

Results of blood and urine tests from your child's visits will be available to the study doctor within about 1 to 2 weeks. Results may be given to you by phone or at your next study visit.

Measurements for growth and body composition will also be done in the follow-up period.

Your child's quality of life, thinking ability and psychological well-being will be measured by having you and your child fill in questionnaires. These questionnaires will be done at the 2 yearly visits during the long-term follow-up period. The results of these measures will be given to you within 4 weeks after testing for the 2 yearly visits.

What are the risks of the study?

Besides the inconvenience of study doctor visits and giving your child shots at home, the procedures in this study may involve the following known risks and discomforts:

PEG-2a:

- Common side effects of interferon treatment have included flu-like symptoms: fever, tiredness, muscle aches, headache, chills and joint aches. Decreased appetite, nausea, vomiting, abdominal pain and diarrhea have also been experienced by some subjects. Interferon may also cause dizziness, hair loss, weight loss, discomfort at the injection site and rashes.
- Temporary changes in laboratory tests measuring white blood cell and platelet (cells that help the blood to clot) counts and liver function have been seen in some subjects. Your child may experience loss of concentration, irritability, confusion, sleep disturbances or depression. Infrequently, fainting, palpitations (rapid and/or irregular heartbeat), heart, lung or kidney disorders have been reported. Interferon may be associated with altered thyroid function tests or certain disorders of your child's body's immune system. These types of thyroid disorders can be controlled with medication, but treatment may have to be life long.
- Since PEG-2a is given by injection under the skin, your child may have pain, redness or swelling at the injection site. The site for injection is rotated to help prevent these side effects.
- If your child experiences side effects, the dose of study medicine may be decreased or stopped. Most side effects (with the possible exception of altered thyroid function) will generally reverse upon stopping treatment.
- Treatment with interferons may represent risks to the embryo or fetus. All fertile subjects and their fertile partners must practice effective birth control while participating in this study (See section on 'Pregnancy').

Ribavirin:

- The major side effects of ribavirin are temporary changes in laboratory tests measuring red blood cell counts, platelet counts and liver function. Rapid decreases in red blood cell counts may infrequently be associated with shortness of breath and heart symptoms.
- Your child may also experience nausea, vomiting and abdominal discomfort.
- If your child experiences side effects, the dose of study medicine may be decreased or stopped. Most side effects will generally reverse upon stopping treatment.
- Ribavirin may produce birth defects. BOTH fertile women and men must practice TWO medically effective forms of birth control while taking ribavirin (See section on 'Pregnancy').

DXA scan:

- Small amount of radiation similar to a chest x-ray. The radiation exposure your child will receive from participating in this study is equivalent to an exposure of approximately 0.002 rem to your whole body. Naturally occurring radiation (cosmic radiation,

radon, etc.) produces whole body radiation exposures of about 0.3 rem per year. Occupationally exposed individuals are permitted to receive whole body exposures of 5 rem per year.

Blood Drawing:

- Blood drawing is mildly painful and can cause bruising and, very rarely, fainting, blood clots or an infection at the site.

Lack of effect of PEG-2a and ribavirin:

- PEG-2a alone or combined with ribavirin may not cure your child's hepatitis. Your child's condition may remain unchanged or could worsen during your participation in the study.

Unknown risks:

- There may be side effects and discomforts that are not yet known.
- Your child's hepatitis may not get better or may become worse while he/she is in this study.

Only the study subject can take the study drugs. The study drugs and injection supplies must be kept out of the reach of children and persons who may not be able to read or understand the labels.

What if there are new findings?

During this study, you will be told any new facts that might change your decision to allow your child to be in this study.

You will be asked to acknowledge in writing that you have been informed of these findings.

What will happen if your child gets pregnant?

If your child is a female of childbearing age she cannot be pregnant, become pregnant or breast-feed during the entire study. If your child is a male, his partner cannot be pregnant during the entire study.

Every effort will be made to have females enter this study on an equal basis with male subjects. Abstinence or TWO medically accepted forms of birth control are required to enter this study. This may include, but is not limited to, using birth control pills, IUDs, condoms with spermicide, diaphragms with spermicide, implants or being surgically sterilized. Note: Due to the potential for ribavirin to be transmitted in the semen, it is recommended that one method should be a barrier-type, such as a condom. However, no birth control method completely eliminates the risk of pregnancy.

If a pregnancy occurs, there may be a risk of miscarriage, birth defects, or other unknown medical conditions.

- You **must** notify your child's study doctor immediately if your child becomes pregnant during the time they are receiving study drug or during the follow-up time after the end of treatment. Treatment with study drug will be stopped.
- You **must** immediately notify your child's study doctor of any pregnancy occurring in a partner during the study. Your child may not continue to receive ribavirin.

If your child or your child's partner becomes pregnant while receiving study drug or during the follow-up time after the end of treatment, the pregnancy will be reported to the Ribavirin Pregnancy Registry managed by the FDA.

Female subjects of childbearing potential are required to have pregnancy tests every 4 weeks during the treatment and future observation periods. Female subjects who are prematurely discontinued from treatment need to have pregnancy tests every 4 weeks for 24 weeks following the last dose of study drug.

This research study may hurt an embryo or fetus in ways we do not currently know.

Are there benefits to being in the study?

Your child's hepatitis C may improve because of treatment with the study medications. However, it is possible that your child may receive no benefit from being in this study. You may be helping future patients by providing important information about the treatment of chronic hepatitis C.

Will it cost you anything to have your child in this study?

All study medications and clinical supplies will be given to your child free of charge. The study sponsor will also provide all laboratory evaluations at no expense to you. The only cost to you will be parking for study visits.

Will your child be paid if they join this study?

Subjects will not be paid to join this study. If it is necessary for you and your child to stay in a hotel close to the hospital before or after a study visit, the hotel fee will be paid for by the study sponsor. You will be required to provide the hotel receipt to the study staff. Payment should be made within one month.

What are the options if you do not want your child to be in the study?

If you decide not to allow your child to join this study, other options are available. Your child does not need to participate in this study to get treatment. Other treatments include:

- Interferon given three times per week by a shot for 6 to 12 months. This is approved for treatment of chronic hepatitis C in the United States. There have been several small studies of interferon in children for the treatment of hepatitis C. The long-term response to interferon in children is low.
- A form of ribavirin called Rebtrol used with Intron A (interferon). This has recently been approved for treating hepatitis C in children at least three years of age and older.
- Your child may also have no treatment at all for hepatitis C. It is possible that without medication the infection will become inactive on its own, go away by itself or remain unchanged for many years.

Do you have to allow your child to join this study?

You do not have to allow your child to join this or any research study. If you do allow your child to join, and later change your mind, your child may quit at any time. If you refuse to allow your child to join or your child withdraws early from the study, you and your child will not be penalized or lose any benefits to which you are otherwise entitled at this site.

Can your child leave the study early?

1. You can agree to allow your child to be in the study now and change your mind later.
2. If you wish your child's participation to stop, please tell us right away.
3. Leaving this study early will not stop your child from getting regular medical care at this site.
4. If your child leaves the study early, Johns Hopkins may use or give out your child's health information that it already has if the information is needed for this study or any follow-up activities.

What could make us take your child out of the study early?

Your child may be taken out of the study by the study doctor or sponsor at any time, without your consent, if:

1. Staying in the study would be harmful.
2. Your child needs treatment not allowed in this study.
3. You/your child fails to follow instructions.
4. Your child becomes pregnant.
5. The study is cancelled.
6. Other reasons that we don't know at this time require us to take your child out of the study.

Subjects whose participation in the study is stopped for any reason will be checked for safety and side effects for at least twelve weeks following their final doses. This is to make sure that any side effects from the study medication that may be affecting your child are identified and properly treated. If continuing to treat your child with study drug is considered unsafe, the study doctor will either reduce the dose or stop the drug. Your child's condition will be monitored.

Will other studies be done on your child's blood, tissue or body fluid samples?

As part of this study, some of your child's clinical data, blood, tissue or body fluid (also called "specimens") will be collected and kept at a central place (also called a repository). The specimens may be used for future research testing on hepatitis C. Some of the research studies in which the specimens may be used are not yet known. All identifying information including your child's name and medical record number will be removed from the specimens. The specimens will be identified by a code. You will receive no results form future testing. There is no cost to you or your insurance company for the storage and testing of the specimens.

There are no plans to compensate you or your child for any commercial use or products that may result from your child's specimens. The specimens may be shared with other institutions and research studies may be done at different locations at the same time.

All blood and tissue samples will be stored for an indefinite period of time after the end of the study. At any time if you would like your child's samples to be removed from storage and destroyed, you may contact Dr. Kathleen Schwarz at (410) 955-8769.

Authorization to use and disclose information for research purposes

Federal regulations give you certain rights related to your child's health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify your child.

What information may be used and given to others?

If you choose to allow your child to be in this study, the study doctor will get personal information about your child. This may include information that might identify your child. The study doctor may also get information about your child's health including:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your child's study visits

- Information obtained during this research about
  - HIV / AIDS
  - Hepatitis infection
  - Physical exams
  - Laboratory, x-ray, and other test results
  - Diaries and questionnaires
  - The diagnosis and treatment of a mental health condition
- Records about any study drug your child received

Who may use and give out information about your child?

Information about your child's health may be used and given to others by the study doctor and staff. They might see the research information during and after the study.

Who might get this information?

Your child's information may be given to the sponsor of this research. "Sponsor" includes any persons or companies that are working for or with the sponsor, or are owned by the sponsor.

For this study, "sponsor" also includes Maryland Medical Research Institute, an agent for the sponsor.

Information about your child and your child's health, which might identify your child, may be given to:

- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Johns Hopkins University
- The Western Institutional Review Board® (WIRB®)

Why will this information be used and/or given to others?

Information about your child and your child's health that might identify your child may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done, and they will be reviewing your child's information for this purpose.

The information may be given to the FDA. It may also be given to governmental agencies in other countries. This is done so the sponsor can receive marketing approval for new products resulting from this research. The information may also be used to meet the reporting requirements of governmental agencies.

The results of this research may be published in scientific journals or presented at medical meetings, but your child's identity will not be disclosed.

The information may be reviewed by WIRB®. WIRB is a group of people who perform independent review of research as required by regulations.

What if I decide not to give permission to use and give out my child's health information?

By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, your child will not be able to be in this research.

May I review or copy the information obtained from my child or created about my child?

You have the right to review and copy your child's health information. However, if you decide to allow your child to be in this study and sign this permission form, you will not be allowed to look at or copy your child's information until after the research is completed.

May I withdraw or revoke (cancel) my permission?

Yes, but this permission will not stop automatically.

You may withdraw or take away your permission to use and disclose your child's health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, your child will not be able to continue being in this study.

When you withdraw your permission, no new health information, which might identify your child, will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Is my child's health information protected after it has been given to others?

If you give permission to give your child's identifiable health information to a person or business, the information may no longer be protected. There is a risk that your child's information will be released to others without your permission.

The Johns Hopkins Medical Institutions
(The Johns Hopkins Hospital
The Johns Hopkins Bayview Medical Center, etc.)

What will the study sponsor pay if your child is injured in this study?

The study sponsor is not responsible for payment of any treatment or hospitalization your child requires if they are injured as a result of being in the study. You will be responsible for such payment. At your request, your insurance company will be billed for payment of any treatment or hospitalization. It is up to you to check with your insurance company before your child starts this study to find out what your insurance company will pay for.

Who will provide the source of funding?

Funding for this research study will be provided by, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and Roche.

Whom should you call if you have study questions, or a study-related problem, or if your child gets injured?

If you have questions about this study, call the study doctor, Kathleen Schwarz, M.D. at 410-955-8769.
If you feel that you have an urgent medical problem related to your child's participation in this study, or have questions about your child's medical care in this study, contact Kathleen Schwarz, M.D. or Pediatric Gastroenterologist on call at 410-955-6070 (page operator).

If you think your child has been injured or are ill as a result of being in the study, contact Kathleen Schwarz, M.D. at 410-955-8769. The services at Johns Hopkins will be open to you in case of any such injury. However, neither Johns Hopkins nor the federal government has a program to pay if your child is hurt or have other bad results.

If you have any questions about your child's rights as a subject in a research study, or think you or your child have not been treated fairly, you may contact:

Western Institutional Review Board® (WIRB®)
3535 Seventh Avenue, SW
Olympia, Washington 98502
Telephone: 1-800-562-4789.

WIRB is a group of people who perform independent review of research.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

By signing this consent form, you have not waived any of the legal rights, which you or your child otherwise would have as a subject in a research study.

The Johns Hopkins Medical Institutions
(The Johns Hopkins Hospital
The Johns Hopkins Bayview Medical Center, etc.)

If you agree to allow your child to participate in this study, we will give you a signed and dated copy of this consent form.

Consent

I have read the information in this consent form. All my questions about the study and my child's participation in it have been answered. I freely consent to allow my child to participate in this research study.

I authorize the use and disclosure of my child's health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form, I have not waived any of the legal rights which I, or my child otherwise would have as a subject in a research study.

Consent and Assent Instructions:
Consent: Is provided by the Legally Authorized Representative
Assent: Is not required for subjects 6 years and younger
Is required for subjects ages 7 through 12 years using the separate Assent Form
Is required for subjects ages 13 through 17 years using the Assent Section below

_____
Subject Name

CONSENT SIGNATURE(S):

_____
Signature of Legally Authorized Representative Date

_____
Authority of Subject's Legally Authorized Representative or Relationship to Subject

_____
Signature of Person Conducting Informed Consent Discussion Date

_____
Witness to Consent Procedures (Optional) Date

The Johns Hopkins Medical Institutions
(The Johns Hopkins Hospital
The Johns Hopkins Bayview Medical Center, etc.)

ASSENT SIGNATURES, For Subjects Ages 13 through 17 years:

Assent:
This research study has been explained to me and I agree to be in this study.

_____

Subject's Signature for Assent Date Age (years)

I confirm that I have explained the study to the extent compatible with the subject's understanding, and that the subject has agreed to be in the study.

_____

Signature of Person Conducting Assent Discussion Date

NOTE: A copy of the signed and dated consent form must be kept by the study doctor and a copy of the consent form must be placed in the subject's record.

The Johns Hopkins Medical Institutions
(The Johns Hopkins Hospital
The Johns Hopkins Bayview Medical Center, etc.)

Subject I.D. Plate

APPROVED
AS CORRECTED
Oct 05, 2004
WIRB®
Olympia, WA

RESEARCH SUBJECT INFORMATION AND ASSENT FORM
For Children Ages 7 to 12

TITLE: PEGYLATED INTERFERON +/- RIBAVIRIN FOR CHILDREN WITH HCV (PEDS-C)

PROTOCOL NO.: WIRB® Protocol #20040045

SPONSOR: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Bethesda, Maryland
United States

Hoffmann-La Roche Inc.
Nutley, New Jersey
United States

INVESTIGATOR: Kathleen B. Schwarz, M.D.
Johns Hopkins University
Johns Hopkins Children's Center
Pediatric GI/Nutrition, Brady 320
600 North Wolfe Street
Baltimore, Maryland 21287
United States
410-955-8769
410-955-6070 (24-hour pager)

SITE(S): Johns Hopkins University
Johns Hopkins Children's Center
Pediatric GI/Nutrition, Brady 320
600 North Wolfe Street
Baltimore, Maryland 21287
United States

The reason for this research study is to collect more information on children that have an infection called hepatitis C. Because you have this infection, we think it is a good idea to give you medicine to try to get rid of the infection.

You will be given one or two kinds of medicine. These medicines have been shown to help adults with this infection. The medicines are called pegylated interferon (also known as PEG or Pegasys) and Ribavirin. PEG is given as a shot once a week. Ribavirin comes as a tablet. You will take one or more tablets once or twice a day depending on your size.

You will have to go to see your study doctor for regular visits in the clinic to see how you are doing. You will come to the clinic every 2 weeks in the beginning and then every month.

At these visits we will need to draw some blood to check on your liver and the hepatitis C infection. We will also check your weight, height, temperature, and blood pressure when you come to the clinic.

> For Girls: The study drug could cause bad birth defects in babies. If you are age 10 years or older you will have pregnancy tests done during the study. If at any time you think you might be pregnant, you must tell the study doctor right away

There are also some special tests you will have a few times during the study to see how you are growing. One is an x-ray like test of your body. One is a test that will measure your body's electricity using sticky patches put on your skin. One is a test of your eyes. We will also ask about the things you eat and your activities.

Your study doctor will also check on how you are doing with other things in your life. You may hear this called quality of life. Your study doctor will also check on how you are thinking and feeling (like happy or sad). You may hear this called thinking ability and psychological well-being. You and your parent will fill out papers with questions on them to help us to know how you are doing.

If you decide not to join this study, we will care for you just the same.

Is there anything you would like to ask us? If there is, please ask now or at any visit.

If you start the study and then you and your family decide you don't want to keep being in the study you can always stop.

ASSENT

This study has been explained to my child in my presence, in language he/she can understand. He/she has been encouraged to ask questions, both now and in the future, about the research study.

_____ _____
Parent/legal guardian Date

_____ _____
Investigator Date

_____
Child

Appendix D

PEDS-C Slide Submission Procedure and Form

Procedure

For each patient enrolled into the study, please request 4 unstained slides from each biopsy. If that is impossible or if no tissue remains in the paraffin blocks, then slides stained with H&E and Masson trichrome can be sent. They can be returned at the end of the study if the center requests.
Labeling slides: Please label the slides with the patient ID study #. The date of the biopsy is not necessary. The costs of shipping liver slides will be the responsibility of the Clinical Center

The slides should be carefully packed in a plastic slide holder – Pathology Departments should have these. Each one can hold 5 slides, so one should be sufficient for each patient. Fill any empty space with tissues and tape the slide holder shut. Pack it with bubble wrap and send it to Dr. Goodman by FedEx or similar service. Do NOT use the US mail as mail to government zip codes in DC gets irradiated. Slides turn gray and paraffin on unstained slides will melt.

Complete a Slide Submission Form for each patient's slides being sent. Make a copy for the study file. Fax a copy of the Slide Submission Form to Dr. Goodman at 202-782-4694 and enclose one copy in the package.

Also, please send an email to Dr. Goodman at Goodman@afip.osd.mil with the following information:
Patient ID number
Date slides are being sent
Tracking # for package

Dr. Goodman will notify the sender when the slides arrive.

If any of the biopsies are inadequate because there was no tissue left in the blocks, Dr. Goodman may ask to review the center's file slides, which can be returned.

The FedEx (or similar service) deliver address is:

Zachary Goodman, M.D.
Hepatic Pathology
Armed Forces Institute of Pathology
14th Street & Alaska Ave NW
Washington, DC 20306

Dr. Goodman's phone #: 202-782-1702

PEDS-C Slide Submission Procedure and Form

Submission Form

Site ID#: _____

Patient numerical ID: _____

Patient letter ID: _____

Date(s) of biopsy/biopsies: _____

Number of slides being sent: _____

Name of person packing slides: _____

Do these slides need returned (circle): YES NO

If yes, return name and address: _____

_____

_____

_____

In addition to this form that will be included with the slides being sent, please send an email to Dr. Zachary Goodman (Goodman@afip.osd.mil) with the following information:

Patient ID # and letter identifier
Date slides are being sent
Tracking # for package

Send via Fed Ex or similar service only. Do NOT use US Mail!

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

Quick Reference

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE grading table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

General Instructions

Estimating Severity Grade

If the need arises to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located at the top of Page 3. For AEs that are not listed in the table but will be collected systematically for a study/trial, protocol teams are highly encouraged to define study-specific severity scales within the protocol or an appendix to the protocol. (Please see "Template Wording for the Expedited Adverse Event Reporting Section of DAIDS-sponsored Protocols".) This is particularly important for laboratory values because the "Estimating Severity Grade" category only applies to clinical symptoms.

Grading Adult and Pediatric AEs

The DAIDS AE grading table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the table. If there is no distinction in the table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

Determining Severity Grade

If the severity of an AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

Definitions

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young Children Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	Adult Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

Contents

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	> 140 – 159 mmHg systolic OR > 90 – 99 mmHg diastolic	> 160 – 179 mmHg systolic OR > 100 – 109 mmHg diastolic	> 180 mmHg systolic OR > 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) **– Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 **–** 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) **– Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric < 18 years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, 1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin (Hgb)				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *1.32 – 1.55 mmol/L*	7.5 – 8.4 g/dL *1.16 – 1.31 mmol/L*	6.50 – 7.4 g/dL *1.01 – 1.15 mmol/L*	< 6.5 g/dL *< 1.01 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *1.55 – 1.69 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *0.39 – 0.53 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *0.54 – 0.68 mmol/L*	7.0 – 8.9 g/dL *1.09 – 1.39 mmol/L* OR Any decrease ≥ 4.5 g/dL *≥ 0.69 mmol/L*	< 7.0 g/dL *< 1.09 mmol/L*
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *1.32 – 1.46 mmol/L*	7.0 – 8.4 g/dL *1.09 – 1.31 mmol/L*	6.0 – 6.9 g/dL *0.93 – 1.08 mmol/L*	< 6.00 g/dL *< 0.93 mmol/L*

* Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *1.47 – 1.63 mmol/L*	8.0 – 9.4 g/dL *1.24 – 1.46 mmol/L*	7.0 – 7.9 g/dL *1.09 – 1.23 mmol/L*	< 7.00 g/dL *< 1.09 mmol/L*
Infant*†, 1 – 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *1.86 – 2.02 mmol/L*	10.0 – 11.9 g/dL *1.55 – 1.85 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L*	< 9.0 g/dL *< 1.40 mmol/L*
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*
CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN

* Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high (corrected for albumin)				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low (corrected for albumin)				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*

* Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*

* Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
URINALYSIS	***Standard International Units are listed in italics***			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

* Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

UTMB POINT OF CARE TESTING PROCEDURES POLICY -	Policy Page 1 of 6	
Pregnancy Test, Urine CLIA WAIVED	Effective: Reviewed:	04/01 02/04

Pregnancy Test, urine (Sure-Vue)

Purpose

This document provides instructions for performing the Sure-Vue hCG test, a self-performing immunoassay for the detection of hCG in urine.

Audience

The information in this document is applicable to all medical, nursing (RN, LVN, HTA, NA), and laboratory personnel.

Policy

A physician's order is required for this test.

Test Principle

Sur-Vue hCG is a rapid qualitative test to detect the presence of hCG in urine. The test utilizes a combination of monoclonal and polyclonal antibody reagents to selectively detect elevated levels of hCG in urine. The assay is conducted by the addition of urine specimen into the test device sample well and observing for the formation of colored lines. The specimen migrates via capillary action along the membrane and reacts with the colored conjugate. A positive specimen reacts with the colored conjugate and forms a colored line in the T (test) window. Absence of this colored line suggests a negative result. To serve as a control for the procedure, a colored line in the C (control) window will always appear regardless of the presence of hCG.

Patient Preparation

None

Specimen

- Any urine specimen is appropriate for hCG testing, but the first morning urine is optimal because it generally contains the highest concentration of hCG.
- A urine sample exhibiting visible precipitates or gross hematuria should be filtered, centrifuged, or allowed to settle (obtaining clear aliquots) before testing. Gross hematuria may prevent an accurate reading of test results by masking the positive line.
- **NOTE:** Urine specimen should be stored in the smallest possible plastic container. Large containers (especially glass) are to be avoided as hCG sticks to the surface of containers.
-

Specimen Storage

If testing is anticipated to be delayed, specimens may be held at room temperature for up to 8 hours; otherwise, samples should be refrigerated (2 to 8°C) for up to 72 hours.

UTMB POINT OF CARE TESTING PROCEDURES POLICY -	Policy Page 2 of 6	
Pregnancy Test, Urine CLIA WAIVED	Effective: Reviewed:	04/01 02/04

Pregnancy Test, urine (Sure-Vue)

Specimen Rejection

Refrigerated specimens older than 72 hrs, or 8 hrs if specimen has sat at room temperature.

Supplies

Plastic urine specimen collection containers
Fisher Sure-Vue (materials mgt# 27050)

- Test Devices
- pipettes
- Quantimetrix UA controls solutions (materials mgt# 32600)
- Disposable gloves

Reagent Storage and Stability

- Kits must be stored at room for the duration of the shelf life or expiration date on box.
- UA control solutions (MM# 32600) are stable until expiration date on vial WHEN STORED AT REFRIGERATION TEMPERATURES. HOWEVER, SHELF LIFE IS SHORTENED TO 1 MONTH WHEN KEPT AT ROOM TEMPERATURE. In such cases a DISCARD DATE SHOULD BE WRITTEN ON BOTH VIALS.

Procedure

Step	Action
1	**NOTE**: test device must remain in sealed pouch until ready for use.
2	Remove Test device from pouch and place on a flat, dry surface. Label device with patient or control identifications.
3	Using the supplied dropper, dispense 4 drops of sample into round sample well. ---Read results **at 4 minutes.** If negative, test can be read after 4 minutes up until 15 minutes. A LINE THAT DEVELOPS AFTER 15 MINUTES SHOULD BE IGNORED. (Refer to interpretation of results section)
4	**The following internal procedural control must be observed prior to reporting a patient result:** a colored line at the Control "C" region. *Note: appearance of a line at the "C" region is not indicative of the test being completed!! (Control line usually develops before 4 minutes).*

UTMB POINT OF CARE TESTING PROCEDURES POLICY -	Policy Page 3 of 6	
Pregnancy Test, Urine CLIA WAIVED	Effective: Reviewed:	04/01 02/04

Pregnancy Test, urine (Sure-Vue)

Interpretation of Results

Positive: Appearance of two colored lines—one at "T" (test) and the other at "C" (control) regions. **NOTE**: LOW LEVELS OF HCG MAY TURN POSITIVE BETWEEN 4 AND 15 MINUTES. **IN SUCH CASES IT IS RECOMMENDED THAT THE TEST BE REPEATED IN 48 HOURS**. ALTERNATIVELY, A SERUM SAMPLE CAN BE DRAWN AND SENT TO THE LABORATORY FOR BETA hCG QUANTITATION IF PATIENT WILL BE UNDERGOING A CRITICAL PROCEDURE.
Negative: Appearance of a colored line at the "C" (control) region, indicates a detectable level of hCG is not present.
Invalid: No band appears at the "C" the test is invalid. Test should be repeated using a separate test device.

Quality Control

There are two types of QC associated with this kit.
1) The Fisher Sure-Vue kit incorporates an internal procedural control in their product: appearance of a colored line at the "C: region. Correct procedural technique and test device performance is confirmed when this line appears. Control line must be documented on respective log **FOR THE FIRST SAMPLE OF EACH DAY**.
2) In addition, two levels of liquid controls (positive and negative)

- Should be run and documented **ONCE PER NEW LOT NUMBER RECEIVED**. Quantimetrix UA Control solutions (MM# 32600) may be used for this purpose. For procedure on how to perform QC refer to section below. **NOTE: WHEN USING Quantimetrix UA control solutions, DEPENDING ON THE LOT NUMBER, LEVEL 1 CONTROL may be POSITIVE while LEVEL 2 may be NEGATIVE.**
- **NOTE: Retain Quality Control records for a minimum of two years.**

Quality Control (Liquid)

Step	Action
1	Test device must remain in sealed pouch until ready for use.
2	Remove 2 Test devices from their individual pouch and place on a flat, dry surface. Label each device with their control identifications ("positive" or "negative").
3	Dispense 4 drops of control solution to the respective labeled test devices. ---Read results **at 4 minutes.**

Pregnancy Test, urine (Sure-Vue)

4	**The positive control** should yield two lines: one at "C" and one at "T" regions. **The negative control** should only yield one: at the "C" region.

Review of Quality Control Data

The operator who performs the test will document the results on QC logs, including any "Out of limits" values and corrective action.

Monthly, the Test Site Manager, will review and sign the Quality Control logs sheet. They will complete and submit the "Monthly Data Collection Tool" and return to Point of Care Testing either electronically (online) or via campus mail, Route 0551.

Semi-annually, Point of Care will review the QC data and report the findings to the Point of Care Director and Nursing Unit Director or Clinic Manager/Director.

Interfering Substances

Hormones and drug compounds were tested with the Fisher Sure-Vue kit for interfering effects, including LH, FSH, TSH, caffeine, acetaminophen, acetylsalicylic acid, ascorbic acid, and glucose. For a complete list of compounds and concentrations tested refer to manufacturer's insert or call 1-888-727-3315.

Sensitivity

- Fisher Sure-Vue will detect urine hCG concentrations of 25 mIU/mL or greater.
- If negative results occur and pregnancy is still suspected, it is good practice to re-sample and re-test after 48 hours.
- In normal pregnancy, 20 mIU/ml is reported to be present in both urine and serum 2 to 3 days before the first missed menstrual period.

Limitations

- Results should be interpreted in conjunction with other clinical and laboratory data available to the clinician. This is a screening test; therefore, negative results should be confirmed using a quantitative hCG assay prior to the performance of any critical medical procedures.
- As mentioned in "Interpretation of Results" section, LOW LEVELS OF HCG MAY TURN POSITIVE BETWEEN 4 AND 15 MINUTES. **IN SUCH CASES IT IS RECOMMENDED THAT THE TEST IS REPEATED IN 48 HOURS**, OR A SERUM SAMPLE BE DRAWN AND SENT TO

UTMB POINT OF CARE TESTING PROCEDURES POLICY -	Policy Page 5 of 6	
Pregnancy Test, Urine CLIA WAIVED	Effective: Reviewed:	04/01 02/04

Pregnancy Test, urine (Sure-Vue)

Limitations (Cont)

LABORATORY FOR BETA hCG QUANTITATION IF PATIENT WILL BE UNDERGOING A CRITICAL PROCEDURE.

- If a urine specimen is too dilute (i.e. low specific gravity) it may not contain representative levels of hCG. If pregnancy is still suspected, a first morning specimen or serum specimen should be obtained from the patient and retested
- A number of conditions other than pregnancy, including trophoblastic disease, cause elevated levels of hCG. These diagnoses should be considered if appropriate to the clinical evidence.
- Specimens from patients who have received preparations of Mouse Monoclonal Antibodies may give false positive results.

Normal Value

- Negative - Urine from healthy men and healthy non-pregnant women should not contain detectable levels of hCG.
- Urine hCG levels in pregnant women begin to rise within nine to twelve days after conception and reach levels of up to 150,000 mIU/ml eight to ten weeks after the last menstrual period.

UTMB POINT OF CARE TESTING PROCEDURES POLICY -	Policy Page 6 of 6	
Pregnancy Test, Urine CLIA WAIVED	Effective: Reviewed:	04/01 02/04

Pregnancy Test, urine (Sure-Vue)

References

Braunstein, G.D., Rasor, J., Alder, D., Danzer, H., and Wade, M.E. Serum Human Chorionic Gonadotropin Levels throughout Normal Pregnancy. Am. J. Obstet. Gynecol. 126:687, 1976.

Bandi, Z.L., et. al. Enzyme Linked Immuno-Sorbent Urine Pregnancy Tests; Clinical Specificity Studies, American Journal of Clinical Pathology, 1986.

Package Insert from Fisher Sure-Vue.

Henry, J.B. Clinical Diagnosis and Management by laboratory Methods 17th ed., 1984, W.B. Saunders Co., Philadelphia.

Anderson, S.C. and Cockayne, S. Clinical Chemistry Concepts and Applications. W. B. Saunders, Philadelphia, 1993, pp. 659-660.

Kaplan, L. A. and Pesce, A.J. Clinical Chemistry. C. B. Mosby Co., St. Louis, 1984, pp. 1147-1153.

APPENDIX G

DSMB Charter
Pegylated Interferon +/- Ribavirin for Children with HCV
Kathleen B. Schwarz, M.D., Principal Investigator
Johns Hopkins University

Issues discussed will include the conduct and progress of the study, including patient recruitment, data quality, general adherence and toxicity issues, compliance with protocol, and any other logistical matters that may affect either the conduct or outcome of the study. Proposed protocol amendments will also be presented in this session. **Patient-specific data and treatment group data may not be presented in the open session.**

Closed Session:
The closed session will be attended only by voting DSMB members, representatives from the NIDDK, and the study biostatistician. **The discussion at the closed session is completely confidential.**

Analyses of blinded outcome data are reviewed by masked intervention groups, including baseline characteristics, primary and secondary outcomes, adverse events, adherence and dropouts, and examination of any relevant subgroups. However, the DSMB may request unmasking of the data for either safety or efficacy concerns. Procedures to accomplish unmasking of either individual or treatment group data are to be specified in the DSMB plan.

Executive Session:
The executive session will be attended by voting DSMB members, the NIDDK Project Officer and the NIDDK executive secretary.

The DSMB will discuss information presented to it during the closed and open sessions and decide whether to recommend continuation or termination, protocol modification or other changes to the conduct of the study. The DSMB can become unblinded if trends develop either for benefit or harm to the participants.

Will the DSMB decide to issue a termination recommendation; full vote of the DSMB will be required. In the event of a split vote, majority vote will rule and a minority report will be appended. Reasons for early termination include:

- Serious adverse effects in entire intervention group or in a dominating subgroup;
- Greater than expected beneficial effects;
- A statistically significant difference by the end of the study is improbable;
- Logistical or data quality problems so severe that correction is not feasible.

Final Open Session (optional):
The final session may be attended by voting DSMB members, the principal investigator, the study biostatistician or other study members, and the NIDDK staff.

The Chair of the DSMB, the Executive Secretary, or the NIDDK Project Officer shall report on the recommendations of the DSMB regarding study continuation and concerns regarding the conduct of the study. Requests regarding data presentation for subsequent meetings will be made. Scheduling of the next DSMB meeting may be discussed.

APPENDIX G

DSMB Charter
Pegylated Interferon +/- Ribavirin for Children with HCV
Kathleen B. Schwarz, M.D., Principal Investigator
Johns Hopkins University

REPORTS

Interim Reports: Interim reports are generally prepared by the study statistician(s) and distributed to the DSMB, the NIDDK Executive Secretary and the NIDDK Project Officer at least 10 days prior to a scheduled meeting. These interim reports are numbered and provided in sealed envelopes within an express mailing package or by secure email as the DSMB prefers. The contents of the report are determined by the DSMB. Additions and other modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Interim data reports generally consist of two parts:

Part 1 (**Open Session Report**) provides information on study aspects such as accrual, baseline characteristics, and other general information on study status. This report is generally shared with all investigators involved with the clinical trial.

Part 2 (**Closed Session Report**) may contain data on study outcomes, including safety data, and depending on the study, perhaps efficacy data. The Closed Session Report is considered confidential and will be destroyed at the conclusion of the meeting. Data files to be used for interim analyses will have undergone established editing procedures to the extent possible. Interim analyses of efficacy data are performed only if they are specified and approved in advance and criteria for possible stopping is clearly defined. This report will not be viewed by any members of the clinical trial except the designated study statistician.

Reports from the DSMB: A meeting summary containing the recommendations for continuation or modifications of the study, prepared by the ES with concurrence from the DSMB, will be sent to the PI. A letter from the NIDDK Project Officer will accompany this report and will contain any recommendations of the NIDDK in reference to the DSMB recommendations. It is the responsibility of the PI to distribute the meeting summary and accompanying letter from the Project Officer to all co-investigators and to assure that copies are submitted to all the IRBs associated with the study.

Each summary report will conclude with a recommendation to continue or to terminate the study. This recommendation will be made by formal majority vote. A termination recommendation may be made by the DSMB at any time by majority vote to the NIDDK. The NIDDK is responsible for notifying the PI of a decision to terminate the study. In the

event of a split vote in favor of continuation, a minority report will be contained within the regular DSMB report. The report will not include unblinded data, discussion of the unblinded data, or any other confidential data.

Mailings to the DSMB: On a scheduled basis (as agreed upon by the DSMB) blinded safety data will be communicated to all DSMB members, the NIDDK project officer, the NIDDK Executive Secretary

and the designated safety officer. Any concerns noted by the DSMB or the safety officers will be brought to the attention of the NIDDK Project Officer.

Access to Interim Data: Access to the accumulating endpoint data will be limited to as small a group as possible. Limiting the access to interim data to the DSMB members relieves the investigator of the burden of deciding whether it is ethical to continue to randomize patients and helps protect the study from bias in patient entry and/or evaluation.

CONFIDENTIALITY

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

F. Hoffmann-La Roche Ltd

INVESTIGATOR'S BROCHURE

Research Document Repository 1010990

Ro 25-8310

Pegasys® (Peginterferon α-2a)

and

Ro 20-9963

Copegus® (Ribavirin)

Seventh Version, March 2003

Replaces Sixth Version, December 2001

Summary of Significant Changes in Updated Investigator's Brochure

Ro 25-8310 Pegasys® (Peginterferon α-2a)

and

Ro 20-9963 Copegus® (Ribavirin)

Seventh Version, March 2003

Section		Changes from previous version of IB
1.	Summary	Updated information
2.	Introduction	Updated information
3.	Chemistry and Formulation: PEG-IFN α-2a	No change
4.	Nonclinical Studies: PEG-IFN α-2a	Shortened sections "Pharmacokinetics and Pharmacodynamics" and "Distribution and Metabolism"
5.	Clinical Studies of PEG-IFN α-2a Monotherapy	
5.1	Clinical Pharmacology	Updated information
5.2.1.	Safety of PEG-IFN in Monotherapy Studies for Treatment of Hepatitis C	Added Appendix 5
5.2.2.	Safety of PEG-IFN α-2a in the Treatment of Hepatitis B	Added data from two ongoing phase III studies
5.2.3.	Safety of PEG-IFN α-2a in the Treatment of Oncology Patients	Updated information
6.	Ribavirin in Combination with PEG-IFN α-2a for the Treatment of Hepatitis C	
6.1	Chemistry and Formulation	Updated information
6.2	Nonclinical Studies	Updated information; added references for "Pharmacokinetics and Pharmacodynamics"
6.3	Clinical Studies with Ribavirin in Combination with PEG-IFN α-2a	
6.3.1.	Clinical Pharmacokinetics of Ribavirin	Updated Information
6.3.2.	Comparison of the Safety of PEG-IFN α-2a Monotherapy and PEG-IFN α-2a Plus Ribavirin Combination Therapy and IFN α-2b Plus Ribavirin Combination Therapy: Study NV15801	Updated Information
6.3.3.	Effect of Duration of Treatment and Daily Dose of Ribavirin in Combination with PEG-IFN α-2a: Study NV15942	Updated information
6.3.4.	Safety Data from Other Trials	Updated information for Studies NR15961 and NV16071
6.3.6	Efficacy Results for Study NV15942	New section
6.3.7	Predictability of Sustained Virological Response	New section
7.	Guidance for the Investigator	Updated information

Table of Contents

List of Tables

List of Figures

List of Appendices

GLOSSARY OF ABBREVIATIONS

ALT, ALAT	alanine aminotransferase (SGPT)
AST, ASAT	aspartate aminotransferase (SGOT)
AUC	area under the serum concentration time curve
AZT	zidovudine
C_{max}	maximum serum concentration
CHB	chronic hepatitis B
CHC	chronic hepatitis C
CL/F	apparent total body clearance
CML	chronic myelogenous leukemia
CTL	cytotoxic T-lymphocyte
DNA	deoxyribonucleic acid
E_{max}	maximum effect
EC_{50}	concentration required for 50% inhibition
EMCV	encephalomyocarditits virus
HBV	hepatitis B virus
HCV	hepatitis C virus
IC	inhibition of cell proliferation
IC_{50}	concentration required for 50% inhibition
IB	Investigator’s brochure
IFN alfa-2a	interferon alfa-2a (Roferon®-A)
IFN alfa-2b	interferon alfa-2b (Intron A)
IL-2	interleukin-2
im	intramuscular
iv	intravenous
kda	kilodalton
LAP	leukocyte alkaline phosphatase

GLOSSARY OF ABBREVIATIONS

MDBK	Madin-Darby bovine kidney
MIU	million international units
MM	malignant melanoma
NHS	N-hydroxysuccinimide ester
2′,5′-OAS	2′, 5′-oligoadenylate synthetase
PBMC	peripheral blood mononuclear cells
PEG	polyethylene glycol
PEG-IFN alfa-2a	peginterferon alfa-2a (Pegasys®, Ro 25-8310)
PEG-IFN α A/D	pegylated form of a hybrid human-mouse interferon α
po	orally
qw	once per week
RCC	renal cell carcinoma
RNA	ribonucleic acid
sc	subcutaneous
SE	standard error of the mean
$t_{1/2}$	terminal phase half-life
tiw	three times per week
T_{max}	time to maximum serum concentrations
V_z/F	apparent volume of distribution
VSV	vesicular stomatitis virus
WBC	white blood cell

1. SUMMARY

Peginterferon alfa-2a (PEG-IFN α-2a, Pegasys®, Ro 25-8310) is synthesized by chemically conjugating one branched polyethylene glycol molecule (PEG) with an average molecular weight of ~40,000 daltons to interferon alfa-2a (IFN α-2a, Roferon®-A, Ro 22-8181). This pegylated compound has been evaluated in numerous nonclinical and clinical studies. Data from studies in animals and clinical pharmacology studies indicate that PEG-IFN α-2a has a pharmacokinetic and pharmacodynamic profile that allows it to be given once a week. PEG-IFN α-2a monotherapy and PEG-IFN α-2a plus ribavirin combination therapy have received marketing approval by regulatory authorities in the United States and Europe as well as in other countries worldwide for the treatment of chronic hepatitis C (CHC). PEG-IFN α-2a has also been evaluated for the treatment of hepatitis B, renal cell carcinoma, chronic myelogenous leukemia, and malignant melanoma.

In the present version of this Investigator's Brochure (IB), the chemistry and formulation of PEG-IFN α-2a are described in section 3, the nonclinical studies of PEG-IFN α-2a are summarized in section 4, the clinical studies of PEG-IFN α-2a monotherapy for the treatment of CHC, hepatitis B, and oncology indications are summarized in section 5, and the clinical studies of PEG-IFN α-2a plus ribavirin combination therapy for the treatment of CHC are presented in section 6. Section 6 also contains information on chemistry, formulation, and the nonclinical studies of ribavirin. For each ongoing study, a clinical data cutoff date for this version of the IB is provided in the respective section.

1.1 Clinical Study Results: PEG-IFN α-2a and Ribavirin Clinical Pharmacology

The biological activity of PEG-IFN α-2a, as measured with 2',5'-oligoadenylate synthetase (2′,5′-OAS), reflected the prolonged circulation of PEG-IFN α-2a. The magnitude and duration of the induction of 2',5'-OAS were increased compared with that of IFN α-2a. The addition of a branched 40 kDa PEG moiety to IFN α-2a resulted in a sustained absorption, a reduced clearance, and a longer terminal half-life of PEG-IFN α-2a compared with IFN α-2a. The volume of distribution of PEG-IFN α-2a was smaller than that of IFN α-2a. Sustained serum concentrations of PEG-IFN α-2a were seen over the weekly dosing interval. The absolute bioavailability of PEG-IFN α-2a administered subcutaneously was greater than 80%. No significant gender effect on the pharmacokinetics of PEG-IFN α-2a was observed. Multiple once weekly dosing of PEG-IFN α-2a reduced the oral clearance of theophylline by about 20%, suggesting a reduction in cytochrome P450 1A2-mediated metabolism of theophylline. The magnitude of this reduction in theophylline metabolism was similar to that reported for standard α-interferons. PEG-IFN α-2a did not seem to affect the in vivo activities of the drug metabolizing cytochrome P450 isozymes 2C9, 2C19, 2D6, and 3A4 in healthy subjects receiving multiple subcutaneous doses of PEG-IFN α-2a. The pharmacokinetics, pharmacodynamics and tolerability of single subcutaneous doses of PEG-IFN α-2a in Japanese healthy male subjects were similar to those seen in non-Japanese subjects.

Ribavirin was absorbed rapidly with a mean time to maximum concentration (T_{max}) of 1.5 hours. Absorption was extensive but absolute bioavailability was only approximately 45% to 65%, likely due to the first-pass metabolism. The volume of distribution of ribavirin was approximately 5000 liters. Ribavirin did not bind to plasma proteins. The ratio of the whole blood to plasma ribavirin concentrations was approximately 60:1, and ribavirin in whole blood largely existed as ribavirin nucleotides sequestered in erythrocytes. Both ribavirin and its metabolites were excreted renally. After multiple-dose oral administrations of 600 mg of ribavirin twice a day, steady state was established by approximately 4 weeks, with a mean steady state plasma concentration of approximately 2200 ng/mL. After discontinuation of the drug, the half-life was approximately 300 hours, probably reflecting slow elimination from the nonplasma compartments. It is recommended that ribavirin be taken with food to achieve its optimal plasma concentration. Ribavirin concentrations were similar when given alone, with PEG-IFN α-2a, or with IFN α-2b. The oral clearance of ribavirin is substantially reduced in patients with renal dysfunction. Ribavirin should be used with caution in patients with severe renal impairment.

1.2 Clinical Study Results: PEG-IFN α-2a Monotherapy

For the PEG-IFN α-2a monotherapy program in treatment-naïve CHC patients, results are available from four completed clinical trials: a phase II dose-finding study (NV15489), a phase II/III study (NV15495, cirrhotic patients only), and two phase III studies (NV15496 and NV15497). For safety, the current version of the IB focuses on the pooled data of 1403 patients from the four studies.who were treated with once weekly dose of either 135 µg or 180 µg of PEG-IFN α-2a (weekly 180 µg is the recommended dose) for 48 weeks or with either 3 MIU of IFN α-2a tiw for 48 weeks or IFN α-2a 6 MIU tiw for 12 weeks followed by 3 MIU tiw for 36 weeks. The incidences and types of adverse events were generally similar among patients treated with PEG-IFN α-2a and IFN α-2a. Most adverse events were of mild to moderate intensity. The most frequently reported adverse events were headache, fatigue, myalgia, pyrexia, rigors, arthralgia, nausea, alopecia, insomnia, diarrhea, abdominal pain, depression, and injection site reaction. The incidence of serious adverse events in patients treated with PEG-IFN α-2a was 9%, compared with an incidence of 7% in patients treated with IFN α-2a. The most common serious adverse events were infections, psychiatric disorders, and gastrointestinal disorders. Treatment-related serious adverse events occurred in 4% and 2% of patients treated with PEG-IFN α-2a and IFN α-2a, respectively. Of these 1403 patients, seven patients died (one in the IFN α-2a 3 MIU group, two in the PEG-IFN α-2a 135-µg group, and four in the PEG-IFN α-2a 180-µg group), of which two deaths were considered related to the study drug (pneumonitis and cerebral hemorrhage). Two additional deaths occurred (one in the 45-µg dose group and another in the 90-µg dose group). Both deaths were unrelated to treatment. In the PEG-IFN α-2a 180-µg treatment group, 27% of patients needed dose modification because of adverse events or predominantly laboratory abnormalities, the incidence being higher than the corresponding incidence of approximately 20% in the other three treatment groups. In spite of this difference, 10% of patients from each treatment group prematurely discontinued treatment because of adverse events or laboratory abnormalities, indicating

that in many patients, these adverse events are manageable by dose modification and do not necessitate premature discontinuation. Depression and fatigue were the most common adverse events and thrombocytopenia and elevation in serum alanine aminotransferase (ALT) concentration were the most common laboratory abnormalities that led to premature discontinuation. Decreases in neutrophil and platelet counts occurred more frequently in PEG-IFN α-2a- than in IFN α-2a-treated patients. In general these laboratory abnormalities were reversible with dose modification and returned quickly toward pretreatment baseline levels after completion of treatment. The 270-µg once weekly regimen of PEG-IFN α-2a, which was assessed in 40 patients in the initial dose-finding phase II study, was generally less well tolerated than the lower PEG-IFN α-2a doses.

In all four studies, PEG-IFN α-2a treatment resulted in a significantly higher sustained virological response and significantly higher sustained biochemical response than IFN α-2a treatment.

In summary, in treatment naïve CHC patients, PEG-IFN α-2a once weekly had a similar clinical safety profile to IFN α-2a three times weekly but achieved a significantly higher sustained virological response and sustained biochemical response. The safety profiles of PEG-IFN α-2a in hepatitis B patients and oncology patients were similar to that in CHC patients. However, the safety profile of PEG-IFN α-2a in oncology patients was significantly affected by their underlying disease.

1.3 Clinical Study Results: PEG-IFN α-2a Plus Ribavirin Combination Therapy

The PEG-IFN α-2a plus ribavirin combination clinical development program for the treatment of CHC in treatment-naïve patients consisted of an initial pilot safety study (NV15800) and two phase III international registration trials, NV15801 and NV15942 (Appendix 1). Safety data in this report focuses on the two phase III studies, which are presented separately. In both phase III studies, the overall safety profile of 180 µg of PEG-IFN α-2a and 1000 or 1200 mg of ribavirin combination therapy for 48 weeks is similar to that with IFN α-2b and ribavirin combination therapy. In Study NV15801, the sustained virological response at week 72 patients treated with PEG-IFN α-2a plus ribavirin combination therapy was 56%, representing an efficacy superiority over both PEG-IFN α-2a monotherapy (29%, $p = 0.001$) and IFN α-2b plus ribavirin combination therapy (44%, $p = 0.001$). In Study NV15942, the highest sustained virological response in patients infected with genotype 1 was achieved with 48 weeks of treatment and 1000 or 1200 mg of ribavirin (52%). This was the case whether patients had a high pretreatment viral load or a low pretreatment viral load (47% and 65%, respectively). In patients infected with genotype non-1, similar sustained virological responses were achieved after treatment for 24 weeks with 800 mg of ribavirin and after treatment for a longer duration or with a higher dose of ribavirin. This was the case whether patients had a high pretreatment viral load or a low pretreatment viral load.

Study NV15801

For study NV15801, data from over 1100 patients were analyzed for safety and efficacy. Comparisons were made among three treatment groups: weekly 180-µg dose of PEG-IFN α-2a plus ribavirin daily 1000/1200 mg, 3 MIU of IFN α-2b three times a week plus daily 1000/1200 mg ribavirin, and weekly 180-µg dose of PEG-IFN α-2a monotherapy. Most common clinical adverse events were reported at a similar frequency with PEG-IFN α-2a, alone or with ribavirin combination therapy, and IFN α-2b and ribavirin therapy.The point estimates of certain interferon-associated events, which included depression and some "flu-like" symptoms (pyrexia, myalgia, and rigors), were lower in the two PEG-IFN α-2a treatment arms (monotherapy and combination therapy) than in the IFN α-2b and ribavirin combination treatment arm.

Three patients died during the study 6-month follow-up period or 1 year after the end of treatment. All three deaths were considered unrelated to treatment. The frequency of serious adverse events (related and unrelated events) was slightly higher with both PEG-IFN α-2a therapies (monotherapy and combination; 12% each) compared with IFN α-2b combination therapy (9%). The incidence of serious adverse events considered related to treatment was 4% with each of the three therapies. A similar frequency of anemia but higher frequencies of neutropenia and thrombocytopenia were observed with PEG-IFN α-2a and ribavirin combination therapy than with IFN α-2b plus ribavirin therapy. Most laboratory abnormalities were successfully managed with dose reduction and therefore did not require withdrawal of the patient. Premature withdrawals for adverse events and laboratory abnormalities were slightly higher with the combination therapies (10% each) compared with PEG-IFN α-2a monotherapy (7%).

Study NV15942

In this study, over 1300 patients were evaluated to assess the effects of either a shorter duration of treatment (ie, 24 weeks vs 48 weeks) or a lower daily dose of ribavirin (ie, 800 mg fixed dose vs 1000 or 1200 mg by body weight category), or both, on safety and efficacy.

The most common clinical adverse events in all four treatment groups were those usually associated with interferon treatment and included headache, fatigue, myalgia, and pyrexia. The incidence of individual clinical adverse events as well as the incidence of adverse events by body system was similar in the four treatment groups. Compared with 48 weeks of treatment with PEG-IFN α-2a and 1000/1200 mg of ribavirin, reducing treatment duration to 24 weeks and ribavirin dose to 800 mg resulted in fewer serious adverse events (11% vs 3%, respectively), fewer premature withdrawals for safety reasons (13% vs 5%, respectively), and fewer modifications of ribavirin dose (39% vs 19%, respectively).

Four patients died in this study; three of the four deaths occurred during treatment, and two of these three deaths were considered by investigators to be related to study medication (septic shock and suicide). The other two deaths were assessed by investigators as unrelated to study medication. The lowest incidence of serious adverse events occurred in patients treated for 24 weeks with the lower dose (800 mg) of

ribavirin. The most common serious adverse events were infections and psychiatric disorders. The incidence of serious infections was higher in patients treated for 48 weeks than in patients treated for 24 weeks and was also higher in patients receiving 1000 or 1200 mg of ribavirin than in patients receiving 800 mg of ribavirin. Serious psychiatric disorders occurred with similar frequencies in the 48 week and the 24 week treatment groups.

Treatment duration and ribavirin dose had little or no effect on the proportion of patients who experienced either a decrease in neutrophil counts to $<0.5 \times 10^9$/L (3% to 5% of patients) or a decrease in platelet counts to between 20 and $<50 \times 10^9$/L (3% to 5% of patients). Platelet counts did not fall below 20×10^9/L in any patient during the study. A decrease in hemoglobin concentration to <10 g/dL appeared to be dependent on the ribavirin dose and to a lesser extent on the duration of treatment. Modification of the PEG-IFN α-2a dose for anemia was very infrequent (3 patients). Very few patients were prematurely withdrawn from treatment for anemia (3 patients).

The majority of laboratory abnormalities were successfully managed with modification of the PEG-IFN α-2a or ribavirin dose and did not require discontinuation of treatment. Anemia was the most frequent laboratory abnormality necessitating modification of the ribavirin dose and was more frequent with the 48-week treatment duration.

The percentage of patients discontinuing treatment for a clinical adverse event or laboratory abnormality in the two groups being treated for 24 weeks was approximately one third that in the two groups being treated for 48 weeks. Ribavirin dose did not appear to have an effect on the frequency of discontinuation of treatment for safety reasons. Psychiatric disorders were the most common reason for discontinuing treatment, the most frequent of these being depression (2% each in patients treated for 24 or 48 weeks).

The highest sustained virological response in patients infected with genotype 1 was achieved with 48 weeks of treatment and 1000 or 1200 mg of ribavirin (52%). This was the case whether patients had a high pretreatment viral load or a low pretreatment viral load (47% and 65%, respectively). In patients infected with genotype non-1, similar sustained virological responses were achieved after treatment for 24 weeks with 800 mg of ribavirin and after treatment for a longer duration or with a higher dose of ribavirin. This was the case whether patients had a high pretreatment viral load or a low pretreatment viral load. In the group of all patients treated for 48 weeks with PEG-IFN α-2a and 1000 or 1200 mg of ribavirin the sustained virological response was 63%.

1.4 PEG-IFN α-2a Clinical Studies

The Roche-sponsored PEG-IFN α-2a clinical trials that are summarized in this IB are listed in Appendix 1.

2. INTRODUCTION

A pegylated version of IFN α-2a has been synthesized by chemically conjugating a branched 40 kilodalton (40-kDa) polyethylene glycol molecule to IFN α-2a [2.1]. PEG-IFN α-2a has been evaluated as monotherapy and in combination with ribavirin for the treatment of CHC. PEG-IFN α-2a monotherapy is also being evaluated for the treatment

of chronic hepatitis B and in three oncology indications: renal cell carcinoma, chronic myelogenous leukemia, and malignant melanoma.

2.1 Interferon

The interferons are a class of proteins produced by the body as part of its natural defensive response on exposure to the foreign constituents of viruses, microbes, and tumor cells. One class of these naturally occurring interferons, the α-interferons (interferon α), comprises a family of closely related, species-restricted proteins that exhibit antiviral, antitumor, and immunomodulatory activities. The genes for a number of these proteins have been cloned, and recombinant forms of interferon α, including interferon α-2a and interferon α-2b, have undergone extensive clinical investigation. To date, interferon α has been approved in numerous countries for the treatment of chronic hepatitis B (CHB), CHC, hairy-cell leukemia, AIDS-related Kaposi's sarcoma, condylomata acuminata, renal cell carcinoma, malignant melanoma, chronic myelogenous leukemia, basal cell carcinoma, non-Hodgkin's lymphoma, multiple myeloma, cutaneous T-cell lymphoma (mycosis fungoides), chronic delta hepatitis and laryngeal papillomatosis [2.2, 2.3]. Interferon α is also being used in combination with a multiplicity of chemotherapeutic agents in the investigational treatment of a variety of malignancies [2.4, 2.5, 2.6] and in combination with ribavirin, amantadine, mycophenolate mofetil, and nonsteroidal anti-inflammatory drugs in the investigational treatment of patients with CHC [2.7, 2.8, 2.9, 2.10].

Current treatment regimens require frequent administration of interferon α. Treatment intervals may range from three times per week to as often as once daily for periods of several months to a year or longer. The frequency of interferon α administration is determined by therapeutic requirements of the disease (daily for certain oncology indications and three times weekly for virology indications) and the pharmacokinetic properties of the protein. In various studies, the reported terminal elimination half-life for interferon α ranges from 4 to 10 hours, with peak serum concentrations occurring at 3 to 8 hours following intramuscular (im) or subcutaneous (sc) administration [2.11]. By 24 hours following intravenous (iv), im, or sc administration, there is little or no detectable interferon α remaining in the serum [2.11, 2.12, 2.12]. Thus, frequent administration of interferon α has been considered necessary for sustained efficacy. Furthermore, treatment with interferon α results in several dose-dependent side effects that cause difficulties associated with frequent administration. The typical acute toxicity profile that tends to occur after every injection includes flu-like symptoms of fever, chills, headache, myalgia, and dizziness.

2.2 Pegylated Proteins

PEGs are amphiphilic polymers of ethylene glycol of varying average molecular weights that can be covalently attached to proteins. Modification of proteins with PEG has resulted in increased serum half-life and reduced immunogenicity for a number of proteins [2.13]. The properties of pegylated proteins vary with the number of PEG molecules attached per protein molecule and the structure (eg, linear or branched) and average molecular weight of the PEG polymer. A number of proteins used for patient

therapy have now been modified with PEG and evaluated clinically [2.14, 2.15, 2.16, 2.17, 2.18]. All of these pegylated proteins have increased half-lives relative to the unmodified proteins. Pegylated proteins are also less immunogenic or nonimmunogenic.

PEG-IFN α-2a is a chemically modified IFN α-2a, produced by covalently attaching one branched methoxy PEG molecule (with an average molecular weight of 40 kDa) to IFN α-2a. Compared with IFN α-2a, PEG-IFN α-2a exhibits sustained absorption, decreased systemic clearance, and an approximately tenfold increase in serum half-life. The biological activity of PEG-IFN α-2a, as measured by 2′,5′-OAS activity, is prolonged, resulting in a significantly improved pharmacodynamic response compared with IFN α-2a. Data from animal studies and early phase I and II human clinical trials indicated that compared with IFN α-2a, the superior pharmacokinetic and pharmacodynamic profile of PEG-IFN α-2a would allow it to be given once a week.

2.3 HCV Infection and Current Treatment With Interferon

Interferon α was the first drug shown to have bioactivity against the hepatitis C virus (HCV). The treatment of patients with CHC infection with unmodified forms of interferon results in a consistent and dose-dependent response that is evident after 1 to 3 months of im or sc injections three times per week. Response is assessed by testing HCV RNA in serum and is defined as undetectable serum levels of HCV RNA. Unfortunately, of the patients who initially respond to interferon treatment, 50% or more lose their response either during treatment or after cessation of treatment. Consequently, IFN α-2a monotherapy given for 12 months results in only 10% to 20% of patients with a sustained virological response in the general CHC population [2.19]. Compared with those with HCV genotypes 2 and 3, patients with HCV genotype 1 respond poorly to interferon α treatment. Moreover, patients with high viral titers (HCV RNA > 1 to 2 million copies/mL) have a lower sustained virological response to interferon α than patients with low viral titers, and patients with cirrhosis have a substantially lower virological response (generally < 5%) than patients without cirrhosis [2.20]. The low sustained (long-term) response is a major challenge in the treatment of patients with chronic HCV infection. PEG-IFN α-2a with its sustained therapeutic concentrations over the weekly dosing intervals and prolonged biological activity may increase the sustained response by providing an adequate exposure of the virus to interferon during treatment.

2.3.1 Combination Therapy of PEG-IFN α-2a With Ribavirin

Ribavirin has been combined with interferon α in the treatment of CHC. Ribavirin is a guanosine analogue that inhibits the in vitro replication of a wide range of RNA and DNA viruses [2.21]. Ribavirin monotherapy has been shown to normalize serum ALT activity and to some degree improve liver histology, but relapse occurs in nearly all patients treated with ribavirin alone. Furthermore ribavirin monotherapy has no consistent effect on serum HCV RNA concentrations [2.22, 2.23]. Results from a phase III clinical study (NV15801) showed that sustained virological responses were significantly higher in patients treated with PEG-IFN α-2a plus ribavirin than in patients treated with PEG-IFN α-2a monotherapy. In addition the percentage of patients who maintained their end of treatment virological response was higher in patients who

received ribavirin in combination with PEG-IFN α-2a compared with those who received PEG-IFN α-2a monotherapy.

Most previous experience has been with ribavirin in combination with interferon α-2b (IFN α-2b), a therapy that has been approved in the United States and Europe for the treatment of CHC. The addition of ribavirin has resulted in an approximately twofold increase in sustained virological response in treatment naïve patients compared with interferon α-2b monotherapy [2.24, 2.25]. The superiority in efficacy with interferon α plus ribavirin combination therapy and the enhanced response with PEG-IFN α-2a in combination with ribavirin that was seen in a phase II study (NV15800) suggested that the combination of PEG-IFN α-2a and ribavirin may result in a further increase in sustained virological response. This was confirmed in two phase III studies (NV15801 and NV15942) evaluating PEG-IFN α-2a plus ribavirin combination therapy; results from the combination therapy program can be found in section 6.

PEG-IFN α-2a (Pegasys) and Roche ribavirin (Copegus) have been approved in the United States as monotherapy and as combination therapy with ribavirin for the treatment of CHC.

2.4 Hepatitis B

Chronic infection with hepatitis B virus (HBV) affects approximately 5% of the world population [2.26]. Chronically infected individuals with HBV replication are at highest risk for progressive disease, leading to cirrhosis, liver failure, and hepatocellular carcinoma [2.27]. The calculated lifetime risk of death from cirrhosis or hepatocellular carcinoma in chronic hepatitis B antigen carriers is 25% to 40% [2.28, 2.29]. A high level of HBV replication or the presence of hepatitis B antigen is predictive of poor survival [2.27, 2.30].

Interferon α, the first treatment approved worldwide for chronic hepatitis B, has both direct antiviral and potent immunomodulatory activity, including stimulation of cytotoxic T-lymphocytes (CTL). CTL response is seen in acute resolving hepatitis B, as well as in chronically infected individuals with spontaneous clearance of HBV. Patients with persisting HBV infection have an incomplete CTL response against multiple hepatitis B epitopes. Interferon α is twice as effective (30 to 40%) in stimulating a CTL response compared to untreated controls (12% to 17%). [2.31]. Nucleoside analogues, such as lamivudine, have been shown to suppress HBV DNA replication in 40% to 60% of patients. However, when treatment is stopped, a quick rebound of HBV DNA can be observed [2.32]. Combination therapy of interferon α and lamivudine may have the potential to increase response and reduce rebound in chronic hepatitis B.

The principal treatment goal for individuals chronically infected with HBV should be to stimulate a successful immune response which will result in long-term viral clearance and avoid the need for suppressive maintenance therapy. As shown by the encouraging results in CHC, PEG-IFN α-2a, because of its increased clinical efficacy, improved tolerability, and once weekly dosing, is currently among the most promising agents being tested in order to achieve this goal.

2.5 Oncology Indications and Current Treatment With Interferon

For oncology patients, there is a need for more effective therapy with an improved tolerability profile. The efficacy of PEG-IFN α-2a was evaluated in four Roche-sponsored clinical trials for the treatment of three indications that have shown responses to interferons: advanced or metastatic renal cell carcinoma (phase I/II), chronic myelogenous leukemia (phases I and III), and metastatic malignant melanoma (phase II). Two clinical trials evaluating the efficacy of PEG-IFN α-2a for the treatment of metastatic melanoma and chronic myelogenous leukemia are currently ongoing.

2.5.1 Chronic Myelogenous Leukemia

Chronic myelogenous leukemia is a myeloproliferative disorder that is a neoplastic transformation of the pluripotential stem cells characterized by an increase in the white blood cell (WBC) count to greater than 10,000 cells/mm^3. A specific cytogenetic abnormality, the Philadelphia chromosome, has been identified in the WBCs of some patients with chronic myelogenous leukemia. Cytogenetic remissions (loss of the Philadelphia chromosome) have been associated with improved survival in patients with chronic myelogenous leukemia [2.33]. Therapy with IFN α-2a has been associated with improved survival in randomized trials compared with therapy with alkylating agents [2.34]. The addition of cytarabine to IFN α-2a has been shown to further improve the rate of cytogenetic remission [2.35].

2.5.2 Malignant Melanoma

Malignant melanoma is a tumor of the pigment-producing cells in the skin. It is essentially a disease of white-skinned individuals and has been identified as one form of cancer that will become a very important public health concern in the absence of effective intervention. The incidence varies regionally from 0.2 to 40 per 100,000 per annum and is predicted to rise by 5% to 6% annually. Metastatic melanoma is invariably a fatal disease. The overall median survival of patients with systemic metastases is about 6 months to 1 year. Currently, the use of immunotherapy (interferon, IL-2) in metastatic melanoma is largely palliative. The overall response of patients with malignant melanoma to conventional interferon-α therapy is approximately 10% to 15% with only very few durable responses (< 5%). New therapies are therefore needed for the treatment of metastatic melanoma. The improved pharmacokinetic profile of PEG-IFN α-2a may increase the tumor response to interferon, prolong survival, and decrease toxicity. The primary use of α interferon in this indication is as adjuvant to surgical treatment, with the goal of preventing or delaying progression to metastatic disease.

2.6 References

2.1 Bailon P, et al. Long lasting forms of polyethylene glycol conjugated interferon α-2a. Roche Research Report N-130915. May 3, 1996.

2.2 Baron S, Tyring SK, Fleischmann WR, et al. The interferons. Mechanisms of action and clinical applications. JAMA. 1991;266:1375-1383.

2.3 Spiegel RJ. Alpha interferons: A clinical overview. Urology. 1989;34:75-79.

2.4 Wadler S and Schwartz EL. Antineoplastic activity of the combination of interferon and cytotoxic agents against experimental and human malignancies: A review. Cancer Res. 1990;50:3473-3486.

2.5 Lipmann SM, Parkinson DR, Itri LM, et al. 13-cis-retinoic acid and interferon α-2a: Effective combination therapy for advanced squamous cell carcinoma of the skin. J Natl Cancer Inst. 1992;84:235-241.

2.6 Lipmann S, Kabanagh JJ, Paredes-Espinoza M, et al. 13-cis-retinoic acid plus interferon α-2a: Highly active systemic therapy for squamous cell carcinoma of the cervix. J Natl Cancer Inst. 1992;84:241-245.

2.7 Smith JP. Treatment of chronic hepatitis C with amantadine-hydrochloride. Gastroenterology. 1996;110:A1330.

2.8 Andreone P, Gramenzi A, Cursaro C, et al. A randomized controlled trial of IFN α + ketoprofen or IFN + ribavirin in HCV chronic active hepatitis (CAH) non-responder to IFN alone. Hepatology. 1995;22:119A.

2.9 El-Zayadi A, Selim O, El Haddad S, et al. Combination treatment of alpha interferon-2b (alpha IFN) and ribavirin in chronic hepatitis C genotype 4 patients resistant to interferon therapy. Hepatology. 1995;22:152A.

2.10 Mazzaferro V, Regalia E, Pulvirenti A, et al. Effect of interferon and ribavirin prophylaxis after liver transplantation in HCV-RNA positive patients. Hepatology. 1995;22:287A.

2.11 Wills RJ. Clinical pharmacokinetics of interferons. Clin Pharmacokinet. 1990;19:390-399.

2.12 Barouki FM, Witter FR, Griffin DE, et al. Time course of interferon levels, antiviral state, 2',5'-oligoadenylate synthetase and side effects in healthy men. J Interferon Res. 1987;7:29-39.

2.13 Nucci ML, Shorr R and Abuchowski A. The therapeutic value of poly(ethylene glycol)-modified proteins. Adv Drug Delivery Rev. 1991;6:133-151.

2.14 Hershfield MS, Buckley RH, Greenberg ML, et al. Treatment of adenosine deaminase deficiency with polyethylene glycol-modified adenosine deaminase. N Engl J Med. 1987;316:589-596.

2.15 Jurgens H, Schwamborn D, Korholz D, et al. Clinical experience with polyethylene glycol coupled E. coli asparaginase in patients with recurrent ALL. Klin Pediatr. 1988;200:184-189.

2.16 Thompson PD, Till GO, Woolliscroft JO, et al. Superoxide dismutase prevents lipid peroxidation in burned patients. Burns. 1990;16:406-413.

2.17 Chua CC, Greenberg ML, Viau AT, et al. Use of polyethylene glycol-modified uricase (PEG-uricase) to treat hyperuricemia in a patient with non-Hodgkin's lymphoma. Ann Int Med. 1988;109:114-117.

2.18 Meyers FJ, Paradise C, Scudder SA, et al. A phase I study including pharmacokinetics of polyethylene glycol conjugated interleukin-2. Clin Pharmacol Ther. 1991;49:307-313.

2.19 Davis GL and Lau JYN. Factors predictive of a beneficial response to therapy of hepatitis C. Hepatology. 1997;26(3)suppl 1:122S-127S.

2.20 Fried M and Hoofnagle J. Therapy of hepatitis C. Semin Liver Dis. 1995;15(1):82-91.

2.21 Sidwell RW, Robins RK and Hillyard IW. Ribavirin: an antiviral agent. Pharmacol Ther. 1979;6:123-146.

2.22 Dusheiko G, Main J, Thomas H. et al. Ribavirin treatment for patients with chronic hepatitis C: Results of a placebo controlled trial. J Hepatol. 1996;25:591-598.

2.23 Di Bisceglie AM, Conjeevaram HS, Fried MW et al. Ribavirin as therapy for chronic hepatitis C. A randomized, double-blind, placebo-controlled trial. Ann Int Med. 1995;123:897-903.

2.24 Lai MY, Kao JH, Yang PM, et al. Long-term efficacy of ribavirin plus interferon alfa in the treatment of chronic hepatitis C. Gastreneterology. 1996;11:1307-1312.

2.25 Reichard O, Nokrans G, Fryden A et al. Randomized, double-blind, placebo-controlled trial of interferon α-2b with and without ribavirin for chronic hepatitis C. Lancet. 1998;351:83-87.

2.26 Kane MA. Progress on the control of HBV infection through immunization. Gut. 1993;34(Suppl):105-125.

2.27 De Jongh FE, et al. Survival and prognostic indicators of HBV surface antigen positive cirrhosis of the liver. Gastroenterology. 1992;103:1630-1635.

2.28 Maynard JE, et al. Control of HBV by immunization: global perspective. In: Zuckerman AJ ed. Viral hepatitis and liver disease. New York: Liss. 1988:967-969.

2.29 Margolis HS, et al. Evolving epidemiology and implications for control. Semin Liver Dis. 1991;11:84-92.

2.30 Weissberg JI, et al. Survival in chronic hepatitis B. Ann Intern Med 1984;101:613-616.

2.31 Wong DKH, et al. Effect of alfa interferon treatment in patients with hepatitis B e antigen positive chronic hepatitis B infection: A meta-analysis. Ann Intern Med. 1993;119:312-323.

2.32 Nevens F, et al. Lamivudine therapy for chronic hepatitis B: A six months randomized dose ranging study. Gastroenterology. 1997;113:1258-1263.

2.33 Talpaz M, Kantarijian H, Kurzrock R, et al. Interferon-alpha produces sustained cytogenetic response in chronic myelogenous leukemia: Philadelphia chromosome positive patients. Ann Intern Med. 1991;114:532-538.

2.34 Goldman JM. Optimizing treatment for chronic myeloid leukemia. New Engl J Med. 1997;337:270-271.

2.35 Guilhot F, Chastang C, Michallet M, et al. Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. New Engl J Med. 1997;337:223-229.

3. CHEMISTRY AND FORMULATION OF PEG-IFN α-2A

3.1 Synthesis and Purification

PEG-IFN α-2a is synthesized by the covalent attachment of a branched monomethoxy PEG molecule to interferon IFN α-2a [3.1].

Interferon is produced biosynthetically using recombinant DNA technology and is the product of a cloned human leukocyte interferon gene inserted into and expressed in E. coli [3.2]. IFN α-2a is purified by sequential chromatographic procedures, including copper chelate, cation and anion exchange resins and exclusion molecular sieving [3.3]. Purified IFN α-2a has 165 amino acids and a molecular weight of 19,237 daltons [3.3]. The primary structure of IFN α-2a is illustrated in Figure 1.

The branched monomethoxy PEG reagent, Ro 26-8955 [3.3], consists of two monomethoxy PEG chains, each with an average molecular weight of ~20,000 daltons, linked to a lysine molecule via urethane bonds. The chemical structure of Ro 26-8955 is illustrated in Figure 2.

PEG-IFN α-2a is synthesized by the chemical conjugation of a branched PEG molecule to lysine residues of IFN α-2a. Purification of PEG-IFN α-2a is accomplished by cation exchange chromatography in conjunction with concentration and diafiltration [3.1]. The final product has an average molecular weight of ~60,000 daltons and contains at least 95% monopegylated interferon, free of unmodified protein and reaction by-products.

3.2 Formulation

PEG-IFN α-2a is formulated as an injectable solution containing benzyl alcohol, sodium chloride, sodium acetate trihydrate, acetic acid (glacial), polysorbate 80, and water for injection. The concentration of PEG-IFN α-2a is dependent on the clinical indication: for studies in hepatitis C, concentrations of 45, 90, 135, 180, and 270 µg/mL were used; for

oncology indications, concentrations of 270, 360, 450, 540, and 630 µg/mL were used. All clinical supplies are packaged as 1 mL unit doses in 2-mL capacity flint glass vials.

PEG-IFN α-2a is also formulated as prefilled syringes. The formulations of PEG-IFN α-2a in prefilled syringes and in flint glass vials contain the same excipients in the same concentrations but differ in the content of active drug substance. For prefilled syringes, the nominal fill volume is 0.5 mL, the drug substance concentrations are 270 and 360 µg/mL, and the syringe dosage strengths are therefore 135 and 180 µg/0.5 mL.

3.2.1 Stability of Formulation

Up to 2 years of stability data have been obtained on clinical lots with concentrations of 135, 180, and 270 µg/mL for the glass vial formulation. The stability data indicate that the formulation is stable when stored unopened at the recommended storage condition of 5°C for up to 24 months.

Figure 1 Primary Structure of IFN α-2a and Major Sites of PEG Attachment

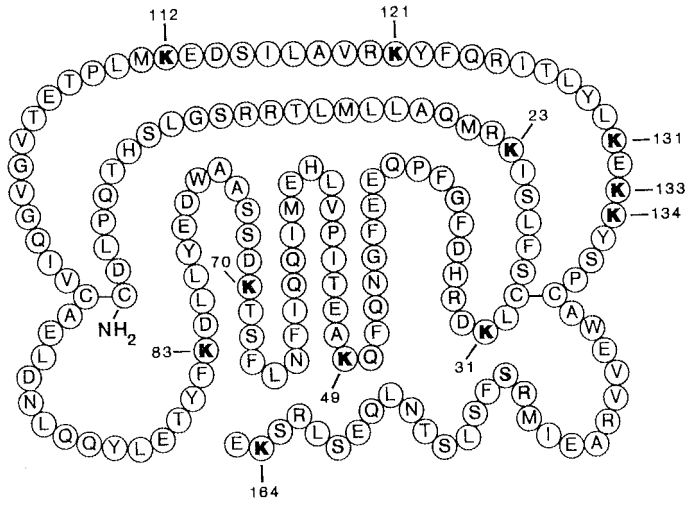
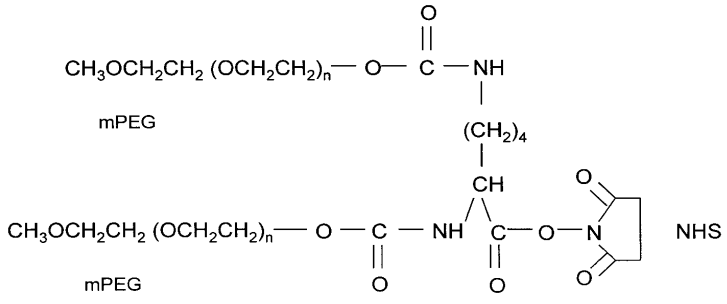


Figure 2 Chemical Structure of the PEG Reagent Ro 26-8955



3.3 References

3.1 Bailon P, Schaffer CA, Spence C, et al. Long lasting forms of polyethylene glycol conjugated interferon α-2a. Roche Research Report N-130915, May 3, 1996.

3.2 Goeddel DV, Yelverton E, Ulrich A, et al, Human leukocyte interferon produced in E. coli. Nature. 1980;287:411-416.

3.3 Supplement to Roferon®-A PLA, second generation interferon alfa-2a CMC section. Submitted June 6, 1997.

3.4 Monfardini CS, Schiavon O, Caliceti P, et al, A branched monomethoxy poly(ethylene glycol) for protein modification. Bioconjugate Chem. 1995;6;62-69.

4. NONCLINICAL STUDIES: PEG-IFN α-2A

4.1 Nonclinical Pharmacology

Nonclinical pharmacology studies on PEG-IFN α-2a demonstrate that it retains the in vitro activities typical of IFN α and has in vivo properties similar or superior to IFN α. Since the biological activity of IFN α-2a is species-restricted, these studies were performed on cells (bovine, human) or animals (cynomolgus monkeys), in which human IFN α-2a is active. Furthermore, no safety findings of clinical importance were seen in the pharmacology studies.

In vitro studies demonstrate that PEG-IFN α-2a qualitatively retains those properties that define IFN α:

- Binding to the IFN α receptor and transduction of a signal [4.1].
- Induction of expression of known IFN α-inducible genes [4.2, 4.3].
- Antiviral activity shown by inhibition of replication of HCV subgenomic RNA in a human hepatoma cell line [4.4, 4.5, 4.6, 4.7] and inhibition of replication of surrogate viruses that are known to be sensitive to IFN α [4.1, 4.8].
- Antiproliferative activity characteristic of IFN α on human tumor cells [4.8, 4.9, 4.10].
- Retention of biological activity by all the separated positional isomers of PEG-IFN α-2a [4.7, 4.11].

The in vivo studies with PEG-IFN α-2a are restricted by the species specificity of IFN α-2a, which limits studies of biological activity to monkeys or to human xenografts in nude mice. In vivo studies demonstrate that PEG-IFN α-2a has a similar biological activity to IFN α-2a in the following models of IFN α activity:

- PEG-IFN α-2a demonstrated at least equivalent maximum biological activity to IFN α-2a in monkeys when induction of 2′,5′-oligoadenylate synthetase (2′,5′-OAS) activity in serum was used as a surrogate pharmacodynamic marker [4.12].
- PEG-IFN α-2a showed antitumor activity (reduction of growth and promotion of regression) superior to that seen with IFN α-2a on a protein weight basis, when administered to nude mice bearing human tumor xenografts [4.9]. The improved pharmacokinetic and pharmacodynamic properties of PEG-IFN α-2a relative to IFN α-2a were demonstrated in this in vivo model, but the enhanced antitumor activity was not predicted by the in vitro antiproliferative test [4.9].
- PEG-IFN α-2a was immunogenic in animals (mice and monkeys) [4.8, 4.18, 4.19, 4.13, 4.14, 4.15]. Since human IFN α is generally immunogenic in animals, results from these studies can not be extrapolated to assess the likelihood of antibody formation in humans.
- Treatment of mice with PEG-IFN αA/D (a pegylated form of a hybrid human IFN α that is active on murine cells) resulted in neutropenia, which was ameliorated by treatment with granulocyte-colony stimulating factor [4.16, 4.17].

A complete battery of safety pharmacology studies conducted on central nervous, gastrointestinal, renal, cardiovascular, and respiratory systems with PEG-IFN α-2a

showed no findings of clinical importance at doses of 6, 60, and 600 µg/kg, the doses being equivalent to approximately 2, 20, and 200 times the anticipated dose of 180 µg for humans, respectively [4.20].

4.2 Pharmacokinetics and Pharmacodynamics

Nonclinical pharmacokinetic and pharmacodynamic studies on PEG-IFN demonstrate:

- PEG-IFN α-2a has a superior pharmacokinetic profile in animals compared with IFN α-2a, with a $T_{1/2}$ that was approximately sevenfold longer in rats and approximately 20-fold longer in cynomolgus monkeys [4.8, 4.12].
- The absorption of PEG-IFN α-2a is sustained from the subcutaneous site, the clearance is reduced, and the volume of distribution is more restricted to interstitial fluids and the blood [4.8, 4.12].
- PEG-IFN α-2a has equivalent biological activity in monkeys compared with IFN α-2a (using the induction of 2′,5′-oligoadenylate synthetase activity in serum as a surrogate pharmacodynamic marker) [4.12].

These pharmacokinetic and pharmacodynamic findings provide a basis for once weekly dosing of PEG-IFN α-2a.

Following multiple dosing in animals, PEG-IFN α-2a exposure decreased over time, which is consistent with the dose- and time-dependent formation of anti-IFN antibodies [4.17].

4.3 Distribution and Metabolism

The distribution and metabolism of PEG-IFN α-2a have been characterized in both single- and multiple-dose studies. The main findings from these studies are:

- The urine was the primary route of excretion after both intravenous and subcutaneous administrations of PEG-IFN α-2a in rats [4.26].
- The majority of radioactively labeled PEG-IFN α-2a was found in major perfused organs at concentrations lower than that found in the blood following both intravenous and subcutaneous administration in rats [4.26].
- Only the intact PEG-IFN α-2a was detected, and no free IFN α-2a was detected in the serum of rats administered daily doses of drug by either intravenous or subcutaneous administration for up to 7 days [4.27].
- Both the liver and the kidney appeared to play a role in the elimination of PEG-IFN α-2a in rats [4.27].
- After subcutaneous administration of [^{14}C] PEG-IFN α-2a in rats, low levels of radioactivity were detected in the milk, indicating a minimal transfer of drug-derived radioactivity [4.28].
- Low levels of radioactivity were detected in rat fetuses indicating a minimal transfer of radioactivity through the placental barrier [4.28].

4.4 Toxicology and Toxicokinetics

The toxicology and toxicokinetic studies with PEG-IFN α-2a are listed in Appendix 2. The main findings from these studies are summarized below.

- At doses of 400-fold greater (1200 µg/kg/week) than the intended clinical dose (180 µg/week, 3 µg/kg for a 60 kg person), toxicologic findings were limited to:
  - Slight transient hematologic changes (ie, decreased platelets and WBCs).
  - Slight transient clinical chemistry changes, including decreases in protein, calcium, and in a few animals, elevated ALT and/or aspartate transferase (AST) (1.4 to 2.3 times baseline).
- As a consequence of an immunogenic response to PEG-IFN α-2a by monkeys, which resulted in marked reduction in serum exposure to PEG-IFN α-2a, a resolution of adverse effects was observed after 2 weeks of treatment during all multiple-dose studies.
- Despite the marked reduction in serum exposure with time, the exposure in animals (AUC, area under the curve; C_{max}, maximum concentration) remained considerably higher than that seen in patients.
- No histopathologic findings were observed in any of the multiple-dose toxicity studies, with the exception of subcutaneous inflammation at the injection sites.
- As with IFN α-2a, PEG-IFN α-2a elicited irregularities in menstrual cycles and cyclic serum sex steroid hormone levels in female monkeys. These effects were reversible after treatment discontinuation. Similar effects in the monkey have previously been associated with the occurrence of spontaneous abortions in addition to impaired female fertility.

4.5 References

4.1 Ackrill AM. Studies on the in vitro biological activities of PEG-IFN (Ro 25-8310), with reference to Roferon-A (Ro 25-8181): (University of Toronto). Research Report W-143195, November 22,1999.

4.2 Certa U. Gene expression patterns of interferon alpha or peginterferon alfa-2a stimulated human melanoma cells using DNA microarrays. Research Report 1005805. August 3, 2001.

4.3 Laxton C, Gilbert S, Ackrill A, et al. Induction of the interferon-inducible human gene, 6-16, by Roferon®-A (Ro 25-8181) and peginterferon alfa-2a (Ro 25-8310). Research Report W-143166, August 12, 1999.

4.4 Carr J, Najera I, Gilbert S, et al. Inhibition of HCV Subgenomic RNA Replication in a human hepatoma cell-based assay by interferon alfa-2a and pegylated interferon alfa-2a. Research Report W-1000515, February 4, 2000.

4.5 Najera I, Laxton C et al. Studies on inhibition of HCV replicon by ribavirin and possible mechanisms of action. Research Report 1003775. February 26, 2001.

4.6 Najera I, Laxton C et al. Use of HCV subgenomic replicon for in vitro combination studies: ribavirin in combination with interferon alfa-2a or pegylated interferon alfa-2a. Research Report 1003860. February 26, 2001.

4.7 Laxton C and Najera I. Inhibition of the HCV subgenomic replicon by isolated positional isomers of peginterferon alfa-2a. Research Report 1005698. August 20, 2001.

4.8 Bailon P, Spence C, Schaffer CA, et al. Long lasting forms of polyethylene glycol conjugated interferon α-2a. Research Report N-130915, May 3, 1996.

4.9 Palleroni AV, Dvorozniak MT and Aglione A. Antiproliferative and antitumor activity of pegylated interferon alpha (RO 25-8310). Research Report N-181005, January 31, 1998.

4.10 Stremlo D, Khan A, et al. Antiproliferative activity of pegylated interferon alpha (Ro 25-8310). Research Report N-181539, February 2000.

4.11 Weyer K, Jermann D et al. Pegasys I: Isolation and characterisation of peginterferon alfa-2a (Ro 25-8310) positional isomers by bioanalytical methods and the antiviral assay. Research Report 1003964. June 11, 2001.

4.12 Holzknecht B, Bosley F and Greway AT. The pharmacokinetics and pharmacodynamics of PEG2-IFN (Ro 25-8310) and ROFERON® A (Ro 22-8181) in the female cynomolgus monkey, following single subcutaneous administrations of PEG2-IFN or ROFERON® A (D95111). Research Report N-138704, October 10, 1996.

4.13 Aglione A, Bailon PS, Dvorozniak MT, et al. Immunogenicity of pegylated recombinant human interferon alpha 2a candidates in mice. Research Report N-138888, July 22, 1996.

4.14 Eliahou CB, Greway A and Palleroni A. Ro 25-8310/000 (PEG2-Interferon alfa-2a): A 4-week subcutaneous toxicity, toxicokinetic and immunogenicity study in the cynomolgus monkey by twice weekly administration (Quintiles Scotland Limited Study No. DHA01001 and HLR Study No. 06862). Research Report N-138905, October 9, 1996.

4.15 Eliahou CB, Buonarati M, Palleroni A, et al. Ro 25–8310/000 (PEG–IFN): Four-week daily subcutaneous injection toxicity, toxicokinetic, and immunogenicity study in the cynomolgus monkey with a four–week recovery period (Quintiles Scotland Limited Study No. DHA01801 and HLR Study No. 06884). Research Report N–139170, July 31, 1997.

4.16 Eliahou CB, Moore DJ, Ostrowski C, et al. Ro 25-8310 (PEG-IFN): Thirteen-week subcutaneous (twice-weekly) toxicity, toxicokinetic, and immunogenicity study in cynomolgus monkey with a four-week recovery period. Research Report N-181321, February 11, 2000.

4.17 Staudner H, Eliahou CB, Moore D, Ostrowski C. Ro 25-8310 (PEG-IFN): A study of the effects of Ro 25-8310 on sex steroid hormones on female cynomolgus monkey. Research Report N-181442, March 7, 2000.

4.18 Slater C, Bohoslawec O and Eliahou C. An investigative study on the effects of a Filgrastim (Neupogen) treatment regiment on the reversal of PEG-IFN α-2aαA/D induced neutropenia in female mice (Study No. 06978). Research Report N-181360, March 22, 1999.

4.19 Slater C, Bohoslawec O and Eliahou C. A two-week study of the effect of a Filgrastim (Neupogen) subcutaneous treatment regimen on the reversal of PEG-IFN α-2aαA/D induced neutropenia in female mice (Study No. 07041). Research Report N-181361, July 29, 1999.

4.20 Catala AR and Eliahou CB. Ro 25-8310 (PEG-IFN α-2a): Safety pharmacology (Quintiles Scotland Limited, study No. DHA02201-02210, Roche study No. 06938). Research Report N-139406, October 6, 1997.

4.21 Merritt JA, Borden EC, Ball LA. Measurement of 2',5'-oligoadenylate synthetase in patients receiving interferon-alpha. J. Interferon Res. 1985;5:191-198.

4.22 Bryson A. Ro 25-8310/000 (pegylated interferon). An acute subcutaneous toxicity study in the cynomolgus monkey (Macaca fascicularis) (Study No. AP656). Roche Research Report W-142580, September 25, 1996.

4.23 Bryson A. Ro 25-8310 (pegylated interferon): An acute intravenous toxicity study in the cynomolgus monkey (Macaca fascicularis) (Study No. AP673). Roche Research Report W-142711, July 14, 1997.

4.24 Albertini S. Mutagenicity evaluation of Ro 25-8310/000 (PEG-IFN α-2a) in the Ames test (Study No. 85M96). Roche Research Report B-165498, March 26, 1996.

4.25 Miller B. Chromosome analysis in human peripheral blood lymphocytes treated in vitro with Ro 25-8310/000 (PEG-IFN α-2a) in the presence and in the absence of a metabolic activation system (Study No. 060M96). Roche Research Report B164915, June 5, 1996.

4.26 Fulton J, Buckmann DK. Mass Balance and tissue distribution after single i.v and s.c administration of [14C] PEG-IFN (14C Ro 25-8310) to male rats. Research Report N –181400. February 11, 2000.

4.27 Buckman DK, Fulton J. Ro 25-8310: Distribution and metabolism of PEG-IFN alfa-2a after single and multiple administrations to male rats. RR 1002849, 2001.

4.28 Buckman DK, Moore D et al. Ro 25-8310: Lacteal and placental transfer of [14C]PEG-IFN after subcutaneous administration to lactaing and pregnant rats. RR 1003387, 2001.

5. CLINICAL STUDIES OF PEG-IFN α-2A MONOTHERAPY

5.1 Clinical Pharmacology

5.1.1 Pharmacodynamics

HCV RNA levels decline in a biphasic manner in responding CHC patients who received PEG-IFN α-2a. The first phase of decline occurred within 24 to 36 hours after the first dose of PEG-IFN α-2a, and the second phase of decline occurred over the next 4 to 16 weeks in patients who achieved a sustained response. Weekly PEG-IFN α-2a 180 µg administration enhanced the virion clearance, improved the virological end of treatment responses and end of follow-up responses (sustained virological response) compared with treatment with standard α interferons.

PEG-IFN α-2a stimulated the production of effector proteins such as serum neopterin and 2′,5′-OAS in a dose-dependent manner. The stimulation of 2',5'-OAS was maximal after single doses of 135 and 180 µg of PEG-IFN α-2a and stayed maximal throughout the 1-week dosing interval. The magnitude and duration of PEG-IFN α-2a-induced 2',5'-OAS activity were reduced in subjects older than 62 years and in subjects with significant renal impairment (creatinine clearances of 20 to 40 mL/min). The clinical relevance of these findings with pharmacodynamic markers of PEG-IFN α-2a is not known.

5.1.2 Pharmacokinetics

The structure of the PEG moiety directly affects the clinical pharmacology of PEG-IFN α-2a. Specifically, the size and branching of the 40 kDa PEG moiety define the absorption, distribution, and elimination of PEG-IFN α-2a. The pharmacokinetics of PEG-IFN α-2a were studied in healthy subjects and HCV-infected patients. Absorption of PEG-IFN α-2a was sustained, peak serum concentrations were reached 72 to 96 hours after dose administration, and measurable concentrations were seen within 3 to 6 hours of a single dose. Within 24 hours, 80% of peak serum concentrations are reached. Dose proportional increases in AUC and C_{max} were seen in patients who received once weekly doses of PEG-IFN α-2a. The absolute bioavailability was 84% and was similar to that seen with IFN α-2a.

The systemic clearance was about 100 mL/h, which was 100-fold lower than that of IFN α-2a. After an intravenous dose, the terminal half-life was about 60 to 80 hours, compared to 3 to 4 hours for standard interferon. The terminal half-life after subcutaneous dosing was longer (about 80 hours, range of 50 to 130 hours). After intravenous dosing, the steady-state volume of distribution was 6 to 14 liters. Based on studies in rats, the drug was distributed to the liver, kidney, and bone marrow as well as being highly concentrated in the blood.

Metabolism is the main clearance mechanism for PEG-IFN α-2a. The kidneys eliminated less than 10% of a dose as the intact PEG-IFN α-2a. The metabolic profile of PEG-IFN α-2a has not been fully characterized. Studies in rats showed that the PEG moiety remained attached as the protein portion was metabolized. The metabolic products of PEG-IFN α-2a (including the PEG moiety attached to the metabolized

interferon) were excreted in the urine and bile. In rats, the half-life of the radiolabeled PEG moiety was about 10 days and, thus, within about 50 to 60 days the PEG moiety was eliminated from the body.

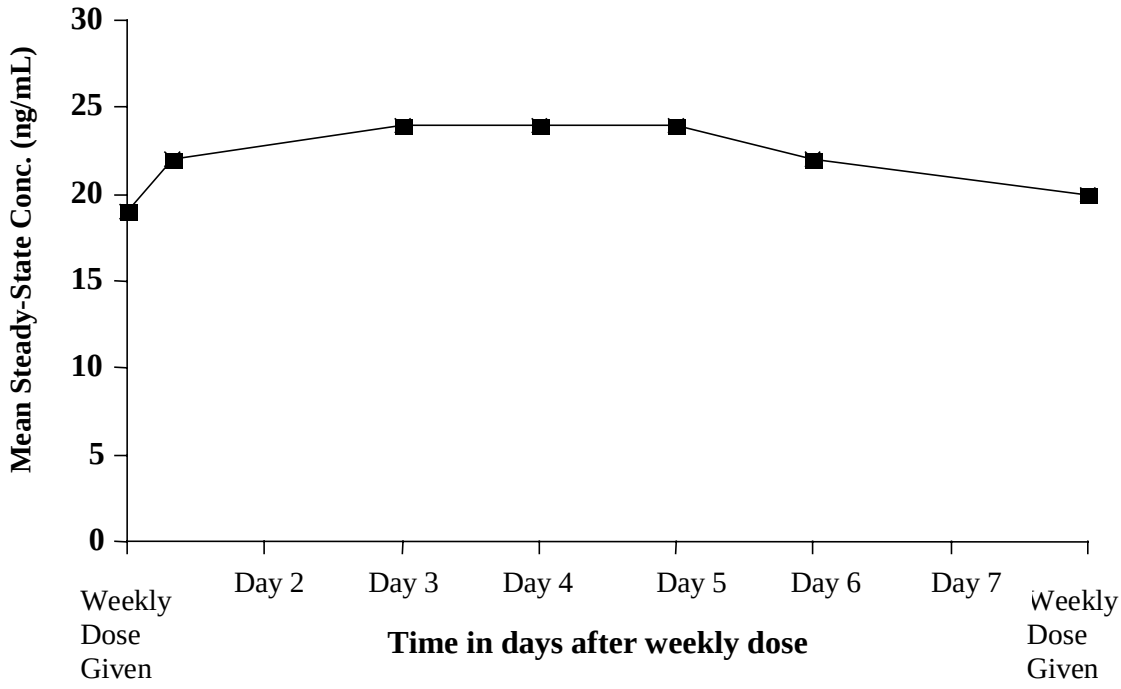
In patients with CHC, steady-state serum concentrations increased twofold to threefold compared with single-dose values and reached steady state within 6 to 8 weeks of once weekly dosing. Once steady state was achieved, there was no further accumulation of PEG-IFN α-2a. The peak to trough ratio after 48 weeks of treatment was about 1.5 to 2.0. PEG-IFN α-2a serum concentrations were sustained throughout the 1-week dose interval (168 hours) (Table 1 and Figure 3).

Table 1 Pharmacokinetic Parameters of PEG-IFN α-2a After Single and Multiple Doses of 180 μg

PEG-IFN α-2a Pharmacokinetic Parameter	Healthy Subjects 180 μg sc (N = 50)	CHC Patients[a] 180 μg sc Treatment (N = 16)	
	Single Dose Mean ± SD (Range)	Single Dose Mean ± SD (Range)	Week 48 Dose Mean ± SD (Range)
C_{max} (ng/mL)	14 ± 5 (6 - 26)	15 ± 4 (7 – 23)	26 ± 9 (10 – 40)
T_{max} (h)	92 ± 27 (48 – 168)	80 ± 28 (23 - 119)	45 ± 36 (0 – 97)
$AUC_{1\text{-}168\ h}$ (ng·h/mL)	1725 ±586 (524 – 3013)	1820 ± 586 (846 – 2609)	3334 ± 994 (1265 – 4824)
Clearance/F (mL/h)	94 ± 56 (34 – 337)	83 ± 50 (33 – 186)	60 ± 25 (37 – 142)
Week 48 Trough Concentration (ng/mL)	Not applicable	Not applicable	16 ± 6 (4 – 28)
Peak to Trough Ratio for Week 48	Not applicable	Not applicable	1.7 ± 0.4 (1.1 - 2.5)
Accumulation ($AUC_{Week\ 48}$/ $AUC_{Single\ Dose}$)	Not applicable	Not applicable	2.3 ± 1.0 (1.1 - 4.0)

[a]From clinical trial NV15496.

Figure 3 Mean Steady-State PEG-IFN α-2a Concentrations in Patients with CHC Following 180 μg of PEG-IFN α-2a in Combination Therapy (Study NV15801)



5.1.3 Special Populations

The pharmacokinetics of PEG-IFN α-2a were comparable in male and female healthy subjects. The AUC was modestly increased in subjects older than 62 years receiving 180 μg of PEG-IFN α-2a, but peak concentrations were similar in those older and younger than 62 years. Based on drug exposure, pharmacodynamic response, and tolerability, a lower starting dose of PEG-IFN α-2a is not needed in the geriatric patient.

The pharmacokinetics of PEG-IFN α-2a were similar between healthy subjects and patients with CHC. Comparable exposure and pharmacokinetic profiles were seen in patients having cirrhosis with compensated liver disease and patients without cirrhosis. PEG-IFN α-2a has not been evaluated in patients with decompensated cirrhosis (eg, Child-Pugh B/C or bleeding esophageal varices).

No significant relationship between PEG-IFN α-2a's pharmacokinetics and creatinine clearance was seen in 23 subjects with normal renal function to significant renal impairment (20 to >100 mL/min creatinine clearance). In patients with end-stage renal disease undergoing hemodialysis, there is a 25% to 45% reduction in the clearance of PEG-IFN α-2a and doses of 135 μg provide exposures similar to those observed in patients with normal renal function receiving 180 μg doses. Regardless of the starting dose or degree of renal impairment, patients should be monitored and appropriate dose reductions of PEG-IFN α-2a during the course of therapy should be made in the event of adverse reactions. It should be noted that the adverse events and laboratory abnormalities

that occurred during the study were those expected following interferon administration and occurred with only slightly greater frequency in subjects with renal impairment.

The pharmacokinetic and pharmacodynamic characteristics of PEG-IFN α-2a (single sc dose) were comparable in Japanese and non-Japanese subjects.

5.1.4 Drug Interactions

Treatment with 180 µg of PEG-IFN α-2a once weekly for 4 weeks had no effect on the pharmacokinetics profiles of tolbutamide (cytochrome P450 CYP 2C9), mephenytoin (CYP 2C19), debrisoquine (CYP 2D6), and dapsone (CYP 3A4) in healthy male subjects. PEG-IFN α-2a is a modest inhibitor of cytochrome P450 1A2, as a 25% of increase in theophylline's AUC was observed in the same study. Comparable effects on theophylline's pharmacokinetics have been seen after treatment with standard α interferons. Alpha interferons have been shown to affect the oxidative metabolism of some drugs by reducing the activity of hepatic microsomal cytochrome P450 enzymes. Theophylline serum concentrations should be monitored, and appropriate dose adjustments of theophylline make it possible for patients to take theophylline and PEG-IFN α-2a concomitantly.

Results from a pharmacokinetic substudy of a phase III trial demonstrated no pharmacokinetic interaction between PEG-IFN α-2a and ribavirin.

5.1.5 Clinical Pharmacology of PEG-IFN α-2a in Patients with Renal Cell Carcinoma

Pharmacokinetic and pharmacodynamic parameters of weekly sc administration of PEG-IFN α-2a were evaluated in 67 patients with advanced renal cell carcinoma.

After single dose administration, serum concentrations of PEG-IFN α-2a were measurable at 6 hours (the first time point of determination) and the T_{max} occurred at 48 hours. The serum concentration of PEG-IFN α-2a remained close to its peak level for the remaining 5 days of the dosing interval, providing a close to sustained-release delivery of PEG-IFN α-2a over a 1-week period. Both C_{max} and $AUC_{0-\infty}$ increased with increasing dose from 180 to 540 µg. With repeated weekly administration, trough levels of PEG-IFN α-2a increased initially by approximately threefold and reached a steady state in about 5 weeks. The serum PEG-IFN α-2a concentrations in these patients were stable during 6 months of repeated weekly dose administration. The pharmacokinetic profile of PEG-IFN α-2a in patients with renal cell carcinoma was similar to that shown in section 5.1.2 for healthy subjects. However, PEG-IFN α-2a serum concentrations for a given dose of PEG-IFN α-2a were lower in patients with advanced renal cell carcinoma than in healthy volunteers.

Significant induction of both neopterin and 2′,5′-OAS was seen in all patients studied. The percentage changes in the concentration-time profile of these pharmacodynamic markers were similar to that of PEG-IFN α-2a. Maximal induction occurred at about 48 hours and was maintained on repeated dose administration over the entire 6 months of treatment without further accumulation of serum makers after week 1. An association

was observed between increasing median serum concentration of PEG-IFN α-2a and more severe neutropenia and greater elevation of serum ALT concentration.

5.2 Safety

5.2.1 Safety of PEG-IFN α-2a In Monotherapy Studies for Treatment of Hepatitis C

The results presented in this section are based on the pooled safety data from four monotherapy studies in treatment-naïve patients with CHC. The studies include two phase III studies (NV15496 and NV15497), a phase II/III study in cirrhotic patients (NV15495), and a phase II dose-ranging study (NV15489). Unless otherwise stated, the safety data were obtained from a mixed population of 1403 patients that included both noncirrhotic and cirrhotic patients. The patients were either treated with 135 µg or 180 µg of PEG-IFN α-2a once a week for 48 weeks, or treated with 3 MIU of IFN α-2a tiw for 48 weeks or 6 MIU of IFN α-2a tiw for 12 weeks followed by 3 MIU of IFN α-2a tiw for 36 weeks. Safety data were collected during the 48-week treatment period and during 8 weeks after the end of treatment; serious adverse events were collected throughout the 72 weeks of the studies. In addition, the safety profile of PEG-IFN α-2a at weekly doses of 45, 90, 135, 180, and 270 µg is summarized in section 5.2.1.10.

5.2.1.1 Adverse Events

In all four treatment groups, 99% to 100% of patients experienced at least one adverse event while on therapy or within 8 weeks after the end of treatment. A similarly high percentage of patients treated with PEG-IFN α-2a (96%) or with IFN α-2a (97% to 99%) had at least one adverse event that was considered by the investigator to be possibly or probably related to the study treatment. Most adverse events reported, however, were of mild to moderate intensity.

- Across all four treatment groups, the most frequently reported adverse events included general disorders (fatigue, rigors, pyrexia, and injection site reaction), neurological disorders (headache and insomnia), musculoskeletal, connective tissue and bone disorders (myalgia and arthralgia), gastrointestinal disorders (nausea, abdominal pain, and diarrhea), skin and subcutaneous tissue disorders (alopecia), and psychiatric disorders (depression and irritability).
- The adverse event profiles of the PEG-IFN α-2a- and the IFN α 2a-treated groups were generally comparable. For those adverse events with a frequency of at least 5% in any pooled treatment group (regardless of treatment relationship), the frequencies of pruritus, dermatitis, and sore throat were at least 1.5-fold higher in the PEG-IFN α-2a-treated patients than in the IFN α-2a-treated patients. The frequency of nausea and vomiting was at least 1.5-fold more frequent in IFN α-2a-treated patients than in PEG-IFN α-2a-treated patients.

5.2.1.2 Deaths

Seven of the 1403 patients (0.5%) died during the 48-week treatment period or 24-week untreated follow-up period (Table 2). Of the seven patients who died, six were from the PEG-IFN α-2a treatment groups and one was from the IFN α-2a treatment groups. Two

deaths were considered by the investigator to be possibly or probably related to the study treatment. The remaining five deaths were considered by the investigators to be unrelated to the study treatment.

Table 2 Summary of Deaths In the Therapeutic Trials for Hepatitis C: Studies NV15489, NV15495, NV15496, and NV15497

Patient No.	Treatment	Cause of Death	Relationship to Study Drug
20777/1059	IFN α-2a (3 MIU)	Pulmonary barotrauma	unrelated
20881/1361	PEG-IFN α-2a (135 µg)	Drug overdose	unrelated
20775/0940	PEG-IFN α-2a (135 µg)	Pneumonitis	probably related
19153/0262	PEG-IFN α-2a (180 µg)	Hepatic failure	unrelated
19301/0163	PEG-IFN α-2a (180 µg)	Malignant hepatic neoplasm	unrelated
20561/0369	PEG-IFN α-2a (180 µg)	Cerebral hemorrhage	possibly related
20983/2689	PEG-IFN α-2a (180 µg)	Drug overdose	unrelated

In addition, one patient from the 45-µg dose group died of a heroin overdose and one patient from the 90-µg dose group died of hepatic failure. Both deaths were considered unrelated to treatment.

5.2.1.3 Serious Adverse Events

Serious adverse events were reported in less than 10% of patients in the two IFN α-2a and two PEG-IFN α-2a treatment groups. The point estimate of serious adverse events in the IFN α-2a 6 MIU/3 MIU dose group (5%) was numerically lower than that in the IFN α-2a 3 MIU dose group (8%), PEG-IFN α-2a 135-µg dose group (10%), and PEG-IFN α-2a 180 µg dose group (9%).

- The most common serious adverse events were infections, psychiatric disorders, and gastrointestinal disorders. In regard to specific serious adverse events, only two serious adverse events occurred in more than two patients in a particular treatment group: depression was reported as a serious adverse event in six patients (1.0%) in the PEG-IFN α-2a 180-µg group and lower respiratory tract infection was reported as a serious adverse event in three patients (1.4%) in the PEG-IFN α-2a 135-µg group.
- Infections of any type were reported as serious adverse events in five (2%), 13 (2%), five (2%), and two (1%) patients in the PEG-IFN α-2a 135-µg, PEG-IFN α-2a 180-µg, IFN α-2a 3 MIU, and IFN α-2a 6 MIU/3 MIU treatment groups, respectively.
- In the PEG-IFN α-2a-treated patients, most of the serious adverse events (70%) occurred after 12 weeks of treatment.

The number and percentage of patients who had treatment-related serious adverse events is shown in Table 3 by body system. The incidence of treatment-related (possible or probably related) serious adverse events was slightly higher in the PEG-IFN α-2a-treated patients (3% and 5%) than in the IFN α-2a-treated patients (1% and 2%).

- In both the PEG-IFN α-2a and IFN α-2a-treated groups, psychiatric disorders and general disorders were the most frequently reported treatment-related serious adverse events. In PEG-IFN α-2a-treated patients, other less frequent treatment-related serious adverse events were blood and lymphatic system disorders, infections, hepato-billiary disorders, and neurological disorders. Events in other body systems occurred in ≤ 2 patients treated with PEG-IFN α-2a or IFN α-2a.
- All but six of the treatment-related serious adverse events were reported by no more than one patient treated with PEG-IFN α-2a or IFN α-2a. The most common treatment-related serious adverse event was depression in both PEG-IFN α-2a and IFN α-2a treated patients.
- The types of treatment-related serious adverse events for both PEG-IFN α-2a and IFN α-2a treatments were consistent with the known adverse event profile for interferon α.
- Most treatment-related serious adverse events resolved without sequelae.

Table 3 Number and Percentage of Patients with Treatment-Related (Possibly or Probably Related) Serious Adverse Events Occurring during Treatment and 8 Weeks Posttreatment in Studies NV15489, NV15495, NV15496, and NV15497 in Patients with Hepatitis C

Body System/ Adverse Event	IFN 3 MIU N = 323 No. (%)	IFN 6 MIU/3 MIU N = 261 No. (%)	PEG-IFN 135 ug N = 215 No. (%)	PEG-IFN 180 ug N = 604 No. (%)	IFN 3 MIU or 6/3 MIU N = 584 No. (%)	PEG-IFN 135 ug or 180 ug N = 819 No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	8 (2)	2 (1)	7 (3)	28 (5)	10 (2)	35 (4)
Total Number of AEs	12	3	7	37	15	44
PSYCHIATRIC DISORDERS						
Total Pts With at Least one AE	3 (1)	2 (1)	0	8 (1)	5 (1)	8 (1)
DEPRESSION	1 (<1)	1 (<1)	0	6 (1)	2 (<1)	6 (1)
SUICIDAL IDEATION	0	1 (<1)	0	2 (<1)	1 (<1)	2 (<1)
PSYCHOSIS	0	1 (<1)	0	1 (<1)	1 (<1)	1 (<1)
SUICIDE ATTEMPT	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
DEPRESSED MOOD	1 (<1)	0	0	0	1 (<1)	0
HYSTERIA	0	0	0	1 (<1)	0	1 (<1)
Total Number of AEs	3	3	0	11	6	11
DISORDERS OF BLOOD & THE LYMPHATIC SYSTEM						
Total Pts With at Least one AE	1 (<1)	0	0	4 (1)	1 (<1)	4 (<1)
IDIOPATHIC THROMBOCYTOPENIC PURPURA	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
THROMBOCYTOPENIA	0	0	0	2 (<1)	0	2 (<1)
NEUTROPENIA	0	0	0	1 (<1)	0	1 (<1)
Total Number of AEs	1	0	0	4	1	4
GASTROINTESTINAL DISORDERS						
Total Pts With at Least one AE	4 (1)	0	0	1 (<1)	4 (1)	1 (<1)
ABDOMINAL PAIN	1 (<1)	0	0	0	1 (<1)	0
ENTERITIS	1 (<1)	0	0	0	1 (<1)	0
HAEMATEMESIS	0	0	0	1 (<1)	0	1 (<1)
NAUSEA	1 (<1)	0	0	0	1 (<1)	0
PANCREATITIS NOS	1 (<1)	0	0	0	1 (<1)	0
Total Number of AEs	4	0	0	1	4	1
GENERAL DISORDERS						
Total Pts With at Least one AE	2 (1)	0	1 (<1)	2 (<1)	2 (<1)	3 (<1)
CHEST PAIN NOS	0	0	1 (<1)	1 (<1)	0	2 (<1)
PYREXIA	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
RIGORS	1 (<1)	0	0	0	1 (<1)	0
Total Number of AEs	2	-	1	2	2	3

NOTE: Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.
AE11 01FEB2000:14:01:34 and AE11 09FEB2000:10:59:31

(Continued)

Table 3 Number and Percentage of Patients with Treatment-Related (Possibly or Probably Related) Serious Adverse Events Occurring during Treatment and 8 Weeks Posttreatment in Studies NV15489, NV15495, NV15496, and NV15497 in Patients with Hepatitis C (Cont.)

Body System/ Adverse Event	IFN 3 MIU N = 323 No. (%)	IFN 6 MIU/3 MIU N = 261 No. (%)	PEG-IFN 135 ug N = 215 No. (%)	PEG-IFN 180 ug N = 604 No. (%)	IFN 3 MIU or 6/3 MIU N = 584 No. (%)	PEG-IFN 135 ug or 180 ug N = 819 No. (%)
INFECTIONS & INFESTATIONS						
Total Pts With at Least one AE	0	0	2 (1)	3 (<1)	0	5 (1)
LOWER RESPIRATORY TRACT INFECTION	0	0	2 (1)	-	0	2 (<1)
CHOLANGITIS ACUTE NOS	0	0	0	1 (<1)	0	1 (<1)
URINARY TRACT INFECTION	0	0	0	1 (<1)	0	1 (<1)
VIRAL INFECTION NOS	0	0	0	1 (<1)	0	1 (<1)
Total Number of AEs	0	0	2	3	0	5
HEPATO-BILIARY DISORDERS						
Total Pts With at Least one AE	0	0	0	4 (1)	0	4 (<1)
HEPATIC FUNCTION ABNORMAL	0	0	0	2 (<1)	0	2 (<1)
HEPATITIS NOS	0	0	0	1 (<1)	0	1 (<1)
LIVER FATTY	0	0	0	1 (<1)	0	1 (<1)
Total Number of AEs	0	0	0	4	0	4
NEUROLOGICAL DISORDERS						
Total Pts With at Least one AE	1 (<1)	0	1 (<1)	2 (<1)	1 (<1)	3 (<1)
COMA NOS	0	0	0	1 (<1)	0	1 (<1)
HEADACHE	1 (<1)	0	0	0	1 (<1)	0
PERIPHERAL NEUROPATHY	0	0	1 (<1)	0	0	1 (<1)
SYNCOPE	0	0	0	1 (<1)	0	1 (<1)
Total Number of AEs	1	0	1	2	1	3
CARDIAC DISORDERS						
Total Pts With at Least one AE	0	0	0	2 (<1)	0	2 (<1)
ATRIAL FLUTTER	0	0	0	1 (<1)	0	1 (<1)
ENDOCARDITIS NOS	0	0	0	1 (<1)	0	1 (<1)
Total Number of AEs	0	0	0	2	0	2
MUSCULOSKELETAL, CONNECTIVE TISSUE & BONE DISORDERS						
Total Pts With at Least one AE	0	0	0	2 (<1)	0	2 (<1)
ARTHRITIS	0	0	0	1 (<1)	0	1 (<1)
MYOSITIS	0	0	0	1 (<1)	0	1 (<1)
Total Number of AEs	0	0	0	2	0	2

NOTE: Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.
AE11 01FEB2000:14:01:34 and AE11 09FEB2000:10:59:31

(Continued)

Table 3 Number and Percentage of Patients with Treatment-Related (Possibly or Probably Related) Serious Adverse Events Occurring during Treatment and 8 Weeks Posttreatment in Studies NV15489, NV15495, NV15496, and NV15497 in Patients with Hepatitis C (Cont.)

Body System/ Adverse Event	IFN 3 MIU N = 323 No. (%)	IFN 6 MIU/3 MIU N = 261 No. (%)	PEG-IFN 135 ug N = 215 No. (%)	PEG-IFN 180 ug N = 604 No. (%)	IFN 3 MIU or 6/3 MIU N = 584 No. (%)	PEG-IFN 135 ug or 180 ug N = 819 No. (%)
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS						
Total Pts With at Least one AE	0	0	1 (<1)	1 (<1)	0	2 (<1)
LUNG DISORDER NOS	0	0	1 (<1)	0	0	1 (<1)
RESPIRATORY ARREST (EXC NEONATAL)	0	0	0	1 (<1)	0	1 (<1)
Total Number of AEs	0	0	1	1	0	2
SKIN & SUBCUTANEOUS TISSUE DISORDERS						
Total Pts With at Least one AE	0	0	1 (<1)	1 (<1)	0	2 (<1)
ALOPECIA	0	0	1 (<1)	0	0	1 (<1)
URTICARIA	0	0	0	1 (<1)	0	1 (<1)
Total Number of AEs	0	0	1	1	0	2
VASCULAR DISORDERS						
Total Pts With at Least one AE	0	0	0	2 (<1)	0	2 (<1)
CEREBRAL HAEMORRHAGE	0	0	0	1 (<1)	0	1 (<1)
PULMONARY EMBOLISM	0	0	0	1 (<1)	0	1 (<1)
Total Number of AEs	0	0	0	2	0	2
DISORDERS OF METABOLISM & NUTRITION						
Total Pts With at Least one AE	0	0	0	1 (<1)	0	1 (<1)
DIABETES MELLITUS	0	0	0	1 (<1)	0	1 (<1)
Total Number of AEs	0	0	0	1	0	1
DISORDERS OF THE EYE						
Total Pts With at Least one AE	0	0	0	1 (<1)	0	1 (<1)
CORNEAL ULCER	0	0	0	1 (<1)	0	1 (<1)
Total Number of AEs	0	0	0	1	0	1
ENDOCRINE DISORDERS						
Total Pts With at Least one AE	0	0	1 (<1)	0	0	1 (<1)
HYPERTHYROIDISM	0	0	1 (<1)	0	0	1 (<1)
Total Number of AEs	0	0	1	0	0	1
INJURY & POISONING						
Total Pts With at Least one AE	1 (<1)	0	0	0	1 (<1)	0
OVERDOSE NOS	1 (<1)	0	0	0	1 (<1)	0
Total Number of AEs	1	0	0	0	1 (<1)	0

NOTE: Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.
AE11 01FEB2000:14:01:34 and AE11 09FEB2000:10:59:31

5.2.1.4 Dose Modification for Adverse Events and Laboratory Abnormalities

The incidence of dose modification (withheld temporarily or reduced) was higher in the PEG-IFN α-2a 180-µg group (27%) than in other treatment groups (20%, 18%, and 21% in the IFN α-2a 3 MIU, IFN α-2a 6 MIU/3 MIU, and PEG-IFN α-2a 135 µg groups, respectively). The dose was modified in 11% of patients in the two IFN α-2a groups and in the for the PEG-IFN α-2a 180-µg group and in 7% of the patients in the PEG-IFN α-2a 135-µg group. Laboratory abnormalities were the reason for dose modification in 15% and 19% of patients in PEG-IFN α-2a 135-µg and 180-µg groups, respectively, which was higher than the corresponding frequency of approximately 9% for both IFN α-2a-treated groups. The most common laboratory abnormality that led to dose modification was neutropenia, the incidence of which was higher for both PEG-IFN α-2a-treated groups (approximately 12%) than for both IFN α-2a-treated groups (6% and 7%). Dose modification for thrombocytopenia occurred more frequently in the PEG-IFN α-2a 180-µg group (7%) than in any other groups (2% to 3%). Elevated ALT levels led to dose modification in a similar proportion of PEG-IFN α-2a and IFN α-2a treated patients (1% to 2% of patients).

5.2.1.5 Premature Withdrawal for Adverse Events and Laboratory Abnormalities

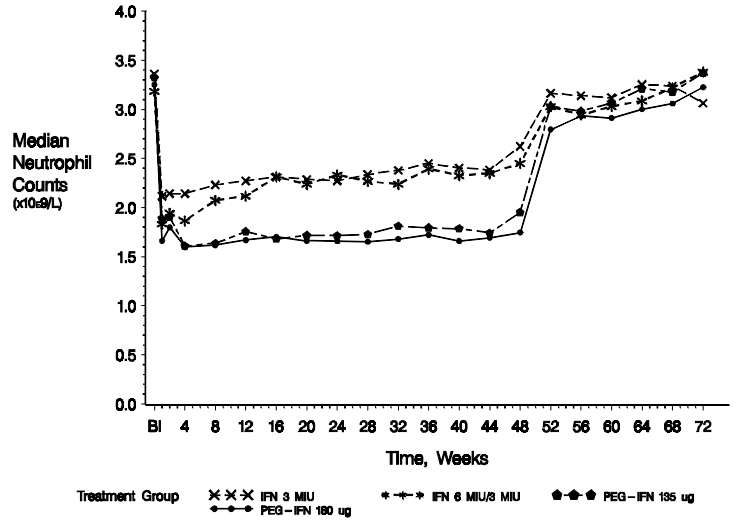
The proportion of patients whose treatment was discontinued prematurely for adverse events or laboratory abnormalities was 10% in all four treatment groups. There was generally little difference among the treatment groups in the percentage of patients who discontinued treatment prematurely for specific types of adverse events or laboratory abnormalities. Depression and fatigue were the two most common adverse events that led to premature treatment discontinuation. Depression was the reason for premature treatment discontinuation in ten patients (1%) treated with PEG-IFN α-2a and in seven patients (1%) treated with IFN α-2a. Fatigue was the reason for premature treatment discontinuation in three (<1%) and five patients (1%) treated with PEG-IFN α-2a and IFN α-2a, respectively. Thrombocytopenia was the most common laboratory abnormality resulting in premature treatment discontinuation and led to the withdrawal of five (1%) PEG-IFN α-2a-treated patients and two (<1%) IFN α-2a-treated patients. Elevation in serum ALT concentration led to the withdrawal of five (1%) PEG-IFN α-2a-treated patients and one (<1%) IFN α-2a-treated patient. Except for depression, headache, elevated serum ALT concentration, thrombocytopenia, fatigue, and abdominal pain, other events resulted in premature treatment discontinuation in no more than two patients in any treatment group.

5.2.1.6 Laboratory Abnormalities: Neutropenia

Median neutrophil counts in both the PEG-IFN α-2a- and IFN α-2a-treated patients decreased rapidly during the first 2 weeks of study treatment, stabilized during the treatment period, and returned rapidly toward their pretreatment baselines between weeks 48 and 52 after the end of the study drug treatment (Figure 4). However, the magnitudes of decreases in median neutrophil counts during treatment were consistently larger for the

PEG-IFN α-2a 180-µg and PEG-IFN α-2a 135-µg groups than for the IFN α-2a 3 MIU and IFN α-2a 6 MIU/3 MIU groups.

Figure 4 **Median Neutrophil Counts during Treatment and 24 Weeks Posttreatment in Studies NV15489, NV15495, NV15496, and NV15497 in Patients with Hepatitis C**



Patients were classified according to their lowest neutrophil count during the 48-week treatment period and the first 8 weeks after the end of treatment (Table 4).

Table 4 **Summary of Patients' Lowest Neutrophil Count during Treatment and 8 Weeks Posttreatment in Studies NV15489, NV15495, NV15496, and NV15497 in Patients with Hepatitis C**

Treatment Group	N	Neutrophil Counts ≥ 2.0 ($\times 10^9$ /L)	1.5 - 1.99 ($\times 10^9$ /L)	1.0 - 1.49 ($\times 10^9$ /L)	0.5 - 0.99 ($\times 10^9$ /L)	< 0.5 ($\times 10^9$ /L)	missing
IFN 3 MIU	323	78 (24.1%)	95 (29.4%)	93 (28.8%)	52 (16.1%)	4 (1.2%)	1 (0.3%)
IFN 6 MIU/3MIU	261	37 (14.2%)	79 (30.3%)	86 (33.0%)	54 (20.7%)	4 (1.5%)	1 (0.4%)
PEG-IFN 135 ug	215	21 (9.8%)	37 (17.2%)	78 (36.3%)	72 (33.5%)	7 (3.3%)	-
PEG-IFN 180 ug	604	34 (5.6%)	88 (14.6%)	214 (35.4%)	245 (40.6%)	23 (3.8%)	-

Source: $PROD/cd01275a/f_neutropenia_ISS_sum.sas (04NOV1999 18:50)

- Compared with the two IFN α-2a treatment groups, the two PEG-IFN α-2a treatment groups had higher proportions of patients with grades 3 and 4 neutropenia as their lowest neutrophil count.
- Compared with the PEG-IFN α-2a 135-µg group, the PEG-IFN α-2a 180-µg group had higher proportions of patients with grade 3 neutropenia, while the proportion of patients with grade 4 neutropenia was similar in the two groups.
- For the 38 patients who developed grade 4 neutropenia:

The lowest neutrophil count in 21 of these patients was between 0.4 and 0.499×10^9. In the remaining patients, the lowest neutrophil count in 10 patients was between 0.3 and 0.399 x 10^9/L and only seven patients had a neutrophil count below 0.3×10^9/L.

- ♦ Temporary or permanent dose reduction occurred in 26 patients, and in only one patient treated with 180 µg of PEG-IFN α-2a was treatment discontinued prematurely for neutropenia.
- ♦ The neutrophil counts of most patients returned to above 0.5×10^9/L after their dose was modified.

5.2.1.7 Laboratory Abnormalities: Thrombocytopenia

Median platelet counts in both PEG-IFN α-2a- and IFN α-2a-treated patients declined rapidly during the first 4 weeks after the start of treatment (Figure 5). Thereafter, median platelet counts tended to stabilize until the end of the 48-week treatment period. Between weeks 48 and 52, median platelet counts of all groups quickly returned toward their pretreatment baseline values. The magnitudes of the decreases in median platelet counts were comparable for the two PEG-IFN α-2a groups, which were greater than those for the two IFN α-2a groups.

Patients were classified according to their lowest platelet count during the 48-week treatment period and the first 8 weeks after the end of treatment. (Table 5).

- A higher proportion of patients treated with PEG-IFN α-2a had grade 3 thrombocytopenia than patients treated with IFN α-2a.
- Compared with the PEG-IFN α-2a 135-µg group, the PEG-IFN α-2a 180-µg group had a higher proportion of patients with grade 3 thrombocytopenia as their lowest platelet count.
- Two patients (one from the IFN α-2a 3 MIU group and one from the PEG-IFN α-2a 180-µg group) experienced grade 4 thrombocytopenia as a result of the development of serious idiopathic thrombocytopenic purpura, which led to the premature withdrawal of both patients.
- None of the patients whose platelet counts fell to between 20 and 49.9 x 10^9/L experenced serious bleeding events.
- The time to onset of grade 3 and grade 4 thrombocytopenia ranged from 58 days to 91 days, suggesting the tendency for this laboratory abnormality to occur within 2 to 3 months after the initiation of treatment. Most patients with grade 3 thrombocytopenia and both patients with grade 4 thrombocytopenia had cirrhosis or transition to cirrhosis.

- Of the 49 patients with grade 3 thrombocytopenia, 33 patients required temporary or permanent dose reduction and an additional seven patients had treatment prematurely discontinued for thrombocytopenia.

In approximately two thirds of the patients with grade 3 thrombocytopenia, platelet counts recovered to at least 50×10^9/L during treatment.

Figure 5 Median Platelet Counts during Treatment and 24 Weeks Posttreatment in Studies NV15489, NV15495, NV15496, and NV15497

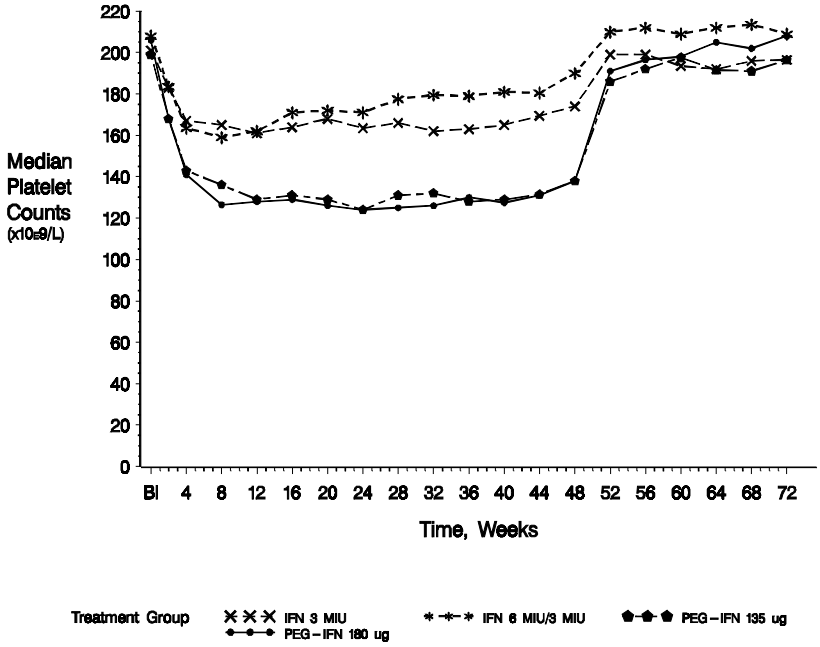


Table 5 Summary of Patients' Lowest Platelet Counts during Treatment and 8 Weeks Posttreatment in Studies NV15489, NV15495, NV15496, and NV15497 in Patients with Hepatitis C

Treatment Group	N	Platelet Counts ≥ 100 x 10^9 /L)	75 - 99.9 (x 10^9 /L)	50 - 74.9 (x 10^9 /L)	20 - 49.9 (x 10^9 /L)	< 20 (x 10^9 /L)	Missing
IFN 3 MIU	323	249 (77.1%)	39 (12.1%)	26 (8.0%)	7 (2.2%)	1 (0.3%)	1 (0.3%)
IFN 6 MIU/3 MIU	261	219 (83.9%)	25 (9.6%)	12 (4.6%)	4 (1.5%)	-	1 (0.4%)
PEG-IFN 135 µg	215	122 (56.7%)	58 (27.0%)	28 (13.0%)	7 (3.3%)	-	-
PEG-IFN 180 µg	604	341 (56.5%)	135 (22.4%)	95 (15.7%)	31 (5.1%)	1 (0.2%)	1 (0.2%)

Source: $PROD/cd01275a/f_thrombocytopenia_ISS_sum.sas (04NOV1999 18:52)

5.2.1.8 Laboratory Abnormalities: Hemoglobin Abnormalities

Median hemoglobin concentrations decreased slightly from baseline levels during treatment and returned to baseline levels after treatment in both the PEG-IFN α-2a- and IFN α-2a-treated groups. The magnitudes of the drop in median hemoglobin concentrations were 1.5, 1.7, 0.8, and 1.0 g/dL for the PEG-IFN α-2a 135-µg, PEG-IFN α-2a 180-µg, IFN α-2a 3 MIU, and IFN α-2a 6 MIU/3 MIU groups, respectively. The median hemoglobin concentrations of all groups remained within the normal range throughout the 48-week treatment period. Most PEG-IFN α-2a-treated patients (> 80%) and IFN α-2a-treated patients (> 90%) maintained their hemoglobin concentrations above 12 g/dL during treatment.

Patients were classified according to their lowest hemoglobin concentration during the 48-week treatment period and the first 8 weeks posttreatment. The percentage of patients whose lowest hemoglobin concentration was <10 g/dL was similar in the two PEG-IFN α-2a groups (1.9% in the 135-µg group and 2.0% in the 180-µg group) and in the IFN α-2a 3 MIU group (1.5%). Only one patient (0.4%) in the IFN α-2a 6 MIU/3 MIU group had a hemoglobin concentration <10g/dL. Hemoglobin concentrations decreased to <8.5 g/dL in five patients. All five patients were in the PEG-IFN α-2a 180-µg group and four of them had cirrhosis. In the 22 patients whose lowest hemoglobin concentrations decreased to <10 g/dL, three patients, all from the PEG-IFN α-2a 180-µg group, had their dose modified and one of the three patients eventually withdrew from the study because of anemia.

5.2.1.9 Laboratory Abnormalities: Other

The types of marked laboratory abnormalities (laboratory test results that were outside the normal range by a predetermined amount and represented a change from baseline of a predetermined percentage) were generally similar for the PEG-IFN α-2a and IFN α-2a dose groups. The laboratory tests that were marked abnormality in ≥10% in any group are shown in Appendix 3. Low neutrophil counts, low platelet counts, low hemoglobin concentrations, and high serum ALT concentrations are not included in this summary table and instead are addressed separately in the previous section or in the case of persistently abnormal serum ALT concentration, was one of the requirements for entry into the four clinical studies.

The most common marked laboratory abnormalities were low WBC and lymphocyte counts, high serum AST concentrations, low serum phosphate concentrations, and high serum triglyceride concentrations. The proportions of patients with markedly high AST concentrations and markedly low calcium and phosphate concentrations were similar across the four treatment groups, while the proportions of patients with markedly low hematocrit, low WBC and lymphocyte counts, and markedly high triglyceride concentrations were higher in the two PEG-IFN α-2a groups than in the two IFN α-2a groups. The greatest difference was seen for low WBC counts.

5.2.1.10 Effect of PEG-IFN α-2a Doses on Safety

Although the safety presentation in this IB for CHC patients who were treated with PEG-IFN α-2a monotherapy focuses mainly on weekly doses of PEG-IFN α-2a at 135 and 180

µg, weekly doses of PEG-IFN α-2a monotherapy ranging from 45 to 270 µg were assessed in these studies. This overall safety population is useful for exploring a possible PEG-IFN α-2a dose-response relationship and is composed of 20, 116, 215, 604, and 40 patients who received a weekly PEG-IFN α-2a dose of 45, 90, 135, 180, and 270 µg, respectively. The results of this analysis suggest that the weekly 270-µg dose of PEG-IFN α-2a was generally less well tolerated than the lower doses (including the recommended weekly 180-µg dose). The adverse events with a frequency ≥ 5% in the 180-µg group are summarized for each dose group in Appendix 4.

- The types of frequently reported adverse events (regardless of treatment relationship) were similar across the different dose groups. The incidence of myalgia, rigors, insomnia, diarrhea, depression, dermatitis, concentration impairment, anxiety, nasopharyngitis, memory impairment, vision blurred, upper respiratory tract infection, and weight decrease was the highest in the 270-µg group. For adverse events that occurred less frequently, lethargy, rhinitis, and confusion were also reported more frequently (at least twofold higher in frequency) in the 270-µg group than in the other dose groups.
- In this study, the following adverse events occurred only in the 270-µg dose group (uncommon adverse events): dysphasia, peroneal nerve palsy, polyneuropathy, simple partial seizures, sleep apnea syndrome, ganglion, eyelid dermatitis, telangietasia, nasal passage irritation, keratoconjunctivitis, pilonidal sinus infected, hypoglycemic coma, deafness, aggravated nocturia, renal cyst, blood pressure fluctuations, cerebral arterial aneurysm, and papilloma.
- The incidence of serious adverse events was the lowest with the 45-mg dose (5%), intermediate and comparable among the 90-mg (9% to 8%), 135-mg (12% to 10%), and 180-mg (10% to 9%) doses, and the highest with the 270-mg dose (15% to 13%). Although the incidence of treatment-related serious adverse events was similar with the 180-ug (6%) and 270-ug (5%) doses (Appendix 5), proportionately more patients in the PEG-IFN a-2a 270-mg group (8%, three patients) withdrew from the study because of serious adverse events, compared with the respective proportions than in the other PEG-IFN a-2a treatment groups (0% to 5%).
- The frequencies of premature treatment discontinuation for safety reasons were comparable across the different treatment groups except for the frequency of premature treatment discontinuation in the PEG IFN α-2a 270-µg group, which was twice (20%) that of the other PEG-IFN α-2a treatment groups (9% to 10%).

5.2.2 Safety of PEG-IFN α-2a in the Treatment of Chronic Hepatitis B (CHB)

5.2.2.1 Safety of PEG-IFN α-2a in Patients with CHB: Study NV16037

Study NV16037 was a phase II, open-label, randomized, multicenter study conducted in Australia, China, New Zealand, Taiwan, and Thailand for assessment of the efficacy and safety of PEG-IFN α-2a therapy in treatment-naïve patients with chronic hepatitis B. Patients were treated with either PEG-IFN α-2a (weekly doses of 90, 180, or 270 µg) or IFN α-2a (4.5 MIU tiw) for 24 weeks and were followed up for an additional 24 weeks. The study is completed and safety data are available for the 191 treated patients.

During the study, 94% or more of patients in each treatment group had one or more adverse events (Appendix 6). The most frequently encountered adverse events were those common for interferon therapy and were similar to the adverse events in CHC patients receiving the same treatment (section 5.2.1). The incidences of neurological disorders, gastrointestinal disorders, infections, respiratory, thoracic and mediastinal disorders, and skin and subcutaneous tissue disorders were somewhat higher for the PEG-IFN α-2a-treated groups than for the IFN α-2a-treated group. Adverse events with notably increased incidence in the IFN α-2a group compared with the PEG-IFN groups included arthralgia, which had a twofold to sixfold higher incidence. A dose dependency for the frequency of adverse events was not apparent for the three PEG-IFN α-2a-treated groups. Thirteen serious adverse events occurred in two (4%), one (2%), four (9%), and five (10%) patients treated with 4.5 MIU of IFN α-2a and 90, 180, and 270 µg of PEG-IFN α-2a, respectively (Table 6). Three serious adverse events (anaphylactic shock, thyroid nodule, and sepsis) were possibly or probably treatment-related, two (tendon rupture and enteritis) required study drug dose modification, and two (anaphylactic shock and sepsis) resulted in premature treatment discontinuation. Overall, treatment was prematurely discontinued in five patients (four clinical adverse events of asthenia, anorexia, sepsis and anaphylactic shock and one for laboratory abnormalities of elevated AST and ALT). There were no deaths during the study.

Table 6 Listing of Patients with Serious Adverse Events during Treatment and 8 Weeks Posttreatment, CHB Patients in Study NV16037

Treatment: RO 22-8181; ROFERON-A; 4.5 MIU; N = 50

CRTN/Pt. No. / Adverse Event	Age yr	Sex	Weight kg	Race	Intensity	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
26160/4026	35	F	62	ORIENTAL	Day of Last Trial Treatment: 167						
ABDOMINAL PAIN NOS*					SEVERE	109	6	UNRELATED	RESO - NO SEQUEL	YES	NONE
26161/4053	41	M	63	ORIENTAL	Day of Last Trial Treatment: 167						
CHOLELITHIASIS*					MODERATE	199	46	UNRELATED	RESO - W. SEQUEL	YES	NONE
Comment: PATIENT ADMIT IN HOSPITAL ON 08/04/01, CHOEYCYSTECTOMY WAS FINISHED ON 09/04/01 AND DISCHARGED FROM HOSPITAL ON 12/04/01.											

Treatment: RO 25-8310; PEGYLATED INTERFERON; 90mcg; N = 48

CRTN/Pt. No. / Adverse Event	Age yr	Sex	Weight kg	Race	Intensity	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
26155/3031	22	M	75	ORIENTAL	Day of Last Trial Treatment: 162						
ENTERITIS*					MODERATE	98	23	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED

Treatment: RO 25-8310; PEGYLATED INTERFERON; 180mcg; N = 45

CRTN/Pt. No. / Adverse Event	Age yr	Sex	Weight kg	Race	Intensity	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
26153/2007	35	F	64	ORIENTAL	Day of Last Trial Treatment: 162						
THYROID NODULE*					MODERATE	124	158	POSSIBLE	RESO - NO SEQUEL	YES	NONE
Comment: ANALGESIA BELOW REQUIRED FOR POST OP PAIN											
26155/3023	32	F	51	ORIENTAL	Day of Last Trial Treatment: 128						
SEPSIS NOS*					SEVERE	136	34	POSSIBLE	RESO - NO SEQUEL	YES	DISCONTINUED
26159/4002	21	M	58	ORIENTAL	Day of Last Trial Treatment: 162						
APPENDICITIS*					SEVERE	42	4	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: APPENDECTOMY AT HATYAI HOSPITAL											

(continued)

Table 6 Listing of Patients with Serious Adverse Events during Treatment and 8 Weeks Posttreatment, CHB Patients in Study NV16037 (Cont.)

Treatment: RO 25-8310; PEGYLATED INTERFERON; 180mcg; N = 45 (Continued)

CRTN/Pt. No. / Adverse Event	Age yr	Sex	Weight kg	Race	Intensity	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
26162/5028	49	M	55	ORIENTAL	Day of Last Trial Treatment: 162						
DIARRHOEA NOS*					MODERATE	115	3	UNRELATED	RESO - NO SEQUEL	YES	NONE

Treatment: RO 25-8310; PEGYLATED INTERFERON; 270mcg; N = 48

CRTN/Pt. No. / Adverse Event	Age yr	Sex	Weight kg	Race	Intensity	Day of Onset	Duration in days	Relation to Trial Treatment	Outcome	Treatment given for AE	Discontinued or Dose Adjusted
26153/2002	25	F	71	NUIE ISLAND	Day of Last Trial Treatment: 15						
ANAPHYLACTIC SHOCK*					SEVERE	15	3	PROBABLE	RESO - NO SEQUEL	YES	DISCONTINUED
26155/3027	33	M	89	ORIENTAL	Day of Last Trial Treatment: 162						
CELLULITIS*					MODERATE	74	8	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: SWELLING AND ERYTHEMATOUS OF RIGHT NIPPLE											
26155/6001	29	M	66	ORIENTAL	Day of Last Trial Treatment: 161						
TENDON RUPTURE*					MODERATE	7	26	UNRELATED	RESO - NO SEQUEL	YES	DOSAGE MODIFIED
26160/4025	23	F	52	ORIENTAL	Day of Last Trial Treatment: 162						
MIGRAINE*					SEVERE	72	10	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: SHE HAS HISTORY OF MIGRAINE FOR MANY YEARS BUT NO ATTACK DURING SIX MONTHS BEFORE TRIAL. AMITRIPTYLINE AND PARACETAMOL WITH CODEINE ARE USED TO PREVENT ATTACK FOR SOME TIMES.											
PYELONEPHRITIS ACUTE NOS*					SEVERE	97	7	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: THE PATIENT TOOK ALL THE GIVEN MEDICATION TO COMPLETE THE WHOLE COURSE EVEN THE SYMPTOM HAS RESOLVED											
26161/4043	29	F	45	ORIENTAL	Day of Last Trial Treatment: 162						
HERPES SIMPLEX OPHTHALMIC*					MODERATE	99	43	UNRELATED	RESO - NO SEQUEL	YES	NONE
Comment: ABSOLUTE NEUTROPHIL>1000 AT THE TIME OF AE											

CRTN = Clinical Research Task Number (center no.)
For processing, missing TT end date and time are replaced by TT start date and time.
* Serious adverse event
AE01 10OCT2001:06:32:44

5.2.2.2 Safety of PEG-IFN α-2a in Patients with CHB: Study WV16240

This study is a phase III, multicenter, multinational, partially double-blinded, randomized, parallel-group trial with an active-control group. The primary objective of this study is to evaluate the efficacy and safety of PEG-IFN α-2a therapy with and without lamivudine to that of lamivudine in the treatment of HbeAg positive patients with CHB virus infection. Patients are enrolled into one of three treatment arms: (A) PEG-IFN α-2a plus placebo; (B) PEG-IFN α-2a plus lamivudine; (C) lamivudine and are treated for 48 weeks plus a 24-week follow-up period. Assignment to lamuvudine or placebo in combination with PEG-IFN α-2a is double-blinded, while assignment to PEG-IFN α-2a or lamivudine monotherapy is open-label. The PEG-IFN α-2a dose of 180 µg is being administered sc once weekly and 100 mg of lamivudine is being taken po daily. The study is ongoing. In order to maintain the blind in this ongoing study, data from the two PEG-IFN α-2a treatment groups have been pooled. As of December 19, 2002, 820 patients had data available on the database; 276 patients are receiving lamivudine therapy (control) and 544 patients are receiving PEG-IFN α-2a therapy with either placebo or lamivudine.

Safety Summary

There have been two deaths in this study; both considered by the investigator to be unrelated to treatment (traffic accident and septic shock following extensive burn trauma).

No patients in the lamivudine control group and 19 patients in the pooled PEG-IFN α-2a with placebo or lamivudine treatment group experienced serious adverse events (Table 7). An external safety review board has been overseeing the progress of both this and the other phase III study below. So far in the review, their comments have been that the nature and incidence of adverse events and laboratory abnormalities have been within their expectations and experience of the therapies being investigated in these studies.

Eleven patients withdrew due to adverse events or laboratory abnormalities; ten patients in the pooled PEG-IFN α-2a treatment groups and one patient in the lamivudine control group.

Table 7 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study WV16240 in Patients with CHB

Body System/ Adverse Event	LAMIVUDINE 100 MG ORALLY ONCE DAILY N = 276 No. (%)	PEG-IFN 180 MCG SC ONCE WEEKLY WITH DAILY ORAL PLACEBO OR 100 MG LAMIVUDINE N = 544 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	-	19 (3)
Total Number of AEs	-	19
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	-	4 (<1)
CELLULITIS	-	1 (<1)
INFLUENZA	-	1 (<1)
SEPSIS NOS	-	1 (<1)
SEPTIC SHOCK	-	1 (<1)
Total Number of AEs	-	4
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	-	3 (<1)
ABDOMINAL PAIN NOS	-	1 (<1)
APPENDICITIS	-	1 (<1)
GASTROENTERITIS NOS	-	1 (<1)
Total Number of AEs	-	3
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total Pts With at Least one AE	-	2 (<1)
BRAIN CONTUSION	-	1 (<1)
ROAD TRAFFIC ACCIDENT	-	1 (<1)
Total Number of AEs	-	2
INVESTIGATIONS		
Total Pts With at Least one AE	-	2 (<1)
ALANINE AMINOTRANSFERASE INCREASED	-	1 (<1)
LABORATORY TEST ABNORMAL NOS	-	1 (<1)
Total Number of AEs	-	2
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Total Pts With at Least one AE	-	2 (<1)
BREAST CANCER NOS	-	1 (<1)
THYROID NEOPLASM NOS	-	1 (<1)
Total Number of AEs	-	2
CARDIAC DISORDERS		
Total Pts With at Least one AE	-	1 (<1)
ARRHYTHMIA NOS	-	1 (<1)
Total Number of AEs	-	1

AE11 31JAN2003:13:08:09 (continued)

Table 7 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study WV16240 in Patients with CHB (Cont.)

Body System/ Adverse Event	LAMIVUDINE 100 MG ORALLY ONCE DAILY N = 276 No. (%)	PEG-IFN 180 MCG SC ONCE WEEKLY WITH DAILY ORAL PLACEBO OR 100 MG LAMIVUDINE N = 544 No. (%)
EAR AND LABYRINTH DISORDERS		
Total Pts With at Least one AE	-	1 (<1)
DEAFNESS NOS	-	1 (<1)
Total Number of AEs	-	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	-	1 (<1)
PYREXIA	-	1 (<1)
Total Number of AEs	-	1
HEPATOBILIARY DISORDERS		
Total Pts With at Least one AE	-	1 (<1)
JAUNDICE NOS	-	1 (<1)
Total Number of AEs	-	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	-	1 (<1)
HYPERVENTILATION	-	1 (<1)
Total Number of AEs	-	1

AE11 31JAN2003:13:08:09

5.2.2.3 Safety of PEG-IFN α-2a in Patients with CHB: Study WV16241

This study is a phase III, multicenter, multinational, partially blinded, randomized, parallel-group trial with an active control group. The primary objective of this study is to evaluate the efficacy and safety of PEG-IFN α-2a therapy with and without lamivudine to that of lamivudine in the treatment of anti-HBe positive patients with CHB virus infection. Patients are enrolled into one of three treatment arms: (A) PEG-IFN α-2a plus placebo; (B) PEG-IFN α-2a plus lamivudine; (C) lamivudine and are treated for 48 weeks plus a 24-week follow-up period. Assignment to lamuvudine or placebo in combination with PEG-IFN α-2a is double-blinded, while assignment to PEG-IFN α-2a or lamivudine monotherapy is open-label. The PEG-IFN α-2a dose of 180 µg is being administered sc once weekly and 100 mg of lamivudine is being taken po daily. The study is ongoing. In order to maintain the blind in this ongoing study, data from the two PEG-IFN α-2a treatment groups have been pooled. As of December 19, 2002, 552 patients had safety data available on the database; 184 patients are receiving lamivudine therapy (control) and 368 patients are receiving PEG-IFN α-2a therapy with either placebo or lamivudine.

Safety Summary

There has been one death in this study, which was considered by the investigator to be unrelated to treatment (thrombotic thrombocytopenic purpura in the pooled PEG-IFN α-2a treatment groups).

Four patients in the lamivudine control group and 18 patients in the pooled PEG-IFN α-2a treatment groups experienced serious adverse events (Table 8).

Ten patients withdrew due to adverse events or laboratory abnormalities; all of these patients were in the pooled PEG-IFN α-2a treatment groups.

Table 8 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study WV16241 in Patients with CHB

Body System/ Adverse Event	LAMIVUDINE 100 MG ORALLY ONCE DAILY N = 184 No. (%)	PEG-IFN 180 MCG SC ONCE WEEKLY WITH DAILY ORAL PLACEBO OR 100 MG LAMIVUDINE N = 368 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	4 (2)	18 (5)
Total Number of AEs	4	20
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	-	3 (<1)
BRONCHITIS ACUTE NOS	-	1 (<1)
PYELONEPHRITIS ACUTE NOS	-	1 (<1)
SEPSIS NOS	-	1 (<1)
YERSINIA INFECTION NOS	-	1 (<1)
Total Number of AEs	-	4
CARDIAC DISORDERS		
Total Pts With at Least one AE	-	2 (<1)
MYOCARDIAL INFARCTION	-	1 (<1)
VENTRICULAR TACHYCARDIA	-	1 (<1)
Total Number of AEs	-	2
ENDOCRINE DISORDERS		
Total Pts With at Least one AE	-	2 (<1)
AUTOIMMUNE THYROIDITIS	-	1 (<1)
HYPERTHYROIDISM	-	1 (<1)
Total Number of AEs	-	2
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	-	2 (<1)
APPENDICITIS	-	1 (<1)
ENTEROCOLITIS	-	1 (<1)
Total Number of AEs	-	2
HEPATOBILIARY DISORDERS		
Total Pts With at Least one AE	1 (<1)	1 (<1)
BILIARY COLIC	1 (<1)	-
JAUNDICE NOS	-	1 (<1)
Total Number of AEs	1	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total Pts With at Least one AE	1 (<1)	1 (<1)
LIMB INJURY NOS	-	1 (<1)
ROAD TRAFFIC ACCIDENT	1 (<1)	-
Total Number of AEs	1	1

AE11 31JAN2003:10:49:35

(continued)

Table 8 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study WV16241 in Patients with CHB (Cont.)

Body System/ Adverse Event	LAMIVUDINE 100 MG ORALLY ONCE DAILY N = 184 No. (%)	PEG-IFN 180 MCG SC ONCE WEEKLY WITH DAILY ORAL PLACEBO OR 100 MG LAMIVUDINE N = 368 No. (%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Total Pts With at Least one AE	-	2 (<1)
BREAST CANCER NOS	-	1 (<1)
RENAL NEOPLASM NOS	-	1 (<1)
Total Number of AEs	-	2
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	-	2 (<1)
ASTHMA NOS	-	1 (<1)
DYSPNOEA NOS	-	1 (<1)
Total Number of AEs	-	2
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	-	1 (<1)
THROMBOTIC THROMBOCYTOPENIC PURPURA	-	1 (<1)
Total Number of AEs	-	1
EAR AND LABYRINTH DISORDERS		
Total Pts With at Least one AE	-	1 (<1)
DEAFNESS UNILATERAL	-	1 (<1)
Total Number of AEs	-	1
SOCIAL CIRCUMSTANCES		
Total Pts With at Least one AE	1 (<1)	-
PREGNANCY OF PARTNER	1 (<1)	-
Total Number of AEs	1	-
SURGICAL AND MEDICAL PROCEDURES		
Total Pts With at Least one AE	-	1 (<1)
PHLEBECTOMY	-	1 (<1)
Total Number of AEs	-	1

AE11 31JAN2003:10:49:35

5.2.3 Safety of PEG-IFN α-2a in the Treatment of Oncology Patients

5.2.3.1 Safety of PEG-IFN α-2a in the Treatment of Renal Cell Carcinoma: Study NO15753

Study NO15753, which is completed, was a combined phase I/II, open-label, nonrandomized, dose-escalation trial of the safety and efficacy of PEG-IFN α-2a in previously untreated patients with locally advanced or metastatic renal cell carcinoma. The phase I dose escalation portion of the study was followed by a phase II noncomparative portion of the study. The doses evaluated in the phase I portion included 180, 270, 360, 450, and 540 µg. Twenty-seven patients were enrolled in the phase I part of the study. Based on the dose-limiting toxicity, the dose chosen for the phase II part of the study was 450 µg. In the phase II noncomparative part of the study, 40 additional patients were enrolled. Of the 67 patients who were enrolled, 29 patients completed the 24-week treatment period.

Results of adverse events from the phase I and II portions of the study are pooled. All 67 patients reported one or more adverse events. The types of adverse events were similar to those commonly seen in patients with unmodified α interferon treatment. The most common adverse events, regardless of relationship to study drug, were fatigue, fever, nausea, headache, rigors, myalgia, back pain, dermatitis, decreased appetite, anorexia, arthralgia, dizziness, and diarrhea. Most adverse events were of mild or moderate intensity.

Serious adverse events were reported by 9 of 27 patients (33%) in phase I and 12 of 40 patients (30%) in phase II. The serious adverse events that were reported included neutropenia, thrombocytopenia, increased liver enzymes, fatigue, headache, pain, angina pectoris, atrial fibrillation, pulmonary embolism, anxiety, convulsions, gastrointestinal perforation/hemorrhage, bacteremia/peritonitis, dehydration, fractures, hematuria, urinary blockage, hemiparesis (brain metastases), and bile duct metastases. About half of the reported serious adverse events were considered related to the study drug and usually required dose reduction or, in a few cases, premature treatment discontinuation. However, most of the serious adverse events resolved without sequelae.

Changes in laboratory values were generally mild to moderate and were consistent with those expected with the use of α interferons. The most important changes were elevated serum liver enzyme concentrations and decreased neutrophil count. Most of these laboratory abnormalities returned to near baseline either on treatment, after withholding a dose, or reducing the dose to a lower level.

A total of 43 patients died. All deaths were due to progression of the underlying disease and were unrelated to study drug treatment.

Study drug treatment was discontinued in 4of 67 patients (6%) because of safety reasons, which included thrombocytopenia (one patient), hyperbilirubinemia (one patient), lethargy (one patient), and seizure, sepsis, and gastrointestinal bleeding (one patient).

5.2.3.2 Safety of PEG-IFN α-2a in the Treatment of Chronic Myelogenous Leukemia: Study NO15764

Study NO15764, which is also completed, is a phase I, open-label, nonrandomized, dose-escalation trial of the safety and efficacy of PEG-IFN α-2a in chronic myelogenous leukemia.A total of 43 patients received either PEG-IFN α-2a monotherapy (three at 270 μg and six each at 360, 450, 540, or 630 μg) or PEG-IFN α-2a plus cytosine arabinoside (ara-C) combination therapy (six at 450 μg of PEG-IFN α-2a plus 10 mg of ara-C, six at 540 μg of PEG-IFN α-2a plus 10 mg of ara-C, and four at 540 μg of PEG-IFN α-2a plus 20 mg of ara-C). The PEG-IFN α-2a doses were given once weekly. The ara-C doses were given daily. However, for patients in the 540-μg PEG-IFN α-2a plus 20-mg ara-C group, ara-C was given only on 10 days a month. Patients were treated until their disease progressed or until they withdrew for other reasons.

All patients from all treatment groups had one or more adverse events. The types of adverse events were similar to those seen with α-interferons. The most frequently observed adverse events included fatigue, headache, rigors, myalgia, arthralgia, decreased

appetite, diarrhea, nausea, vomiting, night sweats, pyrexia, dizziness, insomnia, dyspnea, cough, sore throat, and injection site pain or irritation.

Four patients died. One patient treated with 450 µg of PEG-IFN α-2a died of lymphoma. The reasons for the other three deaths (one from the PEG-IFN α-2a 270-µg group and two from the PEG-IFN α-2a 630-µg group) were not specified. These three deaths occurred 5, 14, and 16 months after treatment ended, and were assumed to have been related to the underlying disease.

Serious adverse events were reported 11 of the 43 patients (28%). All treatment groups had at least one patient who experienced a serious adverse event. The serious adverse events that were reported included thrombocytopenia, transfusion reaction, gastroenteritis, herpes simplex stomatitis, viral infection, pyrexia, device failure, hernia repair, lymphoma, dehydration, diarrhea, liver fatty, blood bilirubin increased, weakness, pleuritic pain, atheroslerosis, and neurogenic bladder. About two thirds of the serious adverse events were considered related to the study drug and usually required dose reduction or, in a few cases, premature treatment discontinuation. However, most of the serious adverse events resolved without sequelae.

A total of 13 of the 43 patients (30%) withdrew from the study for safety-related reasons, including 4 of the 10 patients treated with 540 µg of PEG-IFN α-2a and ara-C. Of the 13 patients whose treatment was discontinued prematurely for safety reasons, nine patients were withdrawn for adverse events including irritation of the buccal mucosa, lymphoma, fatty liver, mucositis and pruritic rash, fatigue, leg pain, neuropathy, and weakness of the lower extremities; and four patients were withdrawn for laboratory abnormalities including thrombocytopenia, elevated liver enzymes, abnormal liver function tests, and elevated bilirubin.

5.2.3.3 Safety of PEG-IFN α-2a in the Treatment of Chronic Myelogenous Leukemia: Study NO16006

Study NO16006 is a phase III, randomized, open-label, parallel-arm, multicenter trial comparing the efficacy and safety of PEG-IFN α-2a and IFN α-2a in patients with recently diagnosed chronic myelogenous leukemia who were never treated with interferons. Patients were randomly assigned to receive subcutaneous injections of either 450 µg of PEG-IFN α-2a once weekly or 9 MIU of IFN α-2a daily (titrated upward from a starting dose of 3 MIU daily) for up to 12 months. Responders to treatment may continue treatment for an additional year. As of January 20, 2003, 71 and 74 patients who received PEG-IFN α-2a and IFN α-2a, respectively, had safety data available.

Most of the patients in both treatment groups had one or more adverse events. The most common adverse events in both treatment groups were similar to those seen with interferon treatmentand included pyrexia, myalgia, fatigue/asthenia, rigors, diarrhea, nausea, arthralgia, headache, alopecia, cough, depression, appetite decreased, and anorexia. Most of these events occurred more frequently in the PEG-IFN α-2a-treated patients than in the IFN α-2a-treated patients, with the exception of respiratory, metabolism, and psychiatric disorders.

Nine patients have died, 4 from the PEG-IFN α-2a group and 5 from the IFN α-2a group. Chronic myeloid leukemia caused three deaths, and thrombotic thrombocytopenic purpura led to the death of one patient. The reasons for the remaining five deaths were not specified.

Serious adverse events were reported by 17% of patients treated with PEG-IFN α-2a and 20% of patients treated with IFN α-2a. About one third of the reported serious adverse events were considered related to the study drug and required dose reduction or premature treatment discontinuation. However, most of these serious adverse events resolved without sequelae. For the PEG-IFN α-2a-treated patients, serious adverse events were reported more often as gastrointestinal disorders, infections, and disorders of blood and the lymphatic system.

Nine PEG-IFN α-2a-treated patients (13%) and seventeen IFN α-2a-treated patients (23%) withdrew because of adverse events or laboratory abnormalities. For the PEG-IFN α-2a treatment group, the safety reasons for patient withdrawal included, thrombocytopenia, depression, rash, aseptic bone infarction, retinal vein thrombosis, thyroid disorder, dyspepsia and hematoxicity.

5.2.3.4 Safety of PEG-IFN α-2a in the Treatment of Malignant Melanoma: Study NO16007

Study NO16007 is a phase II, open-label, randomized, multicenter study for assessing PEG-IFN α-2a tolerability, safety, and efficacy in patients with metastatic malignant melanoma. Patients were randomly assigned to three different dose groups and are receiving 180, 360, or 450 μg of PEG-IFN α-2a once a week for 24 weeks. Patients could receive an extended period of therapy after week 24, dependent on their response to treatment. The study is ongoing. As of December 12, 2002, safety data from 150 patients (48, 53, 49 patients in the PEG-IFN α-2a 180-μg, 360-μg, and 450-μg treatment groups, respectively) were available.

Adverse events were reported by almost all patients. The most frequent adverse events, regardless of relationship to study drug, included fatigue/asthenia, pyrexia, nausea, rigors, vomiting, diarrhea, constipation, headache, pain in limb, back pain, arthralgia, myalgia, anorexia, dizziness, pruritus, cough, dyspnea, and insomnia. A tendency toward a dose-dependent increase in the incidence of adverse events was seen for musculoskeletaland connective tissue disorders, nervous system disorders, metabolism and nutrition disorders, and infections. Most adverse events were considered by the investigator to be treatment-related, but approximately 90% of all the adverse events from any dose group were mild or moderate in intensity.

As of December 12, 2002, 118 patients had died. Almost all the deaths were a result of the progression of the underlying disease, with the exception of two patients who died of acute cardiac failure and bronchial asthma, respectively. All the deaths were considered to be unrelated to the study treatment.

Serious adverse events were reported in 40%, 47%, and 51% of patients treated with the 180, 360, and 450-μg doses of PEG-IFN α-2a, respectively. No apparent differences in

the types and frequencies of the serious adverse events among the three dose groups were seen. The serious adverse events reported most frequently were gastrointestinal disorders; respiratory, thoracic, and mediastinal disorders; infections; and blood and lymphatic system disorders.

Treatment was prematurely discontinued in three (6%), nine (17%), and seven (14%) patients from the PEG-IFN α-2a 180, 360, and 450-µg dose groups, respectively. All these patients withdrew because of adverse events except two who withdrew because of laboratory abnormalities (one patient from the 180-µg dose group with increased lactic dehydrogenase, and one patient from the 360-µg dose group with increased ALT, AST and lactic dehydrogenase). The adverse events that led to premature treatment discontinuation included hepatotoxicity, γ-glutamyltransferase increased, cachexia, general condition aggravated, fatigue/malaise, weight loss, vomiting/headache/bradyphrenia, dyspnea, pleural effusion, optic neuropathy, thyroid disorder, arthralgia, CNS hemorrhage, hypertensive encephalopathy, pruritus, and generalized rash.

5.3 Efficacy in Chronic Hepatitis C

In study NV15489, the phase II dose-finding study, a dose-dependent increase was seen in sustained virological response, with the highest response achieved in the 180-µg group.

The main efficacy results (Table 9) from the three phase III PEG-IFN α-2a monotherapy studies (NV15495, NV15496, and NV15497) are the following:

- In all four studies, PEG-IFN α-2a treatment resulted in a significantly higher sustained virological response and a higher sustained biochemical response than IFN α-2a treatment. This was true regardless of whether IFN α-2a was given as 3 MIU tiw for 48 weeks or as an induction regimen of 6 MIU tiw for 12 weeks followed by 3 MIU tiw for 36 weeks.
- In PEG-IFN α-2a-treated patients, efficacy was generally improved with increasing dose up to 180 µg, with the highest virological response achieved in patients treated with the 180-µg dose.
- PEG-IFN α-2a treatment was also more effective than IFN α-2a in cirrhotic patients. Cirrhotic patients treated with the 180 µg dose of PEG-IFN α-2a achieving a significantly higher sustained virological response and a higher sustained biochemical response than IFN α-2a-treated patients.

Table 9 Sustained Virological and Biochemical Responses at Week 72 in Studies NV15495, NV15496, and NV15497

Study	IFN α-2a 3 or 6/3 MIU	PEG-IFN α-2a 90 μg	PEG-IFN α-2a 135 μg	PEG-IFN α-2a 180 μg
NV15496				
Sustained virological response	11%		28%	28%
Sustained biochemical response	18%		32%	31%
NV15497				
Sustained virological response	19%			39%
Sustained biochemical response	25%			45%
NV15496 and NV15497 Pooled				
Sustained virological response	15%		28%	34%
Sustained biochemical response	22%		32%	39%
NV15495 (Cirrhotics)				
Sustained virological response	8%	15%		30%
Sustained biochemical response	15%	20%		34%

In studies NV15496 and NV15497 a significantly higher proportion of PEG-IFN α-2a treated patients achieved a sustained virological response and a sustained biochemical response than IFN α-2a treated patients. The proportions of PEG-IFN α-2a-treated patients achieving a sustained virological or sustained biochemical response were significantly higher in both the 135-μg and 180-μg PEG-IFN α-2a groups than in the IFN α-2a groups (all $p \leq 0.004$).

Similar results were seen in study NV15495, which recruited only cirrhotic patients. A significantly higher proportion of patients treated with 180 μg of PEG-IFN α-2a achieved a sustained virological response and a sustained biochemical response than patients treated with IFN α-2a. The same superior efficacy in favor of PEG-IFN α-2a treatment was also seen with the 90-μg dose of PEG-IFN α-2a, although the difference at week 72 was not statistically significant.

6. RIBAVIRIN IN COMBINATION WITH PEG-IFN α-2A FOR THE TREATMENT OF CHRONIC HEPATITIS C

6.1 Chemistry and Formulation of Ribavirin

Copegusis the trade name of Roche's market formulation of ribavirin, which is supplied as 100-mg pink immediate-release film-coated tablets. Chemistry and formulation information regarding the tablet are provided below.

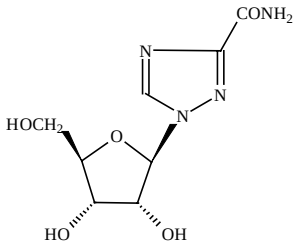
6.1.1 Chemical Properties

Generic Name: Ribavirin

Code Number: Ro 20-9963

Chemical Name: 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide

Chemical Structure:



Empirical Formula: $C_8H_{12}N_4O_5$

Molecular Weight: 244.21

Description: Ribavirin is a nonhygroscopic, white crystalline powder that is freely soluble in water (155.3 mg/mL) and is slightly soluble in ethanol (2.8 mg/mL).

6.1.2 Formulation

Ribavirin is manufactured as a 200 mg immediate release film-coated oval pink tablet which in addition to ribavirin contains: pregelatinized starch, sodium starch glycolate, corn starch, microcrystalline cellulose, magnesium stearate, hydroxypropyl methylcellulose, talc, titanium dioxide, yellow and red iron oxides, ethylcellulose, and triacetin.

6.1.3 Stability of Formulation

Up to 36 months stability data have been obtained for investigational ribavirin tablets (200 mg); the data indicate that the formulation is stable when stored at 25°C for up to 36 months. The tablets may also be stored under refrigeration at 2° to 8°C.

6.2 Nonclinical Studies With Ribavirin

6.2.1 Nonclinical Pharmacology

The nonclinical pharmacology study of PEG-IFN α-2a in combination with ribavirin demonstrated increased efficacy against HCV. In a novel model of HCV-infected cells (HCV replicon assay), PEG-IFN α-2a and ribavirin in combination were more effective than either agent alone for inhibition of autonomous HCV subgenomic RNA replication. Further studies with ribavirin alone investigated its mechanism of action for inhibition of HCV RNA replication in the model of HCV-infected cells and also investigated its immunomodulatory and antiproliferative activities in immune cells. The potency of ribavirin alone in in vitro antiviral and immunomodulatory studies was at similar concentrations to that reported in the plasma of ribavirin-treated CHC patients.

In vitro studies demonstrated the following activities of ribavirin:

- In the HCV replicon assay, the inhibitory effects of PEG-IFN α-2a and ribavirin in combination are more than additive [6.1].
- Ribavirin inhibits HCV subgenomic RNA replication and expression of HCV-specific proteins in the HCV replicon assay [6.1, 6.2]. Inhibition of HCV RNA-dependent RNA polymerase (NS5B) by ribavirin triphosphate could contribute to this inhibition [6.2].
- Ribavirin inhibits proliferation of human T cells in vitro [6.3].
- Ribavirin increases T helper 1 cytokine and decreases T helper 2 cytokine secretion from stimulated human T cells in vitro [6.4, 6.45]. The mechanism by which ribavirin in combination with PEG-IFN α-2a exerts its effects against HCV is unknown, although it possibly involves both direct antiviral and immunomodulatory activities.

No appropriate in vivo pharmacology models are currently available for assessing the combination of PEG-IFN α-2a with ribavirin in hepatitis C.

Repeat-dose toxicity studies with ribavirin in mice, rats, and dogs did not reveal any particular potential central nervous system, renal, or cardiovascular effects. A complete battery of safety pharmacology studies conducted with PEG-IFN α-2a showed no findings of clinical importance. The following safety data have been obtained:

- In a 4-week study in monkeys with PEG-IFN α-2a in combination with ribavirin, there was no evidence of renal, central nervous system, or cardiovascular system adverse effects [6.5]. ECG measurements were performed on all animals at the time of peak exposure to both compounds, and no treatment-related ECG abnormalities were observed.
- Clinical signs from repeat-dose toxicity studies with ribavirin in mice, rats, dogs, and monkeys did not reveal treatment-related effects on the central nervous system [6.5, 6.6, 6.7, 6.8, 6.9].
- Clinical and microscopic pathology data from these repeat-dose studies with ribavirin in rats and dogs showed no adverse effects on renal function [6.7, 6.8, 6.9].
- ECG data in a 6-month study in dogs showed no effects of ribavirin on heart rate or ECG changes [6.9].

6.2.2 Pharmacokinetics and Pharmacodynamics

A single-dose pharmacokinetic study in dogs demonstrated that ribavirin administered as a tablet (Copegus) displayed similar pharmacokinetic attributes as ribavirin administered as a capsule (Rebetol) [6.43]. The absorption, distribution, metabolism, and excretion of ribavirin after single doses in animals have been well characterized and are reported in the literature. No pharmacokinetic interactions were noted in a 4-week combination toxicology study of PEG-IFN α-2a and ribavirin in cynomolgus monkeys [6.28].

The results from multiple-dose toxicokinetic studies of ribavirin in rats, dogs, and monkeys showed that serum ribavirin $AUC_{0\text{-}24\ h}$ was approximately dose proportional in these species, while C_{max} showed inconsistent linearity with increases in dose of ribavirin. This phenomenon has also been reported in humanss [6.41]. The results from these

studies also indicated species differences in the accumulation of ribavirin in red blood cells (RBCs). The differences observed among the monkey, rat, and dog in the accumulation of ribavirin are consistent with findings reported in the literature and may be due to the equilibrium between RBCs and plasma, which is rapid in rats and slow in monkey and human. This observation is consistent with the theory that ribavirin accumulates in RBCs and thus promotes their removal by the reticuloendothelial system (ie, decreases the life span of RBCs), leading to anemia [6.42].

6.2.3 Toxicology and Toxicokinetics

The toxicology and toxicokinetic studies with ribavirin alone or PEG-IFN α-2a plus ribavirin are listed in Appendix 7.

The following are the main findings from the toxicity studies conducted with ribavirin alone and/or from studies reported in the literature:

- At all doses tested in the repeat-dose rodent studies, effects on the erythron (reduced red blood cell count, hemoglobin and/or hematocrit) were noted [6.10, 6.11, 6.12]; at the higher doses tested, these effects were indicative of anemia. In dogs, slight effects on the erythron were noted only at the highest dose tested (20 mg/kg/day) [6.13]. The effects on the erythron were similar to those reported in the literature for monkeys and patients following administration of ribavirin [6.14, 6.15, 6.16].
- Histopathology findings that correlated with the effects on the erythron included extramedullary splenic hematopoiesis in rodents and hypercellularity of the femur marrow for rats. Erythroid hypoplasia in the bone marrow was observed for decedent mice at 200 and 400 mg/kg/day in a 4-week study [6.10] and for rats at the highest dose of 160 mg/kg/day in a 13-week study [6.11].
- Decreased leukocyte and/or lymphocyte counts were observed at relatively high doses in rodents [6.10, 6.11] and at all tested doses (5 to 20 mg/kg/day) in dogs [6.13].
- Consistent with the literature, lymphoid depletion was noted microscopically in the rodent studies at most of the tested doses [6.11, 6.12].
- Gastrointestinal effects (crypt cell necrosis and reduced number of epithelial cells) were noted in rodents that died prematurely [6.10]. Similar findings, as well as chronic inflammation and erosion, were also noted for dogs treated at 10 and 20 mg/kg/day [6.13].
- The majority of the effects noted in the sponsor's repeat-dose studies with ribavirin were reversible upon treatment withdrawal.
- Literature data indicate that ribavirin is teratogenic and a reproductive toxicant [6.17, 6.18, 6.19, 6.20, 6.21, 6.22]. Data from the sponsor-conducted fertility study in rats support ribavirin's embryotoxic effects and show slight effects on sperm counts at the high dose of 100 mg/kg/day [6.23]. Importantly, all effects on reproductive parameters were reversible following treatment withdraw.
- Although the literature and sponsor-conducted studies indicate that ribavirin is genotoxic [6.24, 6.25, 6.26], results from the 6-month carcinogenicity study in p53 (+/-) knockout mice revealed no evidence of treatment-related neoplasia [6.27].

The following are the main findings from a toxicity study conducted in monkeys with PEG-IFN α-2a plus ribavirin combination therapy [6.28]:

- At a dose of 100 mg/kg/day of ribavirin alone, effects on the erythron indicative of a mild anemia were observed. These effects were slightly more severe in monkeys treated with 600 µg/kg/dose of PEG-IFN α-2a twice weekly plus 100 mg/kg/day of ribavirin. These doses are 400 times the intended weekly clinical dose of PEG-IFN α-2a (180 µg/week, 3 µg/kg for a 60 kg person) and approximately six times the intended daily clinical dose of ribavirin (1000 mg/day for a 60 kg person, or 16 mg/kg/day).
- Animals treated with 50 mg/kg/day of ribavirin alone exhibited no effects on the erythron. Animals administered 600 µg/kg of PEG-IFN α-2a twice weekly plus 50 mg/kg/day of ribavirin exhibited decreases in red blood cell parameters.
- Bone marrow cytology and microscopic evaluations showed erythroid hypoplasia in one of ten animals treated with 600 µg/kg of PEG-IFN α-2a twice weekly plus 50 mg/kg/day of ribavirin and in two of ten animals treated with 600 µg/kg of PEG-IFN α-2a twice weekly plus 100 mg/kg/day of ribavirin.
- No new or unexpected toxicities were observed for animals treated with the combination therapy compared to animals treated with ribavirin or PEG-IFN α-2a alone.

It is concluded that the nonclinical toxicity studies with PEG-IFN α-2a alone, ribavirin alone, and the combination therapy characterized the untoward effects of PEG-IFN α-2a and ribavirin combination therapy that may occur in humans. Specifically, for PEG-IFN α-2a, these effects included minor clinical laboratory alterations (platelets, WBCs, protein, ALT and/or AST) and irregularities in menstrual cycles and cyclic serum sex hormone levels, findings that are anticipated for this class of compound. Notably, the PEG modification of the IFN α-2a molecule to produce PEG-IFN α-2a did not induce additional or unexpected toxicities beyond those that have already been observed with interferons. For ribavirin, effects included those anticipated for an inhibitor of cellular proliferation (ie, hematological, gastrointestinal, and reproductive effects) as well as genotoxic activity. These effects were similar to those reported in the published literature. Importantly, the 6-month carcinogenicity study with ribavirin in p53 mice showed no oncogenic potential.

For the combination therapy, effects were similar to or slightly more severe than those observed for PEG-IFN α-2a or ribavirin therapy alone. However, the clinical laboratory adverse effects noted for the combination therapy can be readily monitored in patients and thus manageable by prompt modification of dose level or temporary withdrawal of treatment as necessary. Of the greatest importance is the fact that no new or unexpected toxicities were observed with the combination therapy compared with treatment with PEG-IFN α-2a or ribavirin alone. Thus, the nonclinical toxicological assessment of PEG-IFN α-2a, ribavirin, and the combination therapy fully supports the clinical use of PEG-IFN α-2a plus ribavirin.

6.3 Clinical Studies With Ribavirin In Combination With PEG-IFN α-2a

A project-specific definition for expected serious adverse events has been adopted for all clinical studies conducted with the combination of PEG-IFN α-2a and ribavirin. For serious adverse events attributed by an investigator to both PEG-IFN α-2a and ribavirin, events listed as "expected" for PEG-IFN α-2a or ribavirin are also considered to be expected for the combination. The rationale for this definition is that it is the safety profile of the combination rather than its individual components that is being assessed in these studies.

The same type of definition for expected serious adverse events has been adopted for clinical studies conducted with the combination of IFN α-2a and ribavirin. For serious adverse events attributed by an investigator to both IFN α-2a and ribavirin, events listed as "expected" for IFN α-2a or ribavirin are also considered to be expected for the combination.

6.3.1 Clinical Pharmacokinetics of Ribavirin

6.3.1.1 Pharmacokinetics

Orally administered ribavirin is absorbed rapidly, reaching maximal plasma concentrations between 1 and 2 hours. Absorption is extensive, with about 10% to 15% of a radiolabelled dose excreted in the feces. However, the absolute bioavailability is between 45% and 65%, probably due to high first-pass metabolism. Ribavirin is absorbed from the gastrointestinal tract via an active sodium dependent nucleoside transport process. Since this process is saturable, less than proportional increases in C_{max} were observed for doses above 800 mg. However, the exposure as measured by $AUC_{0\text{-}inf}$ was proportional up to a 2400-mg dose.

Ribavirin partitions into all cells rapidly and extensively, and a very large steady-state volume of distribution of about 850 liters is seen after intravenous dosing. This distribution is facilitated by the sodium independent *es* nucleoside transporter that is present in all types of cells, and thus ribavirin accumulates in erythrocytes, ova and spermatozoa. Ribavirin sequesters in erythrocytes extensively with a ratio of 60:1 between whole blood and plasma concentrations. Ribavirin does not bind to plasma proteins.

Both renal excretion and metabolism are major routes of elimination of ribavirin in humans and animals. Clearance after intravenous dosing was about 20 to 25 L/h, with about 30% accounted for by renal clearance. In humans, about 61% of the radioactivity of a 600-mg oral dose was eliminated in the urine within 336 hours, of which unchanged ribavirin accounted for 17%. Ribavirin is metabolized via two major pathways: 1) a reversible phosphorylation in nucleated cells forming monophosphate, diphosphate and triphosphate metabolites and 2) deribosylation and amide hydrolysis forming the triazole carboxylic acid metabolite. The triazole carboxylic acid and triazole carboxamide were the principal metabolites. The cytochrome P450 enzyme system is not involved in the metabolism of ribavirin.

Due to extensive distribution, the terminal half-life of a single oral or intravenous dose is about 120 to 170 hours. This half-life may be longer in some patients after multiple dosing (ie, 180 to 300 hours). Extensive accumulation of ribavirin is seen after multiple dosing (twice daily) such that the AUC at steady state was 6-fold higher than that of a single dose.

No clinically significant differences in the pharmacokinetics of ribavirin were observed between male and female subjects in a population pharmacokinetic analysis of 3600 sparsely collected serum concentration data from 138 patients.

Food Effect: Bioavailability of a single oral dose of ribavirin was increased by coadministration of a high fat meal. The absorption was slowed (t_{max} was doubled) and the $AUC_{0\text{-}192h}$ and C_{max} increased by 42% and 66%, respectively, when the Copegus film-coated tablet was taken with a high fat meal compared with fasting conditions [6.31].

6.3.1.2 Special Populations

Renal function: Single-dose ribavirin pharmacokinetics were altered (increased AUC_{tf} and C_{max}) in patients with renal dysfunction compared with control subjects whose creatinine clearance was greater than 90 mL/min. The oral clearance of ribavirin was substantially reduced in CHC patients with renal dysfunction. Ribavirin has been used in dialysis patients with CHC at substantially reduced doses of 100 to 300 mg daily. It is recommended that renal function be evaluated in all patients prior to initiation of ribavirin treatment, preferably by estimating the patient's creatinine clearance. Substantial increases in ribavirin plasma concentrations are seen at the recommended dosing regimen in patients with serum creatinine >2mg/dL or with creatinine clearance <50mL/minute [6.30, 6.32, 6.33]. In these patients ribavirin must be administered with caution and drug discontinuation must be considered.

Hepatic function: Single-dose pharmacokinetics of ribavirin in patients with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B or C) were similar to those of normal controls.

Elderly patients (≥ 65 years of age): Specific pharmacokinetic evaluations for elderly subjects have not been performed. In a population pharmacokinetic study, age alone was not a key factor; however, the declining renal function in the elderly will result in higher exposure to ribavirin [6.44].

Patients under the age of 18 years: Specific pharmacokinetic studies have not been fully evaluated in patients under the age of 18 years. Ribavirin in combination with IFN α-2a or PEG-IFN α-2a is indicated for the treatment of CHC only in patients 18 years of age or older.

6.3.1.3 Drug Interactions

Interaction studies have been conducted with ribavirin in combination with IFN α, PEG-IFN α, and antacids [6.30]. Ribavirin concentrations were similar when given concomitantly with IFN α or PEG-IFN α-2a [6.34].

Any potential for interactions may persist for up to 2 months (five half lives for ribavirin) after cessation of Copegus therapy because of the long half-life of ribavirin [6.30].

Results of in vitro studies using both human and rat liver microsome preparations indicated no cytochrome P450 enzyme mediated metabolism of ribavirin. Ribavirin did not inhibit cytochrome P450 enzymes. There was no evidence from toxicity studies that ribavirin induced liver enzymes. Therefore, there is a minimal potential for P450 enzyme-based interactions [6.30].

Antacid: The bioavailability of 600 mg of ribavirin was decreased by coadministration with an antacid containing magnesium, aluminum, and methicone. AUC_{tf} decreased by 14% [6.30]. It is possible that the decreased bioavailability in this study was due to delayed transit of ribavirin or a modified pH. This interaction is not considered to be clinically relevant.

Nucleoside analogs: Ribavirin has been shown in vitro to inhibit phosphorylation of zidovudine and stavudine [6.36, 6.37]. The clinical significance of these findings is unknown. However, these in vitro findings raise the possibility that concurrent use of ribavirin with either zidovudine or stavudine might lead to increased human immunodeficiency virus (HIV) plasma viremia.

Ribavirin has been shown in vitro and in vivo in animals to potentiate the antiretroviral effects of didanosine (ddI) by increasing the formation of the active triphosphate anabolite (ddATP). The clinical significance of these findings is unknown. In one study in patients with HIV disease, the addition of ribavirin to ddI therapy did not result in further reductions in viremia or evidence of adverse pharmacologic interactions [6.38]. Plasma pharmacokinetics of ddI were relatively unchanged in the presence of ribavirin, although intracellular ddATP levels were not measured. However, the in vitro and in vivo animal findings raise the possibility that the concurrent use of ribavirin and ddI may lead to a potential of adverse reactions related to ddI. Adverse effects related to ddI, such as peripheral neuropathy, pancreatitis, and hepatic steatosis with lactic acidosis may occur more frequently with the concomitant use of ribavirin [6.39].

Specific concerns in patients coinfected with HCV/HIV and receiving HIV therapy: Hepatic decompensation, lactic acidosis, and pancreatitis occurred in HCV/HIV coinfected patients concomitantly treated with HIV therapy, IFN alfa, and ribavirin. Close monitoring for these events is appropriate in these patients [6.39].

6.3.2 Comparison of the Safety of PEG-IFN α-2a Monotherapy with PEG-IFN α-2a and IFN α-2b Plus Ribavirin Combination Therapies: Study NV15801

6.3.2.1 Study Overview

Study NV15801 is a completed comparative phase III trial of PEG-IFN afa-2a plus ribavirin and IFN α-2b plus ribavirin and PEG-IFN α-2a monotherapy. This was a randomized, multicenter, partially blinded, active-controlled and placebo-controlled trial. Patients were stratified according to genotype and treated for 48 weeks with PEG-IFN α-

2a or IFN α-2b in combination with 1000 or 1200 mg of ribavirin or with PEG-IFN α-2a plus placebo.

Of the 1117 patients in the safety population, 223 received PEG-IFN α-2a monotherapy, 451 received PEG-IFN α-2a and ribavirin combination therapy, and 443 received IFN α-2b and ribavirin combination therapy. The majority of patients in all three treatment groups were infected with HCV genotype 1. Patients with cirrhosis accounted for 15% of the patients in the PEG-IFN α-2a monotherapy group and 12% of the patients in the two combination therapy groups.

The safety summary focuses on the comparison of PEG-IFN α-2a monotherapy and PEG-IFN α-2a plus ribavirin combination therapy to highlight the effect of the addition of ribavirin on the safety profile of PEG-IFN α-2a.

6.3.2.2 Safety Summary

The safety profile of PEG-IFN α-2a and ribavirin combination therapy is consistent with the safety profiles of the individual drugs and was additive in nature. No new adverse events were observed with the combination that would not have been expected from combination therapy with interferon and ribavirin. Some clinical adverse events and laboratory abnormalities, mainly anemia, that are known side effects of treatment with ribavirin occurred at a higher incidence with PEG-IFN α-2a combination therapy than with PEG-IFN α-2a monotherapy. Key safety data are summarized in Table 10.

Table 10 Overview of Safety Profile in Study NV15801 in Patients with Hepatitis C

Adverse Event	PEG-IFN α-2a (N = 223)	PEG-IFN α-2a + Ribavirin 1000 or 1200 mg (N = 451)	IFN α-2b + Ribavirin 1000 or 1200 mg (N = 443)
Any AE	212 (95%)	446 (99%)	435 (98%)
Severe AEs	63 (28%)	131 (29%)	127 (29%)
Treatment-related AEs[a]	205 (92%)	443 (98%)	435 (98%)
Serious AEs	26 (12%)	53 (12%)	38 (9%)
Treatment-related serious AEs[a]	8 (4%)	16 (4%)	19 (4%)
Deaths	2	0	1
Premature withdrawal for AEs and laboratory abnormalities	15 (7%)	44 (10%)	47 (11%)
Aes	13 (6%)	32 (7%)	43 (10%)
Laboratory abnormalities	2 (<1%)	12 (3%)	4 (<1%)
Dose modification for AEs and laboratory abnormalities			
PEG-IFN α-2a or IFN α-2b	61 (27%)	145 (32%)	81 (18%)
AEs	14 (6%)	48 (11%)	47 (11%)
Neutropenia	38 (17%)	91 (20%)	24 (5%)
Thrombocytopenia	14 (6%)	18 (4%)	1 (<1%)
Ribavirin		181 (40%)	164 (37%)
AEs		95 (21%)	97 (22%)
Anemia		99 (22%)	83 (19%)
Lowest hemoglobin level			
8.5 to <10 g/dL	7 (3%)	40 (9%)	47 (11%)
<8.5 g/dL	1 (<1%)	9 (2%)	1 (<1%)

[a]Events judged by investigator to be remotely, possibly, or probably related to treatment.

In general, the adverse event profile was similar between PEG-IFN α-2a combination therapy and monotherapy. The following clinical adverse events occurred at a higher incidence with PEG-IFN α-2a combination therapy than with PEG-IFN α-2a monotherapy, suggesting that these adverse events are exacerbated by ribavirin: insomnia, decreased appetite, vomiting, weight decrease, dyspnea, cough, and dermatitis (Table 11). These findings are consistent with the known adverse effects of ribavirin. Some differences in the point estimates for certain flu-like symptoms (pyrexia, rigors, and myalgia) and depression were observed between PEG-IFN α-2a and ribavirin combination therapy and IFN α-2b and ribavirin therapy (Table 11).

Table 11 Common Clinical Adverse Events (≥10% of Patients) during Treatment and 24 Weeks Posttreatment in Study NV15801 in Patients with Hepatitis C

Adverse Event	PEG-IFN α-2a N = 223 No. (%)	PEG-IFN α-2a + Ribavirin 1000 or 1200 mg N = 451 No. (%)	IFN α-2b + Ribavirin 1000 or 1200 mg N = 443 No. (%)
FATIGUE	98 (44)	242 (54)	244 (55)
HEADACHE NOS	115 (52)	211 (47)	230 (52)
PYREXIA	85 (38)	195 (43)	247 (56)
MYALGIA	94 (42)	189 (42)	220 (50)
INSOMNIA	52 (23)	168 (37)	174 (39)
NAUSEA	58 (26)	130 (29)	145 (33)
ALOPECIA	48 (22)	128 (28)	151 (34)
RIGORS	52 (23)	106 (24)	157 (35)
ARTHRALGIA	64 (29)	121 (27)	112 (25)
IRRITABILITY	56 (25)	109 (24)	123 (28)
DEPRESSION NOS	44 (20)	95 (21)	131 (30)
PRURITUS	41 (18)	101 (22)	88 (20)
APPETITE DECREASED	24 (11)	96 (21)	98 (22)
DERMATITIS NOS	29 (13)	95 (21)	80 (18)
DIARRHOEA NOS	54 (24)	77 (17)	68 (15)
DIZZINESS (EXC VERTIGO)	31 (14)	81 (18)	70 (16)
ASTHENIA	26 (12)	69 (15)	72 (16)
DYSPNOEA	20 (9)	70 (16)	72 (16)
COUGH	23 (10)	73 (16)	51 (12)
DRY SKIN	20 (9)	50 (11)	64 (14)
ANXIETY	18 (8)	51 (11)	60 (14)
BACK PAIN	29 (13)	52 (12)	46 (10)
ABDOMINAL PAIN UPPER	35 (16)	41 (9)	50 (11)
INJECTION SITE INFLAMMATION	26 (12)	56 (12)	44 (10)
CONCENTRATION IMPAIRMENT	28 (13)	41 (9)	53 (12)
VOMITING NOS	17 (8)	52 (12)	51 (12)
WEIGHT DECREASE	18 (8)	52 (12)	49 (11)
ABDOMINAL PAIN NOS	28 (13)	44 (10)	34 (8)

The incidence of anemia, the main hematological abnormality associated with ribavirin treatment, was higher with PEG-IFN α-2a or IFN α-2b combination therapy than with PEG-IFN α-2a monotherapy (Table 10). The addition of ribavirin resulted in a higher percentage of patients experiencing a decrease in hemoglobin concentration to <10 g/dL in both combination therapy groups (Table 10). However, premature withdrawal from treatment (discontinuation of both PEG-IFN α-2a and ribavirin) for anemia was infrequent with PEG-IFN α-2a combination therapy (two patients). In most patients, anemia could be managed by modification of the ribavirin dose and infrequently by discontinuation of ribavirin only.

Three patients died, two in the PEG-IFN α-2a monotherapy group and one in the IFN α-2b group combination therapy group (Table 12). No deaths occurred during treatment. All three deaths were considered unrelated to treatment.

Table 12 Patient Deaths in Study NV15801 in Patients with Hepatitis C

Treatment Group CRTN/Pt. No.	Age yr	Sex	Weight kg	Race	Cause of Death	Last Trt Day	Day of Death	Relation to Trial Treatment
PEG-IFN alfa-2a 180 ug								
23183/1135	40	F	62	CAUCASIAN	DROWNING	337	485	UNRELATED
23231/1896	57	F	94	CAUCASIAN	MALIGNANT HEPATIC NEOPLASM	316	680	UNRELATED
IFN alfa-2b 3 MIU + Ribavirin 1000-1200 mg								
23219/7401	44	M	106	CAUCASIAN	HYPERTENSIVE HEART DISEASE NOS	295	340	UNRELATED

CRTN = Clinical Research Task Number (center no.)

Serious adverse events occurred at a similar incidence with PEG-IFN α-2a combination therapy, PEG-IFN α-2a monotherapy and IFN α-2b combination therapy (Table 13). The incidence of serious psychiatric disorders was 1% in PEG-IFN α-2a monotherapy and PEG-IFN α-2a plus ribavirin treatment groups and 3% in the IFN α-2b combination therapy. The incidence of serious adverse events grouped under the body system of infections was 3% in both PEG-IFN α-2a combination therapy and PEG-IFN α-2a monotherapy treatment groups compared with 1% in the IFN α-2b combination therapy group. These infections did not, however, appear to be associated with neutropenia and comprised a variety of types of infection (including viral, protozoal, and bacterial) and involved different organ systems. Importantly, all but one event (interstitial pneumonitis – with no actual evidence of infection) resolved without sequelae.

Serious cardiovascular events were experienced by 6 of 451 patients (1%) in the PEG-IFN α-2a combination group and 1 of 223 patients (0.4%, or <1%) in the PEG-IFN α-2a monotherapy group.

Table 13 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study NV15801 in Patients with Hepatitis C

Body System/ Adverse Event	PEG-IFN alfa-2a 180 ug N = 223 No. (%)	PEG-IFN alfa-2a 180 ug Ribavirin 1000-1200 mg N = 451 No. (%)	IFN alfa-2b 3 MIU Ribavirin 1000-1200 mg N = 443 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	26 (12)	53 (12)	38 (9)
Total Number of AEs	31	64	50
INFECTIONS & INFESTATIONS			
Total Pts With at Least one AE	6 (3)	13 (3)	4 (1)
CELLULITIS	2 (1)	1 (<1)	-
PNEUMONIA NOS	-	2 (<1)	1 (<1)
GASTROENTERITIS NOS	-	1 (<1)	1 (<1)
OTITIS EXTERNA (EXC BOIL OF MEATUS) NOS	-	2 (<1)	-
AMOEBIASIS NOS	1 (<1)	-	-
ARTHRITIS INFECTIVE NOS	-	1 (<1)	-
BRONCHIECTASIS NOS	-	1 (<1)	-
CERVICITIS	1 (<1)	-	-
LOWER RESPIRATORY TRACT INFECTION NOS	-	-	1 (<1)
NEUROSYPHILIS	-	1 (<1)	-
PNEUMONIA VIRAL NOS	1 (<1)	-	-
PYELONEPHRITIS NOS	-	-	1 (<1)
SINUSITIS NOS	-	1 (<1)	-
SKIN & SUBCUTANEOUS TISSUE ABSCESS	-	1 (<1)	-
STAPHYLOCOCCAL INFECTION NOS	-	1 (<1)	-
URINARY TRACT INFECTION NOS	-	1 (<1)	-
VIRAL INFECTION NOS	1 (<1)	-	-
Total Number of AEs	6	13	4
PSYCHIATRIC DISORDERS			
Total Pts With at Least one AE	2 (1)	6 (1)	13 (3)
DEPRESSION NOS	-	2 (<1)	6 (1)
SUICIDE ATTEMPT	1 (<1)	2 (<1)	4 (1)
SUICIDAL IDEATION	1 (<1)	-	2 (<1)
DRUG ABUSE	-	1 (<1)	1 (<1)
ALCOHOLISM	-	1 (<1)	-
BIPOLAR AFFECTIVE DISORDER	-	1 (<1)	-
DEPRESSION ENDOGENOUS	-	-	1 (<1)
DRUG DEPENDENCE	-	-	1 (<1)
DRUG WITHDRAWAL SYNDROME	-	-	1 (<1)
PARANOIA	-	-	1 (<1)
Total Number of AEs	2	7	17
GASTROINTESTINAL DISORDERS			
Total Pts With at Least one AE	2 (1)	8 (2)	8 (2)
ABDOMINAL PAIN NOS	-	3 (1)	2 (<1)
APPENDICITIS	-	1 (<1)	2 (<1)
DIARRHOEA NOS	1 (<1)	-	1 (<1)
ABDOMINAL ABSCESS NOS	-	1 (<1)	-
ABDOMINAL PAIN LOWER	-	-	1 (<1)
HAEMATEMESIS	-	-	1 (<1)
HAEMORRHOIDS	-	1 (<1)	-
INTESTINAL FISTULA	-	-	1 (<1)
NAUSEA	-	1 (<1)	-
OESOPHAGEAL REFLUX	1 (<1)	-	-
PERITONITIS BILIARY	-	-	1 (<1)
RECTAL BLEEDING	-	1 (<1)	-
Total Number of AEs	2	8	9

(Continued)

Table 13 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study NV15801 in Patients with Hepatitis C (Cont.)

Body System/ Adverse Event	PEG-IFN alfa-2a 180 ug N = 223 No. (%)	PEG-IFN alfa-2a 180 ug Ribavirin 1000-1200 mg N = 451 No. (%)	IFN alfa-2b 3 MIU Ribavirin 1000-1200 mg N = 443 No. (%)
NEUROLOGICAL DISORDERS			
Total Pts With at Least one AE	2 (1)	5 (1)	2 (<1)
CLUSTER HEADACHES	1 (<1)	-	-
FACIAL PALSY	-	1 (<1)	-
HEADACHE NOS	-	1 (<1)	-
MIGRAINE	-	-	1 (<1)
PERIPHERAL NEUROPATHY NOS	-	-	1 (<1)
POLYNEUROPATHY NOS	1 (<1)	-	-
SYNCOPE	-	1 (<1)	-
TRIGEMINAL NEURALGIA	-	1 (<1)	-
VASOVAGAL ATTACK	-	1 (<1)	-
Total Number of AEs	2	5	2
BENIGN & MALIGNANT NEOPLASMS (INCLUDING CYSTS AND POLYPS)			
Total Pts With at Least one AE	3 (1)	2 (<1)	3 (1)
MALIGNANT HEPATIC NEOPLASM	1 (<1)	2 (<1)	-
COLONIC CANCER	-	-	1 (<1)
OESOPHAGEAL CANCER	-	-	1 (<1)
OVARIAN NEOPLASM NOS	-	-	1 (<1)
PARATHYROID TUMOUR	1 (<1)	-	-
PITUITARY TUMOUR BENIGN	1 (<1)	-	-
Total Number of AEs	3	2	3
GENERAL DISORDERS			
Total Pts With at Least one AE	1 (<1)	4 (1)	2 (<1)
PYREXIA	1 (<1)	2 (<1)	-
CHEST PAIN NOS	-	-	1 (<1)
FATIGUE	-	1 (<1)	-
HAEMORRHAGE NOS	-	-	1 (<1)
PAIN NOS	-	1 (<1)	-
Total Number of AEs	1	4	2
CARDIAC DISORDERS			
Total Pts With at Least one AE	3 (1)	3 (1)	-
ATRIAL FIBRILLATION	1 (<1)	1 (<1)	-
PERICARDITIS NOS	2 (1)	-	-
ARRHYTHMIA NOS	-	1 (<1)	-
MYOCARDIAL ISCHAEMIA	-	1 (<1)	-
Total Number of AEs	3	3	-
INJURY & POISONING			
Total Pts With at Least one AE	2 (1)	4 (1)	-
CARTILAGE INJURY	1 (<1)	-	-
DROWNING	1 (<1)	-	-
HEAD INJURY	-	1 (<1)	-
INJURY NOS	-	1 (<1)	-
RETINAL DETACHMENT	-	1 (<1)	-
ROAD TRAFFIC ACCIDENT	-	1 (<1)	-
Total Number of AEs	2	4	-

(Continued)

Table 13 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study NV15801 in Patients with Hepatitis C (Cont.)

Body System/ Adverse Event	PEG-IFN alfa-2a 180 ug N = 223 No. (%)	PEG-IFN alfa-2a 180 ug Ribavirin 1000-1200 mg N = 451 No. (%)	IFN alfa-2b 3 MIU Ribavirin 1000-1200 mg N = 443 No. (%)
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS			
Total Pts With at Least one AE	-	3 (1)	2 (<1)
DYSPNOEA	-	1 (<1)	1 (<1)
ASTHMA	-	1 (<1)	-
HAEMOPTYSIS	-	-	1 (<1)
PNEUMOTHORAX NOS	-	1 (<1)	-
Total Number of AEs	-	3	2
MUSCULOSKELETAL, CONNECTIVE TISSUE & BONE DISORDERS			
Total Pts With at Least one AE	1 (<1)	2 (<1)	1 (<1)
ARTHRALGIA	1 (<1)	1 (<1)	-
INTERVERTEBRAL DISC LESION NOS	-	1 (<1)	-
MYALGIA	1 (<1)	-	-
POLYARTHRITIS	-	-	1 (<1)
Total Number of AEs	2	2	1
DISORDERS OF BLOOD & THE LYMPHATIC SYSTEM			
Total Pts With at Least one AE	1 (<1)	3 (1)	-
ANAEMIA NOS	-	2 (<1)	-
PANCYTOPENIA	-	1 (<1)	-
THROMBOCYTOPENIA	1 (<1)	-	-
Total Number of AEs	1	3	-
DISORDERS OF METABOLISM & NUTRITION			
Total Pts With at Least one AE	1 (<1)	-	3 (1)
DEHYDRATION	-	-	2 (<1)
DIABETES MELLITUS AGGRAVATED	1 (<1)	-	-
DIABETIC KETOACIDOSIS	-	-	1 (<1)
Total Number of AEs	1	-	3
HEPATO-BILIARY DISORDERS			
Total Pts With at Least one AE	1 (<1)	1 (<1)	2 (<1)
CHOLELITHIASIS	-	-	1 (<1)
HEPATIC DISORDER NOS	-	1 (<1)	-
HEPATOPULMONARY SYNDROME	-	-	1 (<1)
TRANSAMINASE NOS INCREASED	1 (<1)	-	-
Total Number of AEs	1	1	2
SKIN & SUBCUTANEOUS TISSUE DISORDERS			
Total Pts With at Least one AE	2 (1)	1 (<1)	1 (<1)
HAEMANGIOMA NOS	1 (<1)	-	-
LICHEN PLANUS	1 (<1)	-	-
PSORIASIS	-	1 (<1)	-
SEBACEOUS CYST	-	-	1 (<1)
Total Number of AEs	2	1	1
DISORDERS OF THE EAR & LABYRINTH			
Total Pts With at Least one AE	-	3 (1)	-
DEAFNESS NOS	-	1 (<1)	-
TINNITUS	-	1 (<1)	-
VERTIGINOUS DISORDER	-	1 (<1)	-
VERTIGO NOS	-	1 (<1)	-
Total Number of AEs	-	4	-

(Continued)

Table 13 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study NV15801 in Patients with Hepatitis C (Cont.)

Body System/ Adverse Event	PEG-IFN alfa-2a 180 ug N = 223 No. (%)	PEG-IFN alfa-2a 180 ug Ribavirin 1000-1200 mg N = 451 No. (%)	IFN alfa-2b 3 MIU Ribavirin 1000-1200 mg N = 443 No. (%)
ENDOCRINE DISORDERS			
Total Pts With at Least one AE	1 (<1)	2 (<1)	-
HYPOTHYROIDISM	1 (<1)	1 (<1)	-
HASHIMOTO'S DISEASE	-	1 (<1)	-
Total Number of AEs	1	2	-
VASCULAR DISORDERS			
Total Pts With at Least one AE	-	-	2 (<1)
HYPERTENSIVE HEART DISEASE NOS	-	-	1 (<1)
PULMONARY EMBOLISM	-	-	1 (<1)
VENOUS THROMBOSIS DEEP (LIMBS)	-	-	1 (<1)
Total Number of AEs	-	-	3
DISORDERS OF THE EYE			
Total Pts With at Least one AE	-	1 (<1)	1 (<1)
DIPLOPIA	-	-	1 (<1)
RETINAL HAEMORRHAGE	-	1 (<1)	-
Total Number of AEs	-	1	1
DISORDERS OF THE IMMUNE SYSTEM			
Total Pts With at Least one AE	1 (<1)	-	-
ANAPHYLACTIC SHOCK	1 (<1)	-	-
Total Number of AEs	1	-	-
DISORDERS OF THE REPRODUCTIVE SYSTEM AND BREAST			
Total Pts With at Least one AE	1 (<1)	-	-
UTERINE HAEMORRHAGE	1 (<1)	-	-
Total Number of AEs	1	-	-
SURGICAL & MEDICAL PROCEDURES			
Total Pts With at Least one AE	-	1 (<1)	-
CARDIAC PACEMAKER MALFUNCTION	-	1 (<1)	-
Total Number of AEs	-	1	-

Premature withdrawals for adverse events and laboratory abnormalities were slightly higher with PEG-IFN α-2a combination therapy (10%) and IFN α-2b combination therapy (10%) compared with PEG-IFN α-2a monotherapy (7%). The most common types of events leading to discontinuation were psychiatric disorders, mainly depression-related events, (PEG-IFN α-2a monotherapy, 1%; PEG-IFN α-2a plus ribavirin, 3%; IFN α-2b, 4%). More patients in the PEG-IFN α-2a plus ribavirin group withdrew for hematological abnormalities (2%) than in the PEG-IFN α-2a monotherapy group (1%), with thrombocytopenia and neutropenia being the most frequent abnormalities leading to withdrawal. Most adverse events and laboratory abnormalities were successfully managed with dose reduction and therefore did not require withdrawal of the patient. Modification of the PEG-IFN α-2a dose for adverse events or laboratory abnormalities occurred at a similar incidence with PEG-IFN α-2a combination therapy and PEG-IFN α-2a monotherapy (27% and 32%, respectively).

Similar frequency of anemia but higher frequencies of neutropenia and thrombocytopenia were observed with PEG-IFN α-2a and ribavirin combination therapy than with IFN α-2b and ribavirin therapy. Patients receiving PEG-IFN α-2a monotherapy had the lowest frequency of hemoglobin concentrations <10 g/dL (4%) compared with 11% of patients in each of the combination therapy groups. Higher frequencies of neutropenia and

thrombocytopenia were observed with PEG-IFN α-2a as monotherapy or as combination therapy than with IFN α-2b combination therapy. Neutrophil counts decreased to 0.5 to <0.75 x 10^9/L in 15% of patients receiving PEG-IFN α-2a monotherapy and 22% of patients receiving PEG-IFN α-2a combination therapy compared with 7% of patients receiving IFN α-2b and ribavirin. Neutrophil counts decreased to <0.5 x 10^9/L in a higher percentage of patients receiving PEG-IFN α-2a either as monotherapy or in combination with ribavirin (4% and 5%, respectively) than in patients receiving IFN α-2b and ribavirin (1%). Most patients with neutrophil counts <0.5 x 10^9/L required at least a temporary reduction in the dose of PEG-IFN α-2a or IFN α-2b, but <1% of patients in the two combination groups were withdrawn from treatment because of neutrophil counts <0.5 x 10^9/L. Platelet counts did not fall below 20 x 10^9/L in any patient during the study. Platelet counts decreased to between 20 and <50 x 10^9/L in a higher percentage of patients receiving PEG-IFN α-2a either as monotherapy or in combination with ribavirin (6% and 5%, respectively) than in patients receiving IFN α-2b in combination with ribavirin (<1%).

6.3.3 Effect of Duration of Treatment and Daily Dose of Ribavirin in Combination with PEG-IFN α-2a: Study NV15942

6.3.3.1 Study Overview

Study NV15942 is a completed phase III, randomized, multicenter study designed to assess the effects of either a shorter duration of treatment (ie, 24 weeks vs 48 weeks) or a lower daily dose of ribavirin (ie, 800 mg fixed dose vs 1000 or 1200 mg by body weight category), or both, on safety and efficacy. Patients were stratified in this study according to HCV genotype and viral load to assess if patients who have previously been shown to be more responsive to treatment, ie, patients with genotype non-1 infection or low baseline viral load, can be treated successfully for a shorter period of time and with a lower ribavirin dose than patients who have previously been shown to be less likely to respond, (ie, patients infected with genotype 1 or high baseline viral load).

A total of 1311 patients from 99 sites were enrolled in this trial; 1284 patients were evaluable for safety. Patients were stratified by genotype and viral load within each geographical region and randomized following a preplanned unbalanced stratification plan to one of four treatment arms:

Group A: 80 µg of PEG-IFN α-2a administered sc once weekly plus 800 mg of ribavirin given orally daily in split doses for 24 weeks (Safety population: N= 207)

Group B: 180 µg of PEG-IFN α-2a administered sc once weekly plus 1000 mg (for patients weighing <75 kg) or 1200 mg (for patients weighing ≥ 75 kg) of ribavirin given orally daily in split doses for 24 weeks (Safety population: N= 280)

Group C: 180 µg of PEG-IFN α-2a administered sc once weekly plus 800 mg of ribavirin given orally daily in split doses for 48 weeks (Safety population: N= 361)

Group D: 180 µg of PEG-IFN α-2a administered sc once weekly plus 1000 mg (for patients weighing <75 kg) or 1200 mg (for patients weighing ≥ 75 kg) of ribavirin given orally daily in split doses for 48 weeks (Safety population: N= 436)

The proportion of patients with cirrhosis or bridging fibrosis ranged between 21% and 26%. Because of the randomization scheme of the study, which planned to allocate more patients with genotype 1 infection and high viral load to the 48 week treatment groups than to the 24 week treatment groups, pretreatment viral load and the proportion of patients with genotype 1 infection were higher in the 48 week treatment groups than in the 24 week treatment groups.

6.3.3.2 Safety Summary

Treatment-limiting events occurred with the lowest frequency in patients receiving 24 weeks of treatment and the 800 mg dose of ribavirin. These treatment-limiting events included serious adverse events and premature withdrawal for adverse events (Table 14). In addition, the group receiving 800 mg of ribavirin for 24 weeks had the lowest percentage of patients who experienced a decrease in hemoglobin levels to <10 g/dL or who required modification of the ribavirin dose. Hemoglobin levels did not fall to <8.5 g/dL in any patient in this group. Thus, the shorter treatment duration and lower dose of ribavirin offer a safety advantage over 48 weeks of treatment with PEG-IFN α-2a and the higher dose (1000 or 1200 mg) of ribavirin.

In study NV15942, the safety profile in the PEG-IFN α-2a and ribavirin treatment arm common to study NV15801 (48 weeks of treatment with PEG-IFN α-2a and 1000 or 1200 mg of ribavirin) was consistent with that seen in study NV15801.

Table 14 Overall Safety Profile of PEG-IFN α-2a and Ribavirin Combination Therapy in Study NV15942 in Patients with Hepatitis C

	24 Weeks of Treatment		48 Weeks of Treatment	
	PEG-IFN α-2a + Ribavirin 800 mg (N = 207)	PEG-IFN α-2a + Ribavirin 1000 or 1200 mg (N = 280)	PEG-IFN α-2a + Ribavirin 800 mg (N = 361)	PEG-IFN α-2a + Ribavirin 1000 or 1200 mg (N = 436)
Any AE	200 (97%)	275 (98%)	355 (98%)	427 (98%)
Severe AEs	46 (22%)	63 (23%)	116 (32%)	141 (32%)
Treatment-related AEs	198 (96%)	272 (97%)	355 (98%)	425 (97%)
Serious AEs	7 (3%)	19 (7%)	33 (9%)	44 (10%)
Treatment-related serious AEs[a]	3 (1%)	8 (3%)	15 (4%)	14 (3%)
Deaths	0	1	1	2
Premature withdrawal for AEs and laboratory abnormalities	10 (5%)	13 (5%)	59 (16%)	67 (15%)
AEs	8 (4%)	10 (3%)	52 (14%)	55 (12%)
Laboratory abnormalities	2 (1%)	3 (1%)	7 (2%)	12 (3%)
Dose modification for AEs and laboratory abnormalities				
PEG-IFN α-2a	63 (30%)	73 (26%)	120 (33%)	159 (36%)
AEs	15 (7%)	25 (9%)	41 (11%)	60 (14%)
Neutropenia	42 (20%)	46 (16%)	79 (22%)	106 (24%)
Thrombocytopenia	9 (4%)	10 (4%)	14 (4%)	20 (5%)
Ribavirin	39 (19%)	76 (27%)	101 (28%)	166 (38%)
AEs	24 (12%)	50 (18%)	70 (19%)	98 (22%)
Anemia	16 (8%)	31 (11%)	33 (9%)	85 (19%)
Lowest hemoglobin level				
8.5 - <10 g/dL	7 (3%)	24 (9%)	22 (6%)	61 (14%)
<8.5 g/dL	0	4 (1%)	1 (0.3%)	6 (1%)

[a]Events judged by investigator to be remotely, possibly, or probably related to treatment.

Adverse Events

The most common clinical adverse events in all four treatment groups were those usually associated with interferon treatment and included headache (49% to 55%), fatigue (47% to 50%), myalgia (37% to 44%), and pyrexia (39% to 43%). The incidence of individual adverse events as well as the incidence of adverse events by body system was similar in the four treatment groups. Depression occurred with a similar frequency in all four treatment groups and was not more frequent in the groups receiving 48 weeks of treatment (22% and 24%) than in the groups receiving 24 weeks of treatment (22% and 15%).

Deaths

Four patients died in this study; three of the four deaths occurred during treatment, and two of these three deaths were considered by investigators to be related to study medication (septic shock and suicide) (Table 15). The other two deaths (overdose of opiates and overdose from amphetamines, opiates, atropines, and alcohol) were assessed by investigators as unrelated to study medication.

Table 15 Patient Deaths in Study NV15942 in Patients with Hepatitis C

Treatment Group & CRTN/Pt No.	Age y	Sex	Weight kg	Race	Cause of Death	Last Trt Day	Day of Death	Relation to Trial Treatment
PEG-IFN α-2A + ribavirin 1000 or 1200 mg, 24 Weeks								
25769/2335	32	M	101	CAUCASIAN	OVERDOSE NOS	32	33	UNRELATED
PEG-IFN α-2A + ribavirin 800 mg, 48 Weeks								
25965/0641	45	M	62	CAUCASIAN	SEPTICAEMIA NOS	63	65	POSSIBLE
PEG-IFN α-2A + ribavirin 1000 or 1200 mg, 48 Weeks								
25721/3046	38	F	77	CAUCASIAN	SUICIDE (ACCOMPLISHED)	177	182	PROBABLE
25742/0001	40	M	99	CAUCASIAN	DRUG TOXICITY NOS	172	317	UNRELATED

Note: CRTN = clinical research task number (unique number identifying protocol, center, and investigator).

Serious Adverse Events

The lowest incidence of serious clinical adverse events occurred in patients treated for 24 weeks with the lower dose (800 mg) of ribavirin (Table 16). The most common serious adverse events were infections (<1% to 2%) and psychiatric disorders (<1% to 2%). The incidence of serious infections was higher in patients treated for 48 weeks (1% to 2%) than in patients treated for 24 weeks (<1% to 1%) and was also higher in patients receiving 1000 or 1200 mg of ribavirin (1% to 2%) than in patients receiving 800 mg of ribavirin (<1% to 1%). Serious psychiatric disorders occurred with similar frequencies in the 48 week (<1%) and the 24 week treatment groups (<1% to 2%).

Although no single site or organism predominated, infections were the most common serious adverse events (16 events in 15 patients). The incidence of serious infections was lowest in the group of patients treated for 24 weeks with 800 mg of ribavirin (1 patient). Four additional serious adverse events (patient 25730/3608, postoperative wound infection; patient 25721/3055, leg ulcer; patient 25748/2005, peritonitis; and patient 25224/2245, endocarditis) were not grouped under the body system “Infections and Infestations” but are considered to be infections, as they were either confirmed by a culture or treated with antibiotics. All of these events occurred in the 48 week treatment groups (three in the group receiving 1000 or 1200 mg of ribavirin and one in the group receiving 800 mg of ribavirin).

Serious psychiatric disorders occurred with similar frequencies in the 48 week and the 24 week treatment groups (<1% to 2%). Depression was the most common serious psychiatric disorder with <1% of patients in each of the groups treated for 48 weeks and in the groups who received 1000 or 1200 mg of ribavirin for 24 weeks.

All of the 13 patients who experienced a serious cardiovascular event were in the groups of patients treated for 48 weeks. The incidence of serious cardiovascular events was the same in the group of patients receiving 1000 or 1200 mg of ribavirin (7 patients [1.7%]) and the group receiving 800 mg of ribavirin (6 patients [1.6%]). With the exception of one event, none of the serious cardiovascular events were preceded by a hemoglobin concentration below 10 g/dL, suggesting that ribavirin induced anemia was not the primary precipitating factor.

Only four patients experienced serious bleeding events, none of which seemed clearly associated with thrombocytopenia.

The majority of serious adverse events in each treatment group were assessed as unrelated to study medication. The incidence of serious adverse events assessed as related to study medication by the investigator was lowest in the group of patients treated for 24 weeks with 800 mg of ribavirin (1%) (Table 14). Serious adverse events that were considered related to study medication were mostly psychiatric disorders and infections.

Table 16 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study NV15942 in Patients with Hepatitis C

Body System/ Adverse Event	24 Weeks PEG-IFN alfa-2a 180 ug Ribavirin 800 mg N = 207 No. (%)	24 Weeks PEG-IFN alfa-2a 180 ug Ribavirin 1000 or 1200 mg N = 280 No. (%)	48 Weeks PEG-IFN alfa-2a 180 ug Ribavirin 800 mg N = 361 No. (%)	48 Weeks PEG-IFN alfa-2a 180 ug Ribavirin 1000 or 1200 mg N = 436 No. (%)
ALL BODY SYSTEMS				
Total Pts with at Least one AE	7 (3)	19 (7)	33 (9)	44 (10)
Total Number of AEs	8	20	35	52
INFECTIONS & INFESTATIONS				
Total Pts With at Least one AE	1 (<1)	3 (1)	4 (1)	7 (2)
PYELONEPHRITIS NOS	-	1 (<1)	-	2 (<1)
CYSTITIS NOS	1 (<1)	-	-	-
GASTROINTESTINAL INFECTION NOS	-	-	-	1 (<1)
INFECTED SKIN ULCER	-	-	1 (<1)	-
LOWER RESPIRATORY TRACT INFECTION NOS	-	1 (<1)	-	-
OSTEOMYELITIS NOS	-	-	-	1 (<1)
PERIANAL ABSCESS	-	-	-	1 (<1)
PERITONSILLAR ABSCESS NOS	-	-	-	1 (<1)
PNEUMONIA NOS	-	-	1 (<1)	-
PNEUMONIA STREPTOCOCCAL	-	-	1 (<1)	-
PYELONEPHRITIS ACUTE NOS	-	-	-	1 (<1)
SEPTICAEMIA NOS	-	-	1 (<1)	-
UPPER RESPIRATORY TRACT INFECTION NOS	-	1 (<1)	-	-
URINARY TRACT INFECTION NOS	-	-	-	1 (<1)
Total Number of AEs	1	3	4	8
PSYCHIATRIC DISORDERS				
Total Pts With at Least one AE	1 (<1)	5 (2)	3 (<1)	4 (<1)
DEPRESSION NOS	-	2 (<1)	1 (<1)	1 (<1)
ALCOHOLISM	-	-	1 (<1)	-
ANXIETY	-	-	1 (<1)	-
DRUG ABUSE	-	1 (<1)	-	-
HYPOMANIA	-	-	1 (<1)	-
PARANOIA	-	1 (<1)	-	-
PARANOID PSYCHOSIS	-	-	-	1 (<1)
PERSONALITY DISORDER NOS	-	-	-	1 (<1)
PSYCHIATRIC DISORDER NOS	-	1 (<1)	-	-
PSYCHOSIS NOS	1 (<1)	-	-	-
SUICIDE (ACCOMPLISHED)	-	-	-	1 (<1)
Total Number of AEs	1	5	4	4
INJURY & POISONING				
Total Pts With at Least one AE	-	2 (<1)	2 (<1)	7 (2)
BURNS NOS	-	-	1 (<1)	1 (<1)
OVERDOSE NOS	-	1 (<1)	-	1 (<1)
BRAIN DAMAGE (TRAUMATIC)	-	-	-	1 (<1)
FOOT FRACTURE	-	-	-	1 (<1)
HEAD INJURY	-	-	-	1 (<1)
HIP FRACTURE	-	-	-	1 (<1)
INJURY NOS	-	-	-	1 (<1)
NON-ACCIDENTAL INJURY	-	1 (<1)	-	-
RETINAL DETACHMENT	-	-	-	1 (<1)
RIB FRACTURE	-	-	1 (<1)	-
Total Number of AEs	-	2	2	8
GENERAL DISORDERS				
Total Pts With at Least one AE	1 (<1)	-	4 (1)	4 (<1)
CHEST PAIN NOS	-	-	1 (<1)	2 (<1)
PYREXIA	1 (<1)	-	-	1 (<1)
ASTHENIA	-	-	1 (<1)	-
CHEST PAIN (NON-CARDIAC)	-	-	1 (<1)	-
DRUG TOXICITY NOS	-	-	-	1 (<1)
MUCOUS MEMBRANE DISORDER NOS	-	-	1 (<1)	-
PAIN IN LIMB	-	-	-	1 (<1)
Total Number of AEs	1	-	4	5
NEUROLOGICAL DISORDERS				
Total Pts With at Least one AE	-	1 (<1)	5 (1)	3 (<1)
SYNCOPE	-	-	2 (<1)	1 (<1)
HEADACHE NOS	-	1 (<1)	-	1 (<1)
BENIGN INTRACRANIAL HYPERTENSION	-	-	1 (<1)	-
ENTRAPMENT NEUROPATHY	-	-	1 (<1)	-
HEPATIC ENCEPHALOPATHY	-	-	1 (<1)	-
POLYRADICULOPATHY	-	-	-	1 (<1)
Total Number of AEs	-	1	5	3

.

(continued)

Table 16 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study NV15942 in Patients with Hepatitis C (Cont.)

Body System/ Adverse Event	24 Weeks PEG-IFN alfa-2a 180 ug Ribavirin 800 mg N = 207 No. (%)	24 Weeks PEG-IFN alfa-2a 180 ug Ribavirin 1000 or 1200 mg N = 280 No. (%)	48 Weeks PEG-IFN alfa-2a 180 ug Ribavirin 800 mg N = 361 No. (%)	48 Weeks PEG-IFN alfa-2a 180 ug Ribavirin 1000 or 1200 mg N = 436 No. (%)
GASTROINTESTINAL DISORDERS				
Total Pts With at Least one AE	1 (<1)	-	2 (<1)	5 (1)
ABDOMINAL PAIN NOS	1 (<1)	-	1 (<1)	-
COLONIC PERFORATION	-	-	-	1 (<1)
ILEUS	-	-	1 (<1)	-
INGUINAL HERNIA	-	-	-	1 (<1)
PERITONITIS	-	-	-	1 (<1)
RECTAL BLEEDING	-	-	-	1 (<1)
UMBILICAL HERNIA	-	-	-	1 (<1)
Total Number of AEs	1	-	2	5
MUSCULOSKELETAL, CONNECTIVE TISSUE & BONE DISORDERS				
Total Pts With at Least one AE	1 (<1)	1 (<1)	2 (<1)	4 (<1)
ARTHRALGIA	-	1 (<1)	-	-
ARTHRALGIA AGGRAVATED	1 (<1)	-	-	-
CERVICAL DISC LESION	-	-	-	1 (<1)
INTERVERTEBRAL DISC LESION NOS	-	-	-	1 (<1)
JOINT SPRAIN	-	-	1 (<1)	-
RHEUMATOID ARTHRITIS	-	-	1 (<1)	-
ROTATOR CUFF SYNDROME	-	-	-	1 (<1)
SYSTEMIC LUPUS ERYTHEMATOSUS	-	-	-	1 (<1)
Total Number of AEs	1	1	2	4
BENIGN & MALIGNANT NEOPLASMS (INCLUDING CYSTS AND POLYPS)				
Total Pts With at Least one AE	-	2 (<1)	1 (<1)	2 (<1)
CARCINOID TUMOUR	-	-	-	1 (<1)
CARCINOMA NOS	-	1 (<1)	-	-
MALIGNANT BREAST NEOPLASM	-	-	1 (<1)	-
OVARIAN CANCER	-	1 (<1)	-	-
UTERINE FIBROIDS	-	-	-	1 (<1)
Total Number of AEs	-	2	1	2
DISORDERS OF THE IMMUNE SYSTEM				
Total Pts With at Least one AE	1 (<1)	1 (<1)	2 (<1)	1 (<1)
SARCOIDOSIS NOS	1 (<1)	1 (<1)	2 (<1)	1 (<1)
Total Number of AEs	1	1	2	1
VASCULAR DISORDERS				
Total Pts With at Least one AE	-	-	1 (<1)	3 (<1)
ACUTE CIRCULATORY FAILURE	-	-	-	1 (<1)
SUBARACHNOID HAEMORRHAGE	-	-	-	1 (<1)
TRANSIENT ISCHAEMIC ATTACK	-	-	-	1 (<1)
VENOUS THROMBOSIS DEEP (LIMBS)	-	-	1 (<1)	-
Total Number of AEs	-	-	1	3
CARDIAC DISORDERS				
Total Pts With at Least one AE	-	-	1 (<1)	2 (<1)
ANGINA PECTORIS	-	-	-	1 (<1)
ATRIAL FIBRILLATION	-	-	-	1 (<1)
ENDOCARDITIS NOS	-	-	1 (<1)	-
Total Number of AEs	-	-	1	2
DISORDERS OF BLOOD & THE LYMPHATIC SYSTEM				
Total Pts With at Least one AE	-	-	1 (<1)	2 (<1)
APLASTIC ANAEMIA	-	-	-	1 (<1)
HAEMOLYTIC ANAEMIA NOS	-	-	-	1 (<1)
NEUTROPENIA	-	-	1 (<1)	-
Total Number of AEs	-	-	1	2
DISORDERS OF METABOLISM & NUTRITION				
Total Pts With at Least one AE	1 (<1)	-	2 (<1)	-
DEHYDRATION	-	-	1 (<1)	-
DIABETES MELLITUS NOS	1 (<1)	-	-	-
WEIGHT DECREASE	-	-	1 (<1)	-
Total Number of AEs	1	-	2	-

.

(continued)

Table 16 Incidence of Serious Adverse Events during Treatment and 24 Weeks Posttreatment in Study NV15942 in Patients with Hepatitis C (Cont.)

Body System/ Adverse Event	24 Weeks PEG-IFN alfa-2a 180 ug Ribavirin 800 mg N = 207 No. (%)	24 Weeks PEG-IFN alfa-2a 180 ug Ribavirin 1000 or 1200 mg N = 280 No. (%)	48 Weeks PEG-IFN alfa-2a 180 ug Ribavirin 800 mg N = 361 No. (%)	48 Weeks PEG-IFN alfa-2a 180 ug Ribavirin 1000 or 1200 mg N = 436 No. (%)
HEPATO-BILIARY DISORDERS				
Total Pts With at Least one AE	-	2 (<1)	1 (<1)	-
BILIARY COLIC	-	2 (<1)	-	-
HEPATITIS NOS	-	-	1 (<1)	-
Total Number of AEs	-	2	1	-
SKIN & SUBCUTANEOUS TISSUE DISORDERS				
Total Pts With at Least one AE	-	2 (<1)	-	1 (<1)
ECZEMA NOS	-	1 (<1)	-	-
LEG ULCER (EXC VARICOSE)	-	-	-	1 (<1)
PRURITUS	-	1 (<1)	-	-
Total Number of AEs	-	2	-	1
RENAL & URINARY DISORDERS				
Total Pts With at Least one AE	1 (<1)	-	-	1 (<1)
LOIN PAIN	-	-	-	1 (<1)
RENAL IMPAIRMENT NOS	1 (<1)	-	-	-
Total Number of AEs	1	-	-	1
SURGICAL & MEDICAL PROCEDURES				
Total Pts With at Least one AE	-	1 (<1)	-	1 (<1)
POST-OPERATIVE HAEMORRHAGE	-	1 (<1)	-	-
POST-OPERATIVE WOUND INFECTION	-	-	-	1 (<1)
Total Number of AEs	-	1	-	1
CONGENITAL AND FAMILIAL/GENETIC DISORDERS				
Total Pts With at Least one AE	-	-	-	1 (<1)
CEREBRAL PALSY	-	-	-	1 (<1)
Total Number of AEs	-	-	-	1
DISORDERS OF THE EAR & LABYRINTH				
Total Pts With at Least one AE	-	-	1 (<1)	-
VERTIGO POSITIONAL	-	-	1 (<1)	-
Total Number of AEs	-	-	1	-
DISORDERS OF THE EYE				
Total Pts With at Least one AE	-	-	1 (<1)	-
OPTIC NERVE OEDEMA	-	-	1 (<1)	-
Total Number of AEs	-	-	1	-
DISORDERS OF THE REPRODUCTIVE SYSTEM AND BREAST				
Total Pts With at Least one AE	-	-	-	1 (<1)
OVARIAN CYST RUPTURED	-	-	-	1 (<1)
Total Number of AEs	-	-	-	1
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS				
Total Pts With at Least one AE	-	-	1 (<1)	-
DYSPNOEA	-	-	1 (<1)	-
Total Number of AEs	-	-	1	-

Premature Withdrawals from Treatment due to Adverse Events or Laboratory Abnormalities

The percentage of patients discontinuing treatment for a clinical adverse event or laboratory abnormality in the two groups being treated for 24 weeks was approximately one third that in the two groups being treated for 48 weeks (5% and 16%, respectively). The shorter 24-week treatment duration was better tolerated than the longer 48-week treatment duration, while ribavirin dose did not appear to have an effect on the frequency of discontinuation of treatment for safety reasons.

Psychiatric disorders were the most common reason for discontinuing treatment, the most frequent of these being depression (2% each in patients treated for 24 or 48 weeks). In contrast, general disorders (mainly fatigue and asthenia) and hematological disorders

(neutropenia and anemia) more frequently led to discontinuation of treatment in patients treated for 48 weeks (2%) than in patients treated for 24 weeks (<1%).

Dose Modifications due to Adverse Events or Laboratory Abnormalities

The majority of clinical adverse events and laboratory abnormalities were successfully managed with modification of the PEG-IFN α-2a or ribavirin dose and did not require discontinuation of treatment. Although modification of the PEG-IFN α-2a dose was only slightly less frequent in patients being treated for 24 weeks than in patients being treated for 48 weeks, the percentage of patients requiring modification of the ribavirin dose was considerably lower in patients treated for 24 weeks with 800 mg of ribavirin (19%) than in patients treated for 48 weeks with 1000 or 1200 mg of ribavirin (38%) (Table 14). Anemia was the most frequent laboratory abnormality necessitating modification of the ribavirin dose. The proportion of patients requiring modification of the ribavirin dose for anemia was lowest in the group being treated for 24 weeks with the lower ribavirin dose (8%) and highest in the group being treated for 48 weeks with the higher dose of ribavirin (19%).

Neutropenia and Thrombocytopenia

The effects of PEG-IFN α-2a and ribavirin combination therapy on neutrophil and platelet counts in study NV15942 were similar to the effects seen in study NV15801. Treatment duration and ribavirin dose had little or no effect on the proportion of patients who experienced either a decrease in neutrophil counts to $<0.5 \times 10^9$/L (3% to 5% of patients) or a decrease in platelet counts to between 20 and $<50 \times 10^9$/L (3% to 5% of patients). Platelet counts did not fall below 20×10^9/L in any patient during the study.

Anemia

A decrease in hemoglobin concentration to <10 g/dL appeared to be dependent on the ribavirin dose and to a lesser extent on the duration of treatment. Patients treated for 24 weeks with 800 mg of ribavirin had the lowest incidence of hemoglobin concentration decreasing to <10 g/dL, while patients treated for 48 weeks with 1000 or 1200 mg of ribavirin had the highest incidence (Table 14). No patient in the group treated for 24 weeks with 800 mg of ribavirin experienced a decrease in hemoglobin concentration to <8.5 g/dL.

Most patients whose hemoglobin concentration decreased to <10 g/dL were managed by modification of the ribavirin dose rather than premature withdrawal from treatment (discontinuation of both study drugs) or discontinuation of ribavirin only. Very few patients were prematurely withdrawn from treatment for anemia (3 patients). The majority of the dose modifications of ribavirin were permanent dose reductions. Modification of the PEG-IFN α-2a dose for anemia was very infrequent (3 patients).

6.3.4 Safety Data from Other Trials

6.3.4.1 Safety of PEG-IFN α-2a and Ribavirin in HCV and HIV Coinfected Patients: Study NR15961

Study Overview

The study is an ongoing phase III, randomized, partially blinded, active-controlled (for PEG-IFN α-2a), placebo-controlled (for ribavirin), three-arm multicenter trial evaluating the efficacy and safety of PEG-IFN α-2a monotherapy, PEG-IFN α-2a plus ribavirin combination therapy, and IFN α-2a plus ribavirin combination therapy in patients with HCV and HIV coinfection. Assignment to PEG-IFN α-2a or IFN α-2a is open-label, while assignment to ribavirin or placebo in combination with PEG-IFN α-2a is double-blinded. PEG-IFN α-2a is given once weekly as a 180-µg dose, IFN α-2a is given three times a week as a 3-MIU dose, and 800 mg of ribavirin or placebo is given daily in split doses. The treatment duration is 48 weeks, followed by a 24-week treatment free follow-up period. In order to maintain the blind in this ongoing study, data from the two PEG-IFN α-2a treatment groups have been pooled. As of December 13, 2002, a total of 868 patients had been enrolled in the study, 579 in the pooled PEG-IFN α-2a monotherapy and combination therapy (ribavirin) arm and 289 in the IFN α-2a plus ribavirin arm. Preliminary safety data are provided for these patients.

Safety Summary

The most common adverse events in all treatment groups (> 20% in any arm) were fatigue, pyrexia, headache, nausea, diarrhea, myalgia, insomnia, and depression. The incidence of infections was similar in the pooled PEG-IFN α-2a treatment arm (51%) and the IFN α-2a combination treatment arm (44%). The incidence of depression was the same (22%) in both treatment arms. A total of 144 patients have experienced serious adverse events, 18% in the pooled PEG-IFN α-2a treatment arm and 15% in the IFN α-2a combination treatment arm. The body systems with the highest percentage of patients having serious adverse events were infections (4% in the pooled PEG-IFN α-2a treatment arm and 5% in the IFN α-2a combination treatment arm) and gastrointestinal disorders (4% and 3%). Serious disorders of the blood and lymphatic system occurred more commonly in the pooled PEG-IFN α-2a treatment arm (3%) than in the IFN α-2a combination treatment arm (<1%).

A total of twelve patients have died, nine in the pooled PEG-IFN α-2a treatment arm and three in the IFN α-2a combination treatment arm. Three deaths were considered possibly related to treatment, two (suicide and gastrointestinal hemorrhage) in the pooled PEG-IFN α-2a treatment group and one due to HIV infection that occurred in the IFN α-2a combination treatment arm.

A similar percentage of patients in each treatment arm discontinued therapy prematurely for adverse events or laboratory abnormalities (14% in the pooled PEG-IFN α-2a treatment arm and 13% in the IFN α-2a combination treatment arm). The most common events leading to premature treatment discontinuation were depression and fatigue (both arms) and thrombocytopenia (pooled PEG-IFN α-2a treatment arm).

Hepatic Decompensation

Cirrhotic CHC patients coinfected with HIV may be at a possible risk of hepatic decompensation when treated concomitantly with HCV therapy and HIV antiretroviral therapy. Fourteen HCV/HIV coinfected patients participating in study NR15961 developed symptoms of hepatic decompensation, and five of these patients died. An analysis of the cases and a review of more than 4000 HCV-infected patients treated with PEG-IFN α-2a or IFN α-2a as part of the PEG-IFN α-2a monotherapy and combination therapy programs suggested that a constellation of circumstances seemed to predispose patients to the development of hepatic decompensation during anti-HCV therapy, namely, HIV and HCV coinfection, cirrhosis, and the concomitant administration of HIV therapy. All 14 cases of hepatic decompensation were reviewed internally by Roche Drug Safety and externally by the NR15961 Safety Review Board (SRB). Both groups independently concluded the following:

- Decompensation does not seem to be related specifically to treatment with PEG-IFN α-2a (10 of 14 patients who decompensated were treated with PEG-IFN α-2a plus ribavirin or placebo and 4 of 14 patients were treated with IFN α-2a plus ribavirin, reflective of the study's 2:1 randomization scheme).
- Cirrhosis seems to be a risk factor for hepatic decompensation (14 of 14 patients who decompensated were cirrhotic; 11 of 14 patients had Child-Pugh score ≥ 6 at baseline and 6 of 14 patients were Child-Pugh grade B at baseline). The patients with Child-Pugh grade B at baseline violated the entry criteria for the study.
- Concomitant antiretroviral therapy seems to be associated with hepatic decompensation (13 of 14 patients who decompensated were receiving HIV therapy at the onset of decompensation [one patient, although previously treated with HIV therapy, was not receiving HIV therapy at the onset of decompensation]; 9 of 14 patients were on stavudine, 7 of 14 patients were on lamivudine, and 5 of 14 patients were on didanosine.
- The majority of patients who decompensated did so within the first 12 weeks of anti-HCV therapy (9 of 14 patients).

In a multivariate analysis of patient baseline characteristics, two four-variable models associated with hepatic decompensation including didanosine treatment, high total bilirubin, low hemoglobin, and either high alkaline phosphatase or low platelets showed a high level of association between predicted probabilities and observed responses (c=0.95). Age, sex, pretreatment body weight, HIV or HCV viral loads, CD4+ cell count, and histological inflammation score did not exhibit predictive value. The risk associated with didanosine suggests a possible interaction with HCV treatment. The majority of risk factors associated with hepatic decompensation are biological markers for advanced cirrhosis. Therefore, HIV/HCV patients with early-stage cirrhosis may not be at high risk of hepatic decompensation. However, any patient with liver cirrhosis and HIV/HCV coinfection should be monitored closely for the signs and symptoms of hepatic decompensation at every visit.

Hyperlactatemia

Eight cases of symptomatic hyperlactatemia have occurred in patients participating in study NR15961. These cases have been reviewed by both Roche Drug Safety and the SRB. Both groups independently concluded that:

- Symptomatic hyperlactatemia does not seem to be associated with hepatic decompensation or cirrhosis.
- Symptomatic hyperlactatemia seems to be associated with concomitant antiretroviral treatment, as has been reported in the literature (7 of 8 patients with symptomatic hyperlactatemia were taking stavudine, 5 of 8 patients were taking stavudine plus didanosine).
- The incidence of symptomatic hyperlactatemia observed thus far in this trial of 868 HCV/HIV coinfected patients treated with antiretroviral and anti-HCV therapy is consistent with that reported in the literature for HIV-infected patients treated with antiretroviral therapy alone.

6.3.4.2 Safety of PEG-IFN α-2a and Ribavirin in CHC Patients with Persistently Normal ALT Levels: Study NR16071

Study Overview

This study is an ongoing phase III, multicenter, multinational, open-label, randomized, parallel-group trial with an untreated control group. The primary objective of this study is to evaluate the efficacy and safety of PEG-IFN α-2a plus ribavirin combination therapy for 24 weeks or 48 weeks in CHC patients who had persistently normal ALT levels. Patients are enrolled into one of three treatment arms: (A) PEG-IFN α-2a plus ribavirin given for 24 weeks plus an untreated follow-up period of 48 weeks, (B) PEG-IFN α-2a plus ribavirin given for 48 weeks plus an untreated follow-up period of 24 weeks, and (C) untreated control group observed for 72 weeks. The PEG-IFN α-2a dose of 180 µg is being administered sc once weekly and 800 mg of ribavirin is being taken po daily in split doses (morning and evening). As of December 3, 2002, 514 patients had been randomized into this study and had data available on the database; 220 patients were receiving combination therapy for 24 weeks, 221 patients were receiving combination therapy for 48 weeks, and 73 were not receiving treatment (untreated control group). Preliminary safety data are provided for these patients.

Safety Summary

Over 90% of patients in each of the PEG-IFN α-2a plus ribavirin combination therapy groups (208 patients treated for 24 weeks and 206 patients treated for 48 weeks) have experienced adverse events compared with 53 patients (72%) in the untreated control group. In both PEG-IFN α-2a combination therapy groups, the most common adverse events ($\geq$ 20%) were fatigue, pyrexia, rigors, nausea, diarrhea, myalgia, arthralgia, insomnia, depression, irritability, headache, and alopecia. The overall adverse event profiles in both PEG-IFN α-2a combination therapy groups are similar to that observed in study NV15801 (section 6.3.2). In the untreated control group no adverse event was reported at an incidence greater than 20%.

One patient in the untreated control group has died during the study. This patient sustained a head injury, presumably from a fall, that resulted in her death. No other patients have died during the study.

In the PEG-IFN α-2a plus ribavirin combination therapy groups, 18 patients in the 24-week treatment group (8%) and 33 patients in the 48-week treatment group (15%) have experienced serious adverse events compared with 2 of the 74 patients (3%) in the untreated control group. Serious adverse events that occurred in more than one patient were suicide attempt (three patients), depression (two patients), and pneumonia (two patients); all occurred in patients treated for 48 weeks. In the 48-week treatment group, 12% of patients experienced treatment-related serious adverse events compared with 4% of patients in 24-week treatment group treatment group.

Forty patients (18%) receiving combination therapy in the 24-week treatment group and 53 patients (24%) in the 48-week treatment group withdrew prematurely from treatment because of adverse events or laboratory abnormalities. Adverse events leading to premature treatment discontinuation that occurred in more than one patient were nausea, vomiting, dyspepsia, diarrhea, fatigue, asthenia, anemia, dyspnea, viral gastroenteritis, depression, anxiety, rash, pruritus, myalgia, arthralgia, dizziness, headache, and migraine.

6.3.5 Efficacy Results for Study NV15801

The sustained virological response achieved with PEG-IFN α-2a plus ribavirin combination therapy (56%) was superior ($p = 0.001$) than that achieved with IFN α-2b plus ribavirin combination therapy (44%) or with PEG-IFN α-2a monotherapy (29%) [6.46]. Similar results were obtained for sustained biochemical response (Table 17).

PEG-IFN α-2a plus ribavirin combination therapy was also more efficacious than IFN α-2a plus ribavirin combination therapy or than PEG-IFN α-2a monotherapy in genotype 1 and in genotype 2 or 3 patients. The sustained virological responses achieved with PEG-IFN α-2a plus ribavirin combination therapy in genotype 1 and in genotype 2 or 3 patients were significantly higher than those achieved with IFN α-2b plus ribavirin combination therapy or with PEG-IFN α-2a monotherapy.

Table 17 Sustained Virological and Biochemical Responses at Week 72 in Study NV15801 in Patients with Hepatitis C

Response	PEG-IFN α-2a 180 µg Ribavirin 1000 or 1200 mg	IFN α-2b 3MIU Ribavirin 1000 or 1200 mg
Sustained Virological Response		
All Patients	29%	56%	44%
Genotype 1	21%	46%	36%
Genotype 2 or 3	45%	76%	61%
Sustained Biochemical Response	32%	51%	44%

6.3.6 Efficacy Results for Study NV15942

Patients Infected with Genotype 1:

The highest sustained virological response in patients infected with genotype 1 was achieved with the most intensive regimen, 48 weeks of treatment and 1000 or 1200 mg of ribavirin (52%) (Table 18) [6.47]. This was the case whether patients had a high pretreatment viral load or a low pretreatment viral load (47% and 65%, respectively). A reduction in either the ribavirin dose or duration of treatment was associated with a substantial loss of efficacy in both patient subgroups.

Patients Infected with Genotype Non-1:

In patients infected with genotype non-1, similar sustained virological responses were achieved after treatment for 24 weeks with 800 mg of ribavirin and after treatment for a longer duration or with a higher dose of ribavirin (Table 18). This was the case whether patients had a high pretreatment viral load or a low pretreatment viral load.

The genotype non-1 patients in this study were predominantly infected with genotype 2 or 3 (90% of patients), which to a large extent account for the results observed in genotype non-1 patients in this study. In the small number of patients infected with genotype 4 in this study (36 patients), sustained virological response was highest after 48 weeks of treatment with 1000 or 1200 mg of ribavirin (9 of 11 patients), suggesting that these patients respond similarly to patients infected with genotype 1.

All Patients:

In the group of all patients treated for 48 weeks with PEG-IFN α-2a and 1000 or 1200 mg of ribavirin the sustained virological response was 63%.

Table 18 Sustained Virological Response as a Function of Genotype (1, 2, and 3) and Baseline Viral Titer in Study NV15942 in Patients with Hepatitis C

	24 weeks PEG-IFN α-2a 180 µg Ribavirin 800 mg (N=207)	24 weeks PEG-IFN α-2a 180 µg Ribavirin 1000/1200 mg (N=280)	48 weeks PEG-IFN α-2a 180 µg Ribavirin 800 mg (N=361)	48 weeks PEG-IFN α-2a 180 µg Ribavirin 1000/1200 mg (N=436)
Genotype 1	29%	42%	41%	52%
Viral Titers (copies/mL)				
≤ $2x10^6$	41%	52%	55%	65%
>$2x10^6$	16%	26%	36%	47%
Genotype Non-1	80%	80%	77%	81%
Viral Titers (copies/mL)				
≤ $2x10^6$	77%	80%	85%	79%
>$2x10^6$	82%	80%	71%	81%
Genotype 2	90%	85%	87%	80%
Viral Titers (copies/mL)				
≤ $2x10^6$	100%	82%	93%	79%
>$2x10^6$	84%	86%	84%	81%
Genotype 3	81%	79%	72%	80%
Viral Titers (copies/mL)				
≤ $2x10^6$	75%	83%	83%	76%
>$2x10^6$	84%	76%	66%	83%

6.3.7 Predictability of Sustained Virological Response in Patients with Hepatitis C

The product information for some currently available interferon-based therapies for HCV infection suggests that all patients should be treated for a minimum of 24 weeks before considering the discontinuation of therapy because the patient is not responding and unlikely to achieve a sustained virological response with further treatment. The availability of quantitative HCV RNA testing may allow such decisions to be made earlier in the course of treatment by determining how much a patient's pretreatment HCV RNA titer has decreased during therapy rather than using interim viral undetectability as a measure of response to therapy. An assessment with a high negative predictive value at a time point earlier than 24 weeks of therapy could be used clinically to identify patients with little chance of responding to continued therapy, thereby sparing these patients unnecessary treatment.

An analysis of the predictability of sustained virological response based on response by week 12 in patients treated for 48 weeks with PEG-IFN α-2a and 1000 or 1200 mg of ribavirin combination therapy is presented in Table 19. The data from the common arm of studies NV15801 and NV15942 have been pooled for this exploratory analysis. In this analysis, patients who have either unquantifiable HCV RNA or at least a 2-$\log_{10}$ drop from their baseline HCV RNA titer at any time during the initial 12 weeks of treatment were considered to have demonstrated an early virological response by week 12. The

negative predictive value of not achieving an early virological response by week 12 for a sustained virological response is calculated by dividing the number of patients who had neither a response by week 12 nor a sustained virological response by the number of patients who did not have a response by week 12.

In the overall population, 87% of patients being treated for 48 weeks with PEG-IFN α-2a and 1000 or 1200 mg of ribavirin combination therapy had an early virological response by week 12. Of the 113 patients in the overall population who failed to achieve a virological response by week 12 of treatment, 108 failed to achieve a sustained virological response, resulting in a negative predictive value of 96% in the overall population.

The percentage of patients with genotype 1 infection being treated for 48 weeks with PEG-IFN α-2a and 1000 or 1200 mg of ribavirin combination therapy who had an early virological response was similar to that of the overall population (82%). The negative predictive value of not achieving an early virological response by week 12 for sustained virological response in patients with genotype 1 infection was 96%.

In contrast to patients with genotype 1 infection, almost all patients with genotype non-1 infection being treated with PEG-IFN α-2a and ribavirin combination therapy (97%) had an early virological response by week 12; only a small number of patients (11 patients) did not achieve an early virological response. Of the 11 patients with genotype non-1 infection who failed to achieve a virological response by week 12 of treatment, 10 also failed to achieve a sustained virological response.

Table 19 Negative Predictive Value of a Virological Response by Week 12 for Sustained Virological Response in Patients with Hepatitis C

	Overall Population (N = 889)		Genotype 1 Patients (N = 569)		Genotype Non-1 Patients (N = 320)	
	SVR	No SVR	SVR	No SVR	SVR	No SVR
HCV RNA unquantifiable or $\geq 2\log_{10}$ drop by week12						
Yes	488	288	261	206	227	82
No	5	108	4	98	1	10
Week 12 response	87%		82%		97%	
Negative predictive value	108/(5 + 108) = 96%		98/(4 + 98) = 96%		10/(1 + 10) = 91%	

Note: The analysis population is patients treated for 48 weeks with PEG-IFN α-2a and 1000 or 1200 mg of ribavirin from the common arm of studies NV15801 and NV15942. SVR = sustained virological response.

6.4 References

6.1 Najera I, Laxton C et al. Use of HCV subgenomic replicon for in vitro combination studies: ribavirin in combination with interferon alfa-2a or pegylated interferon alfa-2a. Research Report 1003860. February 26, 2001.

6.2 Najera I, Laxton C et al. Studies on inhibition of HCV replicon by ribavirin and possible mechanisms of action. Research Report 1003775. February 26, 2001.

6.3 Hartley J and Austin A. Inhibition of PHA-induced T cell proliferation by ribavirin. Research Report 1003810. March 1, 2001.

6.4 Tam RC, Pai B et al. Ribavirin polarizes human T cell responses towards a type 1 cytokine profile. J. Hepatol. 1999;30:376-382.

6.5 Catala AR, A Four-Week Subcutaneous and Oral Gavage Toxicity and Toxicokinetic Study with Ro 25-8310/000 (PEGASYS) and Ro 20-9963/000 (Ribavirin) in Cynomolgus Monkeys with a 6 Week Recovery (Covance Study No. 6131-279, Roche Study No. 07211) Research Report 1002711, March 12, 2001.

6.6 Pendino K, 4-Week Oral Gavage Dose-Range Finding and Toxicokinetic Study with Ro 20-9963/000 (Ribavirin) in C57BL/6 Mice (Covance Study No. 6131-296, Roche Study No. 07296) Research Report 1002209. April 3, 2001.

6.7 Devanaboyina US, 13-Week Oral Gavage Toxicity and Toxicokinetic Study with Ro 20-9963/000 in Rats (Covance Study No. 6131-299, Roche Study No. 07320) Research Report 1003487. April 3, 2001.

6.8 Devanaboyina US, 26-Week Oral Gavage Toxicity and Toxicokinetic Study with a 6-Week Recovery Phase with Ro 20-9963/000 in Rats (Covance Study No. 6131-300, Roche Study No. 07321) Research Report 1003488. April 3, 2001.

6.9 Devanaboyina US, 26-Week Oral Gavage Toxicity and Toxicokinetic Study with a 6-Week Recovery Phase with Ro 20-9963/000 in Dogs (Covance Study No. 6131-301, Roche Study No. 07322) Research Report 1003489. April 3, 2001.

6.10 Pendino K, 4-Week Oral Gavage Dose-Range Finding and Toxicokinetic Study with Ro 20-9963/000 (Ribavirin) in C57BL/6 Mice (Covance Study No. 6131-296, Roche Study No. 07296) RR 1002209. April 3, 2001.

6.11 Devanaboyina US, 13-Week Oral Gavage Toxicity and Toxicokinetic Study with Ro 20-9963/000 in Rats (Covance Study No. 6131-299, Roche Study No. 07320) RR 1003487. April 3, 2001.

6.12 Devanaboyina US, 26-Week Oral Gavage Toxicity and Toxicokinetic Study with a 6-Week Recovery Phase with Ro 20-9963/000 in Rats (Covance Study No. 6131-300, Roche Study No. 07321) RR 1003488. April 3, 2001.

6.13 Devanaboyina US, 26-Week Oral Gavage Toxicity and Toxicokinetic Study with a 6-Week Recovery Phase with Ro 20-9963/000 in Dogs (Covance Study No. 6131-301, Roche Study No. 07322) RR 1003489. April 3, 2001.

6.14 Canonico, P.G. 1983. Ribavirin: A Review of Efficacy, Toxicity and Mechanisms of Antiviral Activity. Antibiotics. 4:161-186. (Noted as Canonico C in text of E-Report)

6.15 Wannarka GL, Stephen EL, Canonico PG. Preclinical evaluation in monkeys of a ribavirin regimen proposed for use in lassa fever patients. Toxicol. Appl. Pharmacol. 1982; 64: 155-159.

6.16 Canonico PG, Kastello MD, Cosgriff TM, Donovan JC, Ross PE, Spears CT, Stephen EL. Hematological and bone marrow effects of ribavirin in rhesus monkeys. Toxicol. Appl. Pharmacol. 1984; 74:163-172.

6.17 Willhite CC, Ferm VH. Potentiation of ribavirin-induced teratogenesis by natural purines. Exp. Mol. Pathol. 1978; 28:196-201.

6.18 Ferm VH, Willhite CC, Kilham L. Teratogenic effects of ribavirin on hamster and rat embryos. Teratol. 1978; 17:93-102.

6.19 Kochhar DM, Penner JD, Knudsen TB. Embryotoxic, teratogenic, and metabolic effects of ribavirin in mice. Toxicol. Appl. Pharmacol. 1980; 52:99-112.

6.20 Margolis G, Kilham L. Cerebellar, epidermal, and dental defects induced by ribavirin in perinatal hamsters and rats. Exp. Mol. Pathol. 1978; 29:44-54.

6.21 Johnson EM. The effects of ribavirin on development and reproduction: a critical review of published and unpublished studies in experimental animals. J. Am. Coll. Toxicol. 1990; 9:551-561.

6.22 Levine BS, Tomlinson MJ, Parker RM. Onset and reversibility of ribavirin-induced testicular toxicity in mice. Toxic Substances J. 1994; 13:171-186.

6.23 Agnish MD. An Oral Gavage Study for Effects of Ro 20-9963 (Ribavirin) on Fertility and Early Embryonic Development to Implantation in Sprague-Dawley Rats (Covance Study No. 6131-316, Roche Study No. 07392) RR 1003508.

6.24 Rao KPS, Rahiman MA. Cytogenetic effects of ribavirin on mouse bone marrow. Mut. Res. 1989; 224:213-218.

6.25 Phillips MD, Nascimbeni B, Tice RR, Shelby MD. Induction of micronuclei in mouse bone marrow cells: an evaluation of nucleoside analogues used in the treatment of AIDS. Env. Mol. Mutag. 1991; 18:168-183.

6.26 van Birgelen APJM. Ro 20-9963/000 (Ribavirin): L5178Y TK plus or minus Mouse Lymphoma Forward Mutation Assay with a Confirmatory Assay with Ribavirin (Covance Study No. 21537-0-431), Roche Study No. 07404) RR 1003060.

6.27 van Birgelen APJM. Ro 20-9963/000 (Ribavirin): Twenty-six Week Gavage Oncogenicity Study with Ro 20-9963/000 (Ribavirin) in p53 plus or minus C57BL/6 Mice (Covance Study No. 6131-297, Roche Study No. 07402) RR 1003486. July 16, 2001.

6.28 Catala AR. A Four-Week Subcutaneous and Oral Gavage Toxicity and Toxicokinetic Study with Ro 25-8310/000 (PEGASYS) and Ro 20-9963/000 (Ribavirin) in Cynomolgus Monkeys with a 6 Week Recovery (Covance Study No. 6131-279, Roche Study No. 07211) RR 1002711, March 12, 2001.

6.29 Canonico PG. Ribavirin: A Review of Efficacy, Toxicity and Mechanisms of Antiviral Activity. Antibiotics. 1983;4:161-186.

6.30 Glue P. The Clinical Pharmacology Of Ribavirin. Sem Liver Disease 1999:(19) Suppl. 1:17-24.

6.31 Ribavirin Food Effect Roche Clinical Study Report (Protocol NR16230) - A Food Effect Bioavailability Study Of Roche Ribavirin Tablets, Intended For Commercial Use, Administered Orally To Individuals With Current Or Previous Chronic Hepatitis C (CHC) Infection. RR-1003972.

6.32 Bruchfeld A, Stahle, L, Anderson J, Schvarcz R. Ribavirin treatment in dialysis patients with chronic hepatitis C virsu infection – A pilot study. J Viral Hepat 2001;8:287-92.

6.33 Jie K, Rensma PL, Veen S, Bosch FH, Valentijn RM. Safety of interferon and ribavirin therapy in haemodialysis patients with chronic hepatitis C: Results of a pilot study. Nephrol Dial Transplant 200116:193-195.

6.34 Napieralski J, et al. Clinical Study Report (Protocol NV15801) - A phase III, randomized, multicenter, efficacy and safety study comparing the combination of PEG-IFN alfa-2a (Ro 25-8310) and ribavirin to IFN alfa-2b and ribavirin in the treatment of patients with chronic hepatitis C. Research Report 1004549/October 11, 2001 (Vol. R. 12-2).

6.35 Kakhoo S, Glue P, Grellier L, et al. Ribavirin and interferon alfa-2b in chronic hepatitis C: assessment of possible pharmacokinetic and pharmacodynamic interactions. Br J Clin Pharmacol 1998;46:6 563-570.

6.36 Baba M, Pauwels R, Balzarini J, et al. Ribavirin antagonizes the inhibitory effects of pyrimidine 2',3'-dideoxynucleosides but enhances inhibitory effects of purine 2',3'-dideoxynucleosides on replication of human immunodeficiency virus in vitro. Antimicrobial Agents and Chemotherapy 1987;31:1613-1617.

6.37 Sim SM, Hoggard PG, Sales SD, et al. Effect of Ribavirin on Zidovudine Efficacy and Toxicity In Vitro: A Concentration-Dependent Interaction. AIDS Research and Human Retroviruses 1998;14;1661-1667.

6.38 Japour AJ, Lertora JJ, Meehan PM, et al. A phase-I study of the safety, pharmacokinetics, and antiviral activity of combination didanosine and ribavirin in patients with HIV-1 disease: AIDS Clinical Trials Group 231 Protocol Team. J Acquir Immune Defic Syndr Hum Retrovirol 1996;13:235-246.

6.39 Lafeuillade A, Hittinger G, Chadapaud S. Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. Lancet 2001;357:280-281.

6.40 BP16320 – Bioequivalence Study of Ribavirin Formulations Rebetol and Ro 20-9963 Administered Orally to Individuals with Current or Previous Chronic Hepatitis C (CHC) Infection. Research Report No. 1003761. April 11, 2001.

6.41 Laskin OL, et al. Ribavirin disposition in high-risk patients for acquired immunodeficiency syndrome. *Clin Pharmacol Ther*. 1987;41:546-555.

6.42 Canonico PG, et al. Effects of ribavirin on red blood cells. *Toxicol Appl Pharmacol*. 1984;4:155-162.

6.43 Moore D, Habucky K. A Pharmacokinetics Study of Ribavirin in the Dog following Single Oral Administration. Bioanalytical and Toxicokinetic results, Protocol 98-7099. Research Report N-181287, January 4, 1999.

6.44 Jen JF, Glue P et al. Population Pharmacokinetic and Pharmacodynamic Analysis of Ribavirin in Patients With Chronic Hepatitis C. *Therapeutic Drug Monitoring*. 200; 22: 555-565.

6.45 Lad et al. Effect of Ribavirin on Type-1 and Type-2 Cytokine Responses in Human Peripheral Blood Mononuclear Cells, in vitro. Research Report No. 1003792, February 26, 2001.

6.46 Fried NEJM: Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, Haussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002 Sep 26;347(13):975-982.

6.47 Hadziyannis SJ, Cheinquer H, Morgan T, et al. Peginterferon alfa-2a (40KD) (PEGASYS) in combination with ribavirin (RBV): efficacy and safety results from a phase III, randomized, double-blind multicentre study examining effect of duration of treatment and RBV dose. *J Hepatology* 2001; 36 (Suppl. 1):3

7. GUIDANCE FOR THE INVESTIGATOR: PEG-IFN α-2A AND RIBAVIRIN COMBINATION THERAPY

In this section, guidance is provided to investigators conducting clinical trials employing PEG-IFN α-2a plus ribavirin combination therapy. The information in this section is mainly based on the sponsor's core data sheet for PEG-IFN α-2a and ribavirin. To safeguard patients, it is prudent to consider the information contained in this section to be also relevant for patients treated with PEG-IFN α-2a monotherapy.

A project-specific definition for expected serious adverse events has been adopted for all clinical studies conducted with the combination of PEG-IFN α-2a and ribavirin. For serious adverse events attributed by an investigator to both PEG-IFN α-2a and ribavirin in studies with this combination, events listed as "expected" for PEG-IFN α-2a or ribavirin are also considered to be expected for the combination. The rationale for this definition is that it is the safety profile of the combination rather than its individual components that is being assessed in these studies. In addition, events expected for IFN α-2a are also expected for PEG-IFN α-2a and events expected for PEG-IFN α-2a monotherapy or combination therapy with ribavirin in one patient population (ie, CHC) are also expected in other patient populations (ie, CHB and oncology).

7.1 Patients Who Should Not Take PEG-IFN α-2a and Ribavirin Combination Therapy

PEG-IFN α-2a and ribavirin combination therapy should not be taken by:

- patients with known hypersensitivity to α interferons, to E. coli-derived products, to polyethylene glycol, to ribavirin, or to any component of the injection or tablet,
- patients with autoimmune hepatitis,
- patients with decompensated cirrhosis,
- women who are pregnant or men whose female partners are pregnant
- neonates and infants up to 3 years of age.

7.2 Important Information about PEG-IFN α-2a and Ribavirin Combination Therapy

Adverse Events

Treatment with PEG-IFN α-2a or PEG-IFN α-2a and ribavirin should be administered under the guidance of a qualified physician and may lead to moderate to severe adverse experiences requiring dose reduction, temporary dose cessation or discontinuation of further therapy.

The entrance criteria used for the clinical studies of PEG-IFN α-2a alone or in combination with ribavirin may be considered as a guideline to acceptable baseline values for initiation of treatment:

- Platelet count ≥ 90,000 cells/mm^3
- Absolute neutrophil count (ANC) ≥ 1500 cells/mm^3
- TSH and T_4 within normal limits or adequately controlled thyroid function

Before beginning PEG-IFN α-2a monotherapy or PEG-IFN α-2a plus ribavirin combination therapy, standard hematological and biochemical laboratory tests are recommended for all patients. After initiation of therapy, hematological tests should be performed at 2 and 4 weeks, and biochemical tests should be performed at 4 weeks. Additional hematological and biochemical laboratory testing should be performed periodically during therapy.

PEG-IFN α-2a monotherapy or PEG-IFN α-2a and ribavirin combination therapy should be used with caution in patients with baseline neutrophil counts < 1500 cells/mm^3, baseline platelet count < 90,000 cells/mm^3 or baseline hemoglobin < 12 g/dL. As with other interferons, caution should be exercised when administering PEG-IFN α-2a monotherapy or PEG-IFN α-2a and ribavirin combination therapy in combination with other potentially myelosuppressive agents.

PEG-IFN α-2a monotherapy and PEG-IFN α-2a plus ribavirin combination therapy were associated with decreases in both total WBC count and ANC, usually starting within the first 2 weeks of treatment. In clinical studies, progressive decreases thereafter were infrequent. Dose reduction is recommended when ANC decreases to levels below 750 cells/mm^3. For patients with ANC values below 500 cells/mm^3, treatment should be suspended until ANC values return to more than 1000 cells/mm^3. In clinical trials with PEG-IFN α-2a monotherapy or PEG-IFN α-2a plus ribavirin combination therapy, the decrease in ANC was reversible upon dose reduction or cessation of therapy. While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out, particularly in patients with neutropenia.

PEG-IFN α-2a monotherapy and PEG-IFN α-2a plus ribavirin combination therapy were associated with decreases in platelet count, which returned to pretreatment (baseline) levels during the posttreatment observation period. Dose reduction is recommended when platelet count decreases to levels below 50,000/mm^3, and cessation of therapy is recommended when platelet count decreases to levels below 25,000/mm^3.

Anemia (hemoglobin ≤ 10g/dL) was observed in patients who were treated with PEG-IFN α-2a plus ribavirin.. The maximum drop in hemoglobin occurred within 4 weeks of initiation of ribavirin therapy. If there is any deterioration of cardiovascular status, ribavirin therapy should be suspended or discontinued.

Cardiovascular events such as hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with α interferon therapies, including PEG-IFN α-2a and PEG-IFN α-2a and ribavirin combination therapy. It is recommended that patients who have pre-existing cardiac abnormalities have an electrocardiogram prior to initiation of therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued.

Severe psychiatric adverse reactions may manifest in patients receiving therapy with interferons, including PEG-IFN α-2a or PEG-IFN α-2a and ribavirin. Depression, suicidal ideation, and suicide may occur in patients with and without previous psychiatric illness. PEG-IFN α-2a and ribavirin combination therapy should be used with caution in patients who report a history of depression, and physicians should monitor all patients for evidence of depression. Physicians should inform patients of the possible development of depression prior to initiation of PEG-IFN α-2a plus ribavirin combination therapy, and patients should report any sign or symptom of depression immediately. In severe cases therapy should be stopped and psychiatric intervention sought.

In patients with compensated cirrhosis (eg. Child Pugh A), PEG-IFN α-2a has been shown to be effective and safe. PEG-IFN α-2a has not been studied in patients with decompensated cirrhosis (eg. Child Pugh B/C or esophageal varices).

In patients who develop evidence of hepatic decompensation during treatment, PEG-IFN α-2a and ribavirin combination therapy should be discontinued. As with other α-interferons, increases in ALT levels above baseline have been observed in patients treated with either PEG-IFN α-2a or with PEG-IFN α-2a and ribavirin combination therapy, including patients with a virological response. When the increase in ALT levels is progressive despite dose reduction or is accompanied by increased direct bilirubin, therapy should be discontinued.

As with other interferons, PEG-IFN α-2a monotherapy or PEG-IFN α-2a and ribavirin combination therapy may cause or aggravate hypothyroidism and hyperthyroidism. Discontinuation of therapy should be considered in patients whose thyroid abnormalities cannot be adequately treated. Hyperglycemia, hypoglycemia, and diabetes mellitus have been observed in patients treated with α interferons. Patients with these conditions who cannot be effectively controlled by medication should not begin PEG-IFN α-2a monotherapy or PEG-IFN α-2a and ribavirin combination therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should discontinue PEG-IFN α-2a monotherapy or PEG-IFN α-2a and ribavirin combination therapy.

Exacerbation of autoimmune disease has been reported in patients receiving α-interferon therapy; PEG-IFN α-2a monotherapy and PEG-IFN α-2a and ribavirin combination therapy must be used with caution in patients with autoimmune disorders.

Use of α interferons has been associated with exacerbation or provocation of psoriasis. PEG-IFN α-2a alone or in combination with ribavirin must be used with caution in patients with psoriasis, and in case of appearance or worsening of psoriatic lesions, discontinuation of therapy should be considered.

Serious, acute hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction, and anaphylaxis) have been rarely observed during α interferon therapy. If such a reaction develops during treatment with either PEG-IFN α-2a or PEG-IFN α-2a and ribavirin combination, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

As with other α interferons, pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonia, and pneumonitis, including fatality, have been reported with PEG-IFN α-2a alone or in combination with ribavirin. If there is evidence of persistent or unexplained pulmonary infiltrates or pulmonary function impairment, treatment should be discontinued.

As with other interferons, retinopathy including retinal hemorrhages, cotton wool spots, papilledema, optic neuropathy and retinal artery or vein obstruction, which may result in loss of vision, have been reported after treatment with PEG-IFN α-2a. Any patient complaining of decreased or loss of vision must have a prompt and complete eye

examination. Because these ocular events may occur in conjunction with other disease states, a visual examination prior to initiation of PEG-IFN α-2a monotherapy or PEG-IFN α-2a and ribavirin combination therapy is recommended in patients with diabetes mellitus or hypertension. PEG-IFN α-2a or PEG-IFN α-2a and ribavirin combination treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Pregnancy and Lactation

PEG-IFN α-2a should not be used in pregnant women. PEG-IFN α-2a has not been studied for its effect on fertility. As with other α interferons, prolongation of the menstrual cycle accompanied by both a decrease and a delay in the peak of 17β-estradiol and progesterone levels have been observed following administration of PEG-IFN α-2a to female monkeys. A return to normal menstrual rhythm followed discontinuation of treatment.

PEG-IFN α-2a has not been studied for its effect on male fertility. However, treatment with interferon alfa-2a did not affect fertility of male rhesus monkeys treated for 5 months at doses up to 25×10^6 IU/kg/day.

PEG-IFN α-2a has not been studied for its teratogenic effect. Treatment with interferon alfa–2a resulted in a statistically significant increase in abortifacient activity in rhesus monkeys. No teratogenic effects were seen in the offspring delivered at term. However, as with other α interferons, women of childbearing potential receiving PEG-IFN α-2a therapy should be advised to use effective contraception during therapy.

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Ribavirin therapy should not be used in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking ribavirin. Any birth control method can fail. Therefore, it is critically important that women of childbearing potential and their partners must use 2 forms of effective contraception simultaneously, during treatment and for 6 months after treatment has been concluded.

It is not known whether PEG-IFN α-2a or ribavirin are excreted in human milk. Because many drugs are excreted in human milk and to avoid any potential for serious adverse reactions in nursing infants from PEG-IFN α-2a or ribavirin, a decision should be made to discontinue either nursing or treatment, based on the importance of the therapy to the mother.

PEG-IFN α-2a has not been tested for its carcinogenic potential. PEG-IFN α-2a was neither mutagenic nor clastogenic when tested in the Ames bacterial mutagenicity assay and in the *in vitro* chromosomal aberration assay in human lymphocytes, either in the presence or absence of metabolic activation.

Genotoxicity studies have demonstrated that ribavirin does exert some genotoxic activity. Ribavirin was active in an *in vitro* Transformation Assay. Genotoxic activity was observed in *in vivo* mouse micronucleus assays. A dominant lethal assay in rats was

negative, indicating that if mutations occurred in rats they were not transmitted through male gametes. Ribavirin is a possible human carcinogen.

Special Populations

Safety and effectiveness of PEG-IFN α-2a alone or in combination with ribavirin have not been established in patients under age 18. In addition, PEG-IFN α-2a injectable solutions contain benzyl alcohol. There have been rare reports of death in neonates and infants associated with excessive exposure to benzyl alcohol. The amount of benzyl alcohol at which toxicity or adverse effects may occur in neonates or infants is not known. Therefore, PEG-IFN α-2a alone and in combination with ribavirin should not be used in neonates or infants.

No special dosage modification of PEG-IFN α-2a is required for geriatric patients based upon pharmacokinetic, pharmacodynamic, tolerability, and safety data from clinical trials.

In patients with end-stage renal disease, a starting dose of PEG-IFN α-2a 135µg once weekly should be used. Regardless of the starting dose or degree of renal impairment, patients should be monitored and appropriate dose reductions of PEG-IFN α-2a during the course of therapy should be made in the event of adverse reactions.

The pharmacokinetics of ribavirin are altered in patients with renal dysfunction due to reduction of apparent clearance in these patients. Therefore, it is recommended that renal function be evaluated in all patients prior to initiation of ribavirin treatment, preferably by estimating the patients's creatinine clearance. Substantial increases in ribavirin plasma concentrations are seen at the recommended dosing regimen in patients with serum creatinine > 2 mg/dL or with creatinine clearance < 50 mL/minute. There are insufficient data on safety and efficacy in these patients and therefore, ribavirin must be administered with extreme caution and corrective action including drug discontinuation must be considered if adverse events develop.

7.3 Summary of Adverse Events

Table 20 summarizes the most frequent adverse events that were considered possibly or probably related to the study drug by the investigator in patients treated with PEG-IFN α -2a (180 µg) plus ribavirin (800 mg) for 24 weeks, PEG-IFN α -2a (180 µg) plus ribavirin (1000 mg or 1200 mg) for 48 weeks, PEG-IFN α -2a monotherapy (180 µg) for 48 weeks, and IFN α -2b (3 MIU) plus ribavirin (1000 mg or 1200 mg) for 48 weeks.

Table 20 Most Frequent Adverse Events (Incidence ≥ 10% in any Treatment Arm) Considered by Investigator to be Possibly or Probably Related to the Study Drug in Patients with Hepatitis C

Body System	PEG-IFN α -2a 180 µg Ribavirin 800 mg[a] 24 weeks N = 207	PEG-IFN α -2a 180 µg Ribavirin 1000 or 1200 mg[b] 48 weeks N=887	PEG-IFN α -2a 180 µg Monotherapy[c] 48 weeks N=827	IFN α -2b 3 MIU Ribavirin 1000 or 1200 mg[d] 48 weeks N=443
General				
Fatigue	94 (45)	432 (49)	405 (49)	235 (53)
Pyrexia	76 (37)	347 (39)	288 (35)	240 (54)
Rigors	63 (30)	219 (25)	249 (30)	150 (34)
Injection site reaction	57 (28)	189 (21)	178 (22)	68 (15)
Asthenia	38 (18)	137 (15)	56 (7)	71 (16)
Pain	19 (9)	86 (10)	89 (11)	38 (9)
Gastrointestinal disorders				
Nausea	60 (29)	248 (28)	199 (24)	124 (28)
Diarrhea	32 (15)	124 (14)	132 (16)	44 (10)
Abdominal pain	19 (9)	89 (10)	120 (15)	38 (9)
Metabolism and nutrition disorder				
Anorexia	41 (20)	243 (27)	131 (16)	115 (26)
Weight decrease	4 (2)	66 (7)	44 (5)	43 (10)
Musculoskeletal				
Myalgia	86 (42)	336 (38)	307 (37)	216 (49)
Arthralgia	41 (20)	195 (22)	211 (26)	103 (23)

Note: Numbers provided in parentheses are the percentage of patients.

[a] Data are from the combination therapy study NV15942.

[b] Data are pooled from the combination therapy arms of studies NV15801 and NV15942.

[c] Data are pooled from the monotherapy program and the monotherapy arm of the combination therapy study NV15801.

[d] Data are from the combination therapy study NV15801.

(continued)

Table 20 Most Frequent Adverse Events (Incidence ≥ 10% in any Treatment Arm) Considered by Investigator to be Possibly or Probably Related to the Study Drug in Patients with Hepatitis C (Cont.)

Body System	PEG-IFN α -2a 180 µg Ribavirin 800 mg[a] 24 weeks N = 207	PEG-IFN α -2a 180 µg Ribavirin 1000 or 1200 mg[b] 48 weeks N=887	PEG-IFN α -2a 180 µg Monotherapy[c] 48 weeks N=827	IFN α -2b 3 MIU Ribavirin 1000 or 1200 mg[d] 48 weeks N=443
Neurological and psychiatric disorders				
Headache	100 (48)	420 (47)	428 (52)	216 (49)
Insomnia	63 (30)	280 (32)	166 (20)	163 (37)
Irritability	58 (28)	213 (24)	141 (17)	118 (27)
Depression	36 (17)	183 (21)	148 (18)	126 (28)
Dizziness	27 (13)	131 (15)	119 (14)	60 (14)
Concentration Impairment	16 (8)	90 (10)	76 (9)	57 (13)
Anxiety	17 (8)	74 (8)	51 (6)	55 (12)
Respiratory disorder				
Dyspnea	23 (11)	115 (13)	39 (5)	60 (14)
Cough	16 (8)	112 (13)	36 (4)	33 (7)
Skin				
Alopecia	52 (25)	216 (24)	186 (22)	144 (33)
Pruritus	52 (25)	188 (21)	103 (12)	78 (18)
Dermatitis	32 (15)	140 (16)	71 (9)	58 (13)
Dry skin	26 (13)	108 (12)	41 (5)	58 (13)

Note: Numbers provided in parentheses are the percentage of patients.
[a] Data are from the combination therapy study NV15942.
[b] Data are pooled from the combination therapy arms of studies NV15801 and NV15942.
[c] Data are pooled from the monotherapy program and the monotherapy arm of the combination therapy study NV15801.
[d] Data are from the combination therapy study NV15801.

The following table provides a list of all less common adverse events (incidence ≥1% to 10%) considered by the investigator as causally related to treatment or of unknown causality for PEG-IFN α-2a monotherapy or PEG-IFN α-2a plus ribavirin combination therapy.

Table 21 Less Common Adverse Events Considered by the Investigator to be Causally Related to Treatment or Unknown for PEG-IFN α-2a Monotherapy or PEG-IFN α-2a plus Ribavirin Combination Therapy

System Organ Class	Adverse Event
Skin and Subcutaneous Tissue Disorders	rash, sweating increased, night sweats, urticaria, psoriasis, photosensitivity reaction, eczema (eg., skin disorder)
Musculoskeletal Connective Tissue Disorders	back pain, muscle cramps, neck pain, musculoskeletal pain, bone pain, muscle weakness, arthritis
Nervous System Disorders	memory impairment, dysgeusia, paraesthesia, tremor, hypoesthesia, migraine, somnolence, syncope, hyperaesthesia
Psychiatric Disorders	mood alteration, emotional disturbance, nervousness, libido decreased, aggression, nightmares
Eye Disorders	eye inflammation, dry eye, eye pain, vision blurred
Ear & Labyrinth Disorders	vertigo, ear pain
Gastrointestinal Disorders	vomiting, dry mouth, dyspepsia, mouth ulceration, flatulence, gingival bleeding, stomatitis, dysphagia, glossitis
Endocrine Disorders	hypothyroidism, hyperthyroidism
Cardiac Disorders	palpitations, tachycardia
Vascular Disorders	hot flushes, flushing
Respiratory, Thoracic & Mediastinal Disorders	sore throat, epistaxis, nasopharyngitis, rhinitis, bronchitis, dyspnea exertional, sinus congestion, nasal congestion
Blood & Lymphatic System Disorders	anemia, lymphadenopathy
Reproductive System & Breast Disorders	erectile dysfunction
General Disorders & Administration Site Conditions	flu-like illness, malaise, lethargy, chest pain, peripheral edema
Infections & Infestations	upper respiratory tract infection, herpes simplex, oral candidiasis

Note: causally related adverse events include those probably, possibly or remotely related to treatment; data are pooled from PEG-IFN α-2a monotherapy and combination therapy clinical trials in Hepatitis C, Hepatitis B and Oncology.

In addition, uncommon (<1%) and rare adverse events (events considered to be causally related or unknown) reported in patients receiving PEG-IFN α-2a monotherapy or PEG-IFN α-2a plus ribavirin combination therapy are included in the following table. This list is based on information obtained as of January 31, 2003 from all Roche-sponsored PEG-IFN α-2a and PEG-IFN α-2a plus ribavirin combination therapy clinical trials.

Table 22 Uncommon (<1%) and Rare Adverse Events (Events Considered by the Investigator to be Causally Related to Treatment or Unknown) in Patients Receiving PEG-IFN α-2a Monotherapy or PEG-IFN α-2a Plus Ribavirin Combination Therapy

Body System	Adverse Event
Skin and Subcutaneous Tissue Disorders	skin lesion, erythematous rash, erythema, exanthem, atopic dermatitis, exfoliative dermatitis, lichen planus, neurodermatitis, contusion
Musculoskeletal Connective Tissue Disorders	muscle twitching, myositis, bursitis, synovitis, polyarthritis, intervertebral disc herniation, rhabdomyolysis, rheumatoid arthritis, lupus-like syndrome, bone infarction, pain in limb
Immune System Disorders	cell mediated allergic reaction, liver transplant rejection, sarcoidosis, hypersensitivity, anaphylactic reaction
Nervous System Disorders	hyperkinesia, peripheral neuropathy, polyneuropathy, nerve root lesion, trigeminal neuralgia, facial palsy, cranial nerve disorder, encephalopathy, cerebral atrophy, loss of consciousness, coma, convulsions, hepatic encephalopathy, cerebral hemorrhage, subarachnoid hemorrhage, subdural hematoma, transient ischemic attack, cerebral infarction, cerebral vascular accident, vasovagal attack
Psychiatric Disorders	mental disorder, confusional state, abnormal behavior, delirium, psychotic disorder, acute psychosis, agitation, panic disorder, mood disorder, mental status changes, personality disorder, conversion disorder, bipolar disorder, mania, hallucination, schizoaffective disorder, post-traumatic stress disorder, sleep disorder, paranoia, alcoholism, drug addiction, intentional self-injury suicidal ideation, suicide attempt, completed suicide
Eye Disorders	corneal ulcer, retinal disorder (eg., retinal vein thrombosis, retinal artery thrombosis, retinitis, retinopathy, retinal hemorrhage), vitreous hemorrhage, macular edema, uveitis, chorioretinitis, papilledema, (eg., optic papillitis), diplopia, amaurosis fugax, blindness (optic ischemic neuropathy),eye hemorrhage, optic neuropathy
Ear & Labyrinth Disorders	deafness, tinnitus

Note: causally related adverse events include those probably, possibly or remotely related to treatment; data are pooled from PEG-IFN α-2a monotherapy and combination therapy clinical trials in Hepatitis C, Hepatitis B and Oncology.

(continued)

Table 22 Uncommon (<1%) and Rare Adverse Events (Events Considered by the Investigator to be Causally Related to Treatment or Unknown) in Patients Receiving PEG-IFN α-2a Monotherapy or PEG-IFN α-2a Plus Ribavirin Combination Therapy (Cont.)

Body System	Adverse Event
Gastrointestinal Disorders	eructation, gastroenteritis, aphagia, periodontitis, gastritis, enteritis, gastrointestinal hemorrhage (eg., hematemesis, esophageal varices hemorrhage, rectal hemorrhage melena), peptic ulcer, pancreatitis (eg., reversible pancreatic reaction, blood amylase increased, blood lipase increased with or without abdominal pain), peritonitis, enterocolitis, appendicitis colitis, ascites, peritoneal hemorrhage, celiac disease
Hepatobiliary Disorders	hepatic function abnormal (eg., jaundice, hepatitis, cholestatic hepatitis, hepatic cirrhosis, hepatic failure), fatty liver, cholangitis, cholelithiasis, cholecystitis, autoimmune hepatitis, GGT increased, blood alkaline phosphatase increased, transaminase increased, blood bilirubin increased
Metabolism & Nutrition Disorders	dehydration, electrolyte imbalance, hypocalcemia, hypoglycemia, hyperglycemia, diabetes mellitus (diabetic ketoacidosis), lactic acidosis, hyperammonemia, gout
Endocrine Disorders	goiter, thyroiditis, thyrotoxicosis, adrenal insufficiency, thyroid cyst, thyroid nodule, autoimmune thyroiditis
Cardiac Disorders	superventricular tachycardia, atrial flutter atrial fibrillation, arrhythmia, bundle branch block, ECG abnormal, angina pectoris, (eg., unstable angina, myocardial ischemia), acute myocardial infarction, congestive heart failure, cardiac failure, pericarditis, pulmonary edema, pulmonary hypertension, coronary artery disease
Vascular Disorders	phlebitis (eg., deep vein thrombosis), vasculitis, hypertension, hypertensive crisis, orthostatic hypotension, hemorrhage, circulatory collapse
Respiratory, Thoracic & Mediastinal Disorders	pulmonary congestion, hyperventilation, hypoxia, pleural effusion, pneumonia, asthma, lung disorder (eg., alveolitis, pneumonia aspiration, interstitial pneumonitis with fatal outcome, pulmonary fibrosis, obliterative bronchiolitis, respiratory arrest), respiratory failure, pulmonary embolism
Blood & Lymphatic System Disorders	hemolytic anemia, aplastic anemia, pancytopenia, bone marrow depression, leukopenia, neutropenia, febrile neutropenia, agranulocytosis, aPTT prolonged, thrombocytopenia, idiopathic thrombocytopenia purpura, thrombotic thrombocytopenic purpura, lymphocyte count decreased
Neoplasms Benign, Malignant and Unspecified (incl. Cysts & Polyps)	benign brain neoplasm, malignant hepatic neoplasm, non-Hodgkin's lymphoma

Note: causally related adverse events include those probably, possibly or remotely related to treatment; data are pooled from PEG-IFN α-2a monotherapy and combination therapy clinical trials in Hepatitis C, Hepatitis B and Oncology.

(continued)

Table 22 Uncommon (<1%) and Rare Adverse Events (Events Considered by the Investigator to be Causally Related to Treatment or Unknown) in Patients Receiving PEG-IFN α-2a Monotherapy or PEG-IFN α-2a Plus Ribavirin Combination Therapy (Cont.)

Body System	Adverse Event
Renal & Urinary Disorders	hematuria, micturition disorder, nephrolithiasis, renal impairment, nephrotic syndrome, glomerulonephritis membranous, renal failure
Reproductive System & Breast Disorders	cervicitis, menorrhagia, vaginal hemorrhage, uterine hemorrhage
Infections & Infestations	lower respiratory tract infection, bacterial infection (staphylococcal infection, streptococcal infection, abscess, tooth abscess, cellulitis, pyelonephritis, osteomyelitis, endocarditis), viral infection, candidal infection, tuberculosis, otitis, septic shock, skin infection, bacterial peritonitis, urinary tract infection, pleural infection
Pregnancy, Puerperium & Perinatal Conditions	unintended pregnancy, spontaneous abortion
General Disorders & Administration Site Conditions	injection site pain, drug withdrawal syndrome, chest pressure sensation, chest tightness, sudden death

Note: causally related adverse events include those probably, possibly or remotely related to treatment; data are pooled from PEG-IFN α-2a monotherapy and combination therapy clinical trials in Hepatitis C, Hepatitis B and Oncology.

Other serious adverse events reported in patients receiving IFN α-2a that were considered causally related or unknown by the investigator and are considered expected for PEG-IFN α-2a treatment are included in the following table.

Table 23 Other Serious Adverse Events that Have Been Reported and Considered Causally Related by the Investigator to Treatment or Unknown in Patients Receiving IFN α-2a

Body System	Adverse Event
Skin & Subcutaneous Tissue Disorders	rash papular, skin eruption, seborrhea, vitiligo, purpura
Musculoskeletal & Connective Tissue Disorders	arthropathy, myopathy
Nervous System Disorders	myasthenic syndrome, epilepsy, depressed level of consciousness, dementia, neuritis, parosmia, aphasia, monoplegia, cerebral ischemia
Psychiatric Disorders	mood swings
Eye Disorders	iritis, visual disturbance, conjunctivitis
Gastrointestinal Disorders	gingivitis, Crohn's disease, gastrointestinal hypermotility, epigastric discomfort, ischemic colitis, gastric ulcer, ileus paralytic, gastrointestinal obstruction,
Hepatobiliary Disorders	hepatic pain
Metabolism & Nutrition Disorders	hypokalemia
Cardiac Disorders	cardiorespiratory arrest, cyanosis
Vascular Disorders	Raynaud's phenomenon, shock, thrombosis, hematoma
Respiratory, Thoracic & Mediastinal Disorders	rhinorrhea, hemoptysis, dry throat
Blood & Lymphatic System Disorders	lymphocytosis, monocytosis, coagulopathy
Renal & Urinary Disorders	proteinuria
Reproductive System & Breast Disorders	menstruation irregular, sexual dysfunction

Note: causally related adverse events include those probably, possibly or remotely related to treatment; data are pooled from IFN α-2a clinical trials in Hepatitis C, Hepatitis B and Oncology.

(continued)

Table 23 Other Serious Adverse Events that Have Been Reported and Considered Causally Related by the Investigator to Treatment or Unknown in Patients Receiving IFN α-2a (Cont.)

Body System	Adverse Event
Neoplasms Benign, Malignant and Unspecified (incl. Cysts & Polyps)	neoplasm progression
General Disorders & Administration Site Conditions	edema, injection site irritation
Investigations	antinuclear antibodies, antibody positive, blood creatine phosphokinase increased, liver function test abnormal, red blood cell sedimentation rate increased, blood album decreased, blood creatinine increased, blood urea increased, blood lactate dehydrogenase increased

Note: causally related adverse events include those probably, possibly or remotely related to treatment; data are pooled from IFN α-2a clinical trials in Hepatitis C, Hepatitis B and Oncology.

Serious Adverse Events reported for IFN α-2a Oncology

Other serious adverse events reported in patients receiving IFN α-2a for oncology indications that were considered causally related or unknown by the investigators include: cardiac arrest, disorientation, hypotension, oliguria, anuria, abdominal distension, amnesia, apathy, aphonia, ataxia, bronchospasm, claustrophobia, dysarthria, dysphasia, ecchymosis, salivary hypersecretion, gait abnormal, gastric irritation, attention deficit, hyperactivity disorder, hypertriglyceridemia, dyskinesia, petechiae, psychomotor retardation, sedation, tachypnea, tooth disorder.

Serious Adverse Events reported for Ribavirin

Other serious adverse events reported in patients receiving ribavirin include: leukocytosis, eosinophilia, thrombocythemia, blood uric acid decreased, furuncle, gastric cancer, herpes zoster, hirsutism.

Manifestations of HCV Infection

There are several comanifestations of HCV that may occur during the natural course of HCV illness; these include both hepatic and extrahepatic manifestations. Extrahepatic comanifestations include essential cryoglobulinemia, membranous glomerulonephritis, and membranoproliferative glomerulonephritis. The occurrence of extrahepatic manifestations and progression of hepatic disease with subsequent need for hepatic transplantation will not engender expedited reporting to health authorities and principal investigators, as they are consistent with the disease. However, their occurrence will be reflected in subsequent updates of the IB and in periodic safety update reports sent to health authorities. An excess incidence of these conditions that suggests a drug effect will result in expedited reporting to health authorities and principal investigators.

7.4 Information for the Patient

Patients (male and female) must be advised of the teratogenic and embryocidal risks of ribavirin and must be instructed to use two forms of effective contraception simultaneously during combination therapy and for 6 months posttherapy. Patients (male and female) should be advised to notify the physician immediately if pregnancy does occur during treatment or during 6 months posttherapy. In case of pregnancy, patients or partner of the patients must be advised of the significant teratogenic risk of ribavirin therapy to the fetus.

Patients should be cautioned not to change to other formulations of pegylated interferon and ribavirin or switch to other α interferons without medical consultation, as a change in dose may be required.

Patients who develop dizziness, confusion, somnolence, or fatigue during treatment with PEG-IFN α-2a and ribavirin should be cautioned to avoid driving or operating machinery.

Patients should be informed regarding the potential benefits and risks attendant to the use of combination therapy with PEG-IFN α-2a and ribavirin. Instructions on appropriate home use should be given A puncture-resistant container for the disposal of used syringes and needles should be supplied to the patients. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of any needles and syringes. The full container should be disposed of according to the directions provided by the physician.

7.5 Drug Interactions

Please see section 5.1.4 for PEG-IFN α-2a drug interactions and section 6.3.1.3 for ribavirin drug interactions.

7.6 Overdosage

Overdoses with PEG-IFN α-2a involving at least two injections on consecutive days (instead of weekly interval) up to daily injections for 1 week (ie, 1260 µg/week) have been reported. None of these patients experienced unusual, serious or treatment-limiting events. Weekly doses of up to 540 and 630 µg have been administered in renal cell carcinoma and chronic myelogenous leukemia clinical trials, respectively. Dose-limiting toxicities were fatigue, elevated liver enzymes, neutropenia and thrombocytopenia consistent with interferon therapy. Hemodialysis and peritoneal dialysis are not effective in the event of a PEG-IFN overdose. No cases of overdose of ribavirin have been reported in clinical trials.

Appendix 1 Summary of PEG-IFN α-2a Clinical Studies

Indication and Type of Study	Protocol No Report No. (Status)	Population	Study Design	No. Centers and Location	Study Treatment Regimen, Dose, and Route of Administration	Number of Patients or Subjects Enrolled
Chronic Hepatitis C: PEG-IFN α-2a Monotherapy						
Adequate and Well-Controlled Studies Phase II/III and Phase III	NV15495 N-181406 (Completed)	CHC with cirrhosis or transition to cirrhosis	Randomized, open-label, parallel-group, multicenter 48-wk trt period followed by 24 wks untreated FU	30 centers Australia, Canada, UK, US	IFN α-2a 3 MIU tiw sc PEG-IFN α-2a 90 µg qw sc PEG-IFN α-2a 180 µg qw sc	271
	NV15496 N-181408 (Completed)	CHC with or without cirrhosis or transition to cirrhosis	Randomized, open-label, parallel-group, multicenter, 48-wk trt period followed by 24 wks untreated FU	52 centers Australia, Canada, France, UK, US	IFN α-2a 3 MIU tiw sc PEG-IFN α-2a 135 µg qw sc PEG-IFN α-2a 180 µg qw sc	639
	NV15497 N-181410 (Completed)	CHC with or without cirrhosis or transition to cirrhosis	Randomized, open-label, parallel-group, multicenter, 48-wk trt period followed by 24 wks untreated FU	36 centers Australia, Canada, Germany, Mexico, New Zealand, Spain, Switzerland, Taiwan, UK	IFN α-2a 6 MIU tiw for 12 wks, followed by IFN 3 MIU tiw for 36 wks sc PEG-IFN α-2a 180 µg qw sc	531
Dose-Finding Study Phase II	NV15489/ N-181405 (Completed)	CHC without cirrhosis	Randomized, open-label, ascending-dose, multicenter, 48-wk trt period followed by 24 wks untreated FU	11 centers US	IFN α-2a 3 MIU tiw sc PEG-IFN α-2a 45 µg qw sc PEG-IFN α-2a 90 µg qw sc PEG-IFN α-2a 180 µg qw sc PEG-IFN α-2a 270 µg qw sc	159

NOTE: ara-C = cytosine arabinoside; CHC = chronic hepatitis C; CML = chronic myelogenous leukemia; FU = follow-up; iv = intravenous; No. = number; PD = disease progression; PK = pharmacokinetic; po = oral; qd = once daily; qw = once weekly; RCC = renal cell cancer; sc = subcutaneous; trt = treatment; tiw = three times weekly; UK = United Kingdom; US = United States; wks = weeks.

(Continued)

Appendix 1 Summary of PEG-IFN α-2a Clinical Studies (Cont.)

Indication and Type of Study	Protocol No. Report No. (Status)	Population	Study Design	No. Centers Location	Study Treatment Regimen, Dose, and Route of Administration	Number of Patients or Subjects Enrolled
Chronic Hepatitis C: PEG-IFN + Ribavirin Combination Therapy						
Uncontrolled Phase II	NV15800 N-181407 (Completed)	CHC without cirrhosis	Randomized, open-label, parallel-group, 24-wk trt period; except 48 wks in genotype 1 responders at wk 24	2 centers US	PEG-IFN α-2a 180 µg qw sc + ribavirin 1000 mg, po (body weight <75 kg) or 1200 mg po (body weight ≥75 kg) Ribavirin taken with food Ribavirin taken without food	20
Adequate and Well-Controlled Studies Phase III	NV15801 1004549 (Completed)	CHC with or without cirrhosis or transition to cirrhosis	Randomized, partially blinded, active- and placebo-controlled, multicenter 48-wk trt period followed by 24 wks untreated FU	81 centers US, Europe, Australia, Taiwan, Brazil, Mexico	IFNα-2b 3 MIU tiw sc + ribavirin 1000 mg qd, po (body weight < 75 kg) or 1200 mg qd, po (body weight ≥ 75 kg) PEG-IFN α-2a 180 µg qw sc + ribavirin 1000 mg qd po (body weight < 75 kg) or 1200 mg, qd, sc (body weight ≥ 75 kg) PEG-IFN α-2a 180 µg qw sc + placebo qd po	1149

NOTE: ara-C = cytosine arabinoside; CHC = chronic hepatitis C; CML = chronic myelogenous leukemia; FU = follow-up; iv = intravenous; No. = number; PD = disease progression; PK = pharmacokinetic; po = oral; qd = once daily; qw = once weekly; RCC = renal cell cancer; sc = subcutaneous; trt = treatment; tiw = three times weekly; UK = United Kingdom; US = United States; wks = weeks.

(Continued)

Appendix 1 Summary of PEG-IFN α-2a Clinical Studies (Cont.)

Indication and Type of Study	Protocol No. Report No. (Status)	Population	Study Design	No. Centers Location	Study Treatment Regimen, Dose and Route of Administration	Number Of Patients or Subjects Enrolled
Chronic Hepatitis C: PEG-IFN + Ribavirin Combination Therapy (Continued)						
Adequate and Well-Controlled Studies Phase III	NV15942 1007456 (Completed)	CHC with or without cirrhosis or transition to cirrhosis	Randomized, parallel-group, multicenter; trt duration is double-blind through week 24 24-wk or 48-wk trt period followed by 24 wks untreated FU	99 centers Europe, North America, South America, Australia, New Zealand, Taiwan	PEG-IFN α-2a 180 µg, qw sc + ribavirin 800 mg qd po for 24 weeks PEG-IFN α-2a 180 µg, qw, sc + ribavirin 1000 mg, qd, po (body weight <75 kg) or 1200 mg, qd, po (body weight ≥75 kg), for 24 weeks PEG-IFN α-2a 180 µg, qw, sc + ribavirin 800 mg, qd, po for 48 weeks PEG-IFN α-2a 180 µg, qw, sc + ribavirin 1000 mg, qd, po (body weight <75 kg) or 1200 mg, qd, po (body weight ≥75 kg), for 48 weeks	1311
	NR15961 (Ongoing)	CHC coinfected with HIV	Randomized, partially blinded, active and placebo-controlled, parallel group 48-wk trt period followed by 24-wk untreated FU	Multicenter	PEG-IFN α-2a 180 µg qw sc + placebo qd po PEG-IFN α-2a 180 µg qw sc + ribavirin 800 mg qd po IFN α-2a 3 MIU tiw sc + ribavirin 800 mg qd po	868
	NR16071 (Ongoing)	CHC with persistently normal ALT levels	Randomized, open-label, parallel-group with an untreated group 24-wk or 48-wk trt period followed by 48 or 24 wks untreated FU	Multicenter	PEG-IFN α-2a 180 µg qw sc + ribavirin 800 mg qd po for 24 weeks followed by a 48-week untreated follow-up PEG-IFN α-2a 180 µg qw sc + ribavirin 800 mg qd po for 48 weeks followed by a 24-week untreated follow-up 72-week observation for the untreated control group	514

NOTE: ara-C = cytosine arabinoside; CHC = chronic hepatitis C; CML = chronic myelogenous leukemia; FU = follow-up; iv = intravenous; No. = number; PD = disease progression; PK = pharmacokinetic; po = oral; qd = once daily; qw = once weekly; RCC = renal cell cancer; sc = subcutaneous; trt = treatment; tiw = three times weekly; UK = United Kingdom; US = United States; wks = weeks.

(Continued)

Appendix 1 Summary of PEG-IFN α-2a Clinical Studies (Cont.)

Indication and Type of Study	Protocol No. Report No. (Status)	Population	Study Design	No. Centers Location	Study Treatment Regimen, Dose and Route of Administration	Number of Patients or Subjects Enrolled
Chronic Hepatitis B						
Dose-Finding Study Phase II	NV16037 1005189 (Completed)	CHB HbeAg positive disease	Randomized, open-label, multicenter, 24-wk trt period followed by 24 wk untreated FU	18 centers in Australia, China, New Zealand, Taiwan, Thailand	IFN α-2a 4.5 MIU tiw sc PEG-IFN α-2a 90 µg qw sc PEG-IFN α-2a 180 µg qw sc PEG-IFN α-2a 270 µg qw sc	194
Adequate and Well-Controlled Studies Phase III	WV16240 (ongoing)	CHB, HbeAg positive disease	Randomized, open label PEG-IFN, double blind combination therapy, multicenter, 48-wk trt period followed by 24 wk untreated FU	67 centers in Asia-Pacific, Europe, North and South America	PEG-IFN α-2a 180 µg qw sc + placebo qd po PEG-IFN α-2a 180 µg qw sc + Lamivudine 100 mg qd po Lamivudine 100 mg qd po	820
	WV16241 (ongoing)	CHB, anti-Hbe positive disease	Randomized, open label PEG-IFN, double blind combination therapy, multicenter, 48-wk trt period followed by 24 wk untreated FU	54 centers in Asia-Pacific, Europe and Canada.	PEG-IFN α-2a 180 µg qw sc + placebo qd po PEG-IFN α-2a 180 µg qw sc + Lamivudine 100 mg qd po Lamivudine 100 mg qd po	552

NOTE CHB = chronic hepatitis B; FU = follow-up; iv = intravenous; No. = number; po = oral; qd = once daily; qw = once weekly; sc = subcutaneous; trt = treatment; wks = weeks.

Appendix 1 Summary of PEG-IFN α-2a Clinical Studies (Cont.)

Indication and Type of Study	Protocol No. Report No. (Status)	Population	Study Design	No. Centers Location	Study Treatment Regimen, Dose and Route of Administration	Number of Patients or Subjects Enrolled
Chronic Myelogenous Leukemia						
Dose-Finding (Phase I)	NO15764 (Ongoing)	CML	Open-label, dose escalation, nonrandomized 48-wk trt period followed by 8 wks untreated FU	1 center US	PEG-IFN α-2a 270 µg qw sc PEG-IFN α-2a 360 µg qw sc PEG-IFN α-2a 450 µg qw sc PEG-IFN α-2a 540 µg qw sc PEG-IFN α-2a 630 µg qw sc PEG-IFN α-2a 450 µg qw,sc + ara-C 10 mg qd sc PEG-IFN α-2a 540 µg qw sc + ara-C 10 mg qd sc PEG-IFN α-2a 540 µg qw sc + ara-C 20 mg/M^2 for 10 days/mo sc	45
Controlled trial (Phase III)	NO16006 (Ongoing)	CML	Open label, parallel arm, randomized 12-month treatment and extended treatment for responders in the first 12 months; 4 wks follow-up for safety and 5 years follow-up for survival	Multicenter	PEG-IFN α-2a 450 µg qw sc IFN 9 MIU qd	146
Renal Cell Carcinoma						
Dose-Finding (Phase I/II)	NO15753 (Completed)	Advanced or metastatic RCC	Open-label, dose escalation (Phase I), nonrandomized 24-wk trt period followed by 4 wks untreated FU Pts without signs of PD at end of trt period continued until PD (Phase II)	**Phase I:** 1 center US **Phase II:** 8 centers Australia, Canada, France, Germany, UK, US	**Phase I:** PEG-IFN α-2a 180 µg qw sc PEG-IFN α-2a 270 µg qw sc PEG-IFN α-2a 360 µg qw sc PEG-IFN α-2a 450 µg qw sc PEG-IFN α-2a 540 µg qw sc **Phase II:** PEG-IFN α-2a 450 µg qw sc	67

NOTE: ara-C = cytosine arabinoside; CHC = chronic hepatitis C; CML = chronic myelogenous leukemia; FU = follow-up; iv = intravenous; No. = number; PD = disease progression; PK = pharmacokinetic; po = oral; qd = once daily; qw = once weekly; RCC = renal cell cancer; sc = subcutaneous; trt = treatment; tiw = three times weekly; UK = United Kingdom; US = United States; wks = weeks.
(Continued)

Appendix 1 Summary of PEG-IFN α-2a Clinical Studies (Cont.)

Indication and Type of Study	Protocol No. Report No. (Status)	Population	Study Design	No. Centers Location	Study Treatment Regimen, Dose and Route of Administration	Number of Patients or Subjects Enrolled
Malignant Melanoma						
Dose-Finding (Phase II)	NO16007 (Ongoing)	Metastatic malignant melanoma	Open-label, randomized, parallel group 24-wk treatment, optional extended therapy after wk 24	Multicenter	PEG-IFN α-2a 180 µg qw sc PEG-IFN α-2a 360 µg qw sc PEG-IFN α-2a 450 µg qw sc	150
Clinical Pharmacology Studies: PEG-IFN α-2a						
Entry-into-human (Phase I)	NP15330 N-181328 (Completed)	Healthy volunteers	Double-blind, serial ascending dose. IFN 18 MIU administered open-label	1 center UK	IFN α-2a 3 MIU sc single dose PEG-IFN α-2a 45 µg sc single dose PEG-IFN 135 α-2a µg sc single dose PEG-IFN α-2a 270 µg sc single dose IFN α-2a 18 MIU sc single dose	92
Absolute Bioavailability (Phase I)	NP15537 N-181142 (Completed)	Healthy volunteers	Open-label, randomized, two-way crossover, 35-day washout period	1 center UK	PEG-IFN α-2a 90 µg iv single dose PEG-IFN α-2a 180 µg sc single dose	20
Relative Bioavailability (Phase I)	NP15762 N-181460 (Completed)	Healthy volunteers	Open-label, randomized, parallel-group	1 center UK	PEG-IFN α-2a 90 µg iv single dose PEG-IFN α-2a 180 µg sc single dose, needle injection PEG-IFN α-2a 180 µg sc single dose, needle-free injection	54

NOTE: ara-C = cytosine arabinoside; CHC = chronic hepatitis C; CML = chronic myelogenous leukemia; FU = follow-up; iv = intravenous; No. = number; PD = disease progression; PK = pharmacokinetic; po = oral; qd = once daily; qw = once weekly; RCC = renal cell cancer; sc = subcutaneous; trt = treatment; tiw = three times weekly; UK = United Kingdom; US = United States; wks = weeks.

(Continued)

Appendix 1 Summary of PEG-IFN α-2a Clinical Studies (Cont.)

Indication and Type of Study	Protocol No. Report No., and Status	Population	Study Design	No. Centers Location	Study Treatment Regimen, Dose and Route of Administration	Number of Patients or Subjects Enrolled
Clinical Pharmacology Studies: PEG-IFN α-2a (Continued)						
Bioequivalence and Relative Bioavailability (Phase I)	NP15989 N-181607 (Completed)	Healthy volunteers	Open-label, randomized, parallel-group	2 centers UK	PEG-IFN α-2a 180 µg sc single dose, needle injection to abdomen or thigh PEG-IFN α-2a 180 µg sc single dose, needle-free injection to abdomen or thigh	173
Gender (Phase I)	NP15538 N-181141 (Completed)	Healthy volunteers	Open-label, nonrandomized	1 center UK	PEG-IFN α-2a 180 µg sc single dose	24
Renal function (Phase I)	NP15579 N-181145 (Completed)	Healthy and renally impaired volunteers	Open-label, nonrandomized, sequential	1 center UK	PEG-IFN α-2a 90 µg sc single dose Healthy volunteers Renally impaired volunteers	30
Japanese PK/PD study (Phase I)	JP15722 N181609 (Completed)	Healthy volunteers	Open-label, nonrandomized, parallel-group	1 center Japan	PEG-IFN α-2a 90 µg sc single dose PEG-IFN α-2a 180 µg sc single dose PEG-IFN α-2a 270 µg single dose	36
Age (Phase I)	NP15580 N-181144 (Completed)	Healthy volunteers	Open-label, nonrandomized, parallel-group	1 center UK	PEG-IFN α-2a 180 µg sc single dose Young volunteers (18-25 years) Elderly volunteers (>60 years)	24
Drug interaction using CYP P450 probes (Phase I, 3 parts)	NP15581 N-181143 (Completed)	Healthy volunteers who were extensive metabolizers	Open-label, nonrandomized, multiple-dose CYP P450 Probes: days 1 and 37 PEG-IFN α-2a: 4 weeks qw starting on day 15	1 center UK	CYP P450 Probes: Dapsone, 100 mg po Debrisoquine, 10 mg po Mephenytoin, 100 mg po Theophylline, 125 mg po Tolbutamide, 500 mg po PEG-IFN α-2a 180 µg sc qw	16

NOTE: ara-C = cytosine arabinoside; CHC = chronic hepatitis C; CML = chronic myelogenous leukemia; FU = follow-up; iv = intravenous; No. = number; PD = disease progression; PK = pharmacokinetic; po = oral; qd = once daily; qw = once weekly; RCC = renal cell cancer; sc = subcutaneous; trt = treatment; tiw = three times weekly; UK = United Kingdom; US = United States; wks = weeks. (Continued)

Appendix 1 Summary of PEG-IFN α-2a Clinical Studies (Cont.)

Indication and Type of Study	Protocol No. Report No., and Status	Population	Study Design	No. Centers Location	Study Treatment Regimen, Dose and Route of Administration	Number of Patients or Subjects Enrolled
Clinical Pharmacology Studies: Ribavirin						
Bioequivalence	BP16131 B-113413 (Completed)	Current or previous CHC	Open-label, single dose, randomized, crossover (7 to 10 days washout)	Single center France	Treatment A: Rebetol® 600 mg po Treatment B: Virazole® 600 mg po	46
Relative bioavailability	NP15904 1003974 (Completed)	CHC	Open-label, single-dose, randomized, parallel group	10 centers US	Roche ribavirin tablets (clinical lot C193518) 600 mg po Roche ribavirin tablets (clinical lot C194999) 600 mg po Schering ribavirin capsules 600 mg po	120
Bioequivalence	BP16320 1003761 (Completed)	Current or previous CHC	Open-label, single dose, randomized, crossover (7 to 10 days washout)	Single center France	Roche ribavirin tablets (lot C199970) 600 mg po Schering ribavirin capsules 600 mg po	40
Food effect, bioavailability	NR16230 1003972 (Completed)	Current or previous CHC	Open-label, single-dose, randomized, crossover (7 to 10 days washout)	Single center US	Roche ribavirin (intended for commercial use) 600 mg po fasted Roche ribavirin (intended for commercial use) 600 mg po fed	52
Bioequivalence	NR16231 1003973 (Completed)	Current or previous CHC	Open-label, single-dose, randomized, crossover (7 to 10 days washout)	Single center US	Roche ribavirin (clinical trial material) 600 mg po Roche ribavirin (commercial product) 600 mg po	47

NOTE: ara-C = cytosine arabinoside; CHC = chronic hepatitis C; CML = chronic myelogenous leukemia; FU = follow-up; iv = intravenous; No. = number; PD = disease progression; PK = pharmacokinetic; po = oral; qd = once daily; qw = once weekly; RCC = renal cell cancer; sc = subcutaneous; trt = treatment; tiw = three times weekly; UK = United Kingdom; US = United States; wks = weeks.

Appendix 2 Toxicology Studies with PEG-IFN α-2a

Reference	Study Type	Species	Duration and Design	Dose, Route and Regimen
[4.22]	Acute toxicity	Cynomolgus monkey (1/sex)	Single dose	6750 µg/kg sc
[4.23]	Acute toxicity	Cynomolgus monkey (1/sex/group)	Single dose	0, 15, 70, 300 µg/kg iv
[4.14]	Subchronic toxicity	Cynomolgus monkey (3/sex/group)	4 weeks	0, 15, 187.5, 562.5 µg/kg sc, twice weekly
[4.15]	Subchronic toxicity	Cynomolgus monkey (5/sex/group)	4 weeks + 4-week recovery	0, 15, 100, 600 µg/kg sc, daily
[4.16]	Subchronic toxicity	Cynomolgus monkey (5/sex/group)	13 weeks + 4-week recovery	0, 15, 50, 150 µg/kg sc, twice weekly
[4.24]	Mutagenicity	in vitro	Ames test	11.25 to 1125 µg/plate
[4.25]	Genotoxicity	in vitro	Chromosome aberrations	12.5 to 50 µg/mL
[4.16]	Reproductive toxicity (pilot study)	Cynomolgus monkey (2 females/group)	1 menstrual cycle	100, 300, 600 µg/kg sc, three times weekly; IFN α-2a (positive control) 25 MIU/kg/day im, daily
[4.1]	Reproductive toxicity	Cynomolgus monkey (5 females/group)	1 menstrual cycle	0, 100, 600 µg/kg sc, three times weekly; IFN α-2a (positive control) 25 MIU/kg/day im, daily

In all studies reported here, PEG-IFN α-2a was formulated in a vehicle containing polysorbate 80 and 20 mM acetate buffer (pH 5.0 or 6.0).

Appendix 3 Summary of Marked Laboratory Abnormalities during Treatment and 8 Weeks Posttreatment in Studies NV15489, NV15495, NV15496, and NV15497 in Patients with Hepatitis C

Laboratory abnormality	IFN α-2a 3 MIU N = 322[a]	IFN α-2a 6 MIU/ 3 MIU N = 260[a]	PEG-IFN α-2a 135 μg N = 215	PEG-IFN α-2a 180 μg N = 604
Hematology				
Hematocrit (fraction) – low	16 (5%)	8 (3%)	35 (16%)	108 (18%)
WBC (10^9/L) – low	80 (25%)	68 (26%)	125 (58%)	393 (65%)
Lymphocytes (10^9/L) – low	106 (33%)	100 (38%)	99 (46%)	288 (48%)
Liver function				
ASAT (SGOT) (u/L) – high	97 (30%)	66 (25%)	52 (24%)	152 (25%)
Miscellaneous				
Calcium (mmol/L) – low	22 (7%)	30 (12%)	15 (7%)	68 (11%)
Phosphate (mmol/L) – low	75 (23%)	46 (18%)	67 (31%)	146 (24%)
Triglycerides (mmol/L) – high	106 (33%)	94 (36%)	96 (45%)	272 (45%)

[a] These measurements were not performed in one patient.

Appendix 4 Summary of Adverse Events with Frequency ≥ 5% in the PEG-IFN α-2a 180-ug Group in Studies NV15489, NV15495, NV15496, and NV15497 in Patients with Hepatitis C

Adverse Event	PEG-IFN 45 ug N = 20 No. (%)	PEG-IFN 90 ug N = 116 No. (%)	PEG-IFN 135 ug N = 215 No. (%)	PEG-IFN 180 ug N = 604 No. (%)	PEG-IFN 270 ug N = 40 No. (%)
HEADACHE	8 (40)	64 (55)	124 (58)	351 (58)	21 (53)
FATIGUE	14 (70)	68 (59)	112 (52)	354 (59)	28 (70)
MYALGIA	8 (40)	48 (41)	78 (36)	239 (40)	19 (48)
RIGORS	1 (5)	40 (34)	75 (35)	206 (34)	20 (50)
PYREXIA	3 (15)	31 (27)	64 (30)	228 (38)	13 (33)
ARTHRALGIA	4 (20)	41 (35)	68 (32)	203 (34)	14 (35)
NAUSEA	9 (45)	32 (28)	64 (30)	164 (27)	12 (30)
ALOPECIA	1 (5)	20 (17)	39 (18)	145 (24)	10 (25)
INSOMNIA	5 (25)	21 (18)	44 (20)	145 (24)	13 (33)
DIARRHOEA	5 (25)	30 (26)	53 (25)	153 (25)	15 (38)
ABDOMINAL PAIN	8 (40)	29 (25)	46 (21)	144 (24)	12 (30)
INJECTION SITE REACTION	10 (50)	35 (30)	55 (26)	134 (22)	15 (38)
DEPRESSION	6 (30)	29 (25)	42 (20)	135 (22)	16 (40)
IRRITABILITY	7 (35)	27 (23)	46 (21)	97 (16)	13 (33)
PAIN	6 (30)	25 (22)	49 (23)	93 (15)	10 (25)
ANOREXIA	3 (15)	19 (16)	19 (9)	117 (19)	6 (15)
BACK PAIN	0	17 (15)	39 (18)	103 (17)	6 (15)
DIZZINESS (EXC VERTIGO)	2 (10)	23 (20)	27 (13)	114 (19)	7 (18)
PRURITUS	2 (10)	18 (16)	29 (13)	101 (17)	5 (13)
DERMATITIS	3 (15)	8 (7)	29 (13)	84 (14)	11 (28)
CONCENTRATION IMPAIRMENT	6 (30)	10 (9)	16 (7)	52 (9)	13 (33)
NAUSEA AND VOMITING	4 (20)	12 (10)	17 (8)	51 (8)	1 (3)
COUGH	1 (5)	12 (10)	19 (9)	60 (10)	4 (10)
SORE THROAT	4 (20)	11 (9)	26 (12)	48 (8)	5 (13)
ANXIETY	1 (5)	13 (11)	15 (7)	45 (7)	8 (20)
NASOPHARYNGITIS	2 (10)	4 (3)	18 (8)	51 (8)	5 (13)
SWEATING INCREASED	2 (10)	4 (3)	14 (7)	38 (6)	4 (10)
RASH	0	5 (4)	17 (8)	47 (8)	1 (3)
ASTHENIA	0	0	31 (14)	31 (5)	0
INFLUENZA	2 (10)	7 (6)	9 (4)	37 (6)	1 (3)
DRY MOUTH	2 (10)	3 (3)	9 (4)	49 (8)	3 (8)
MUSCLE CRAMPS	1 (5)	11 (9)	12 (6)	39 (6)	2 (5)
PARAESTHESIA	0	8 (7)	16 (7)	35 (6)	1 (3)
MEMORY IMPAIRMENT	2 (10)	6 (5)	7 (3)	38 (6)	7 (18)
SINUSITIS	2 (10)	15 (13)	11 (5)	28 (5)	4 (10)
DRY SKIN	3 (15)	3 (3)	13 (6)	37 (6)	4 (10)
VISION BLURRED	1 (5)	4 (3)	9 (4)	36 (6)	5 (13)
UPPER RESPIR. TRACT INFECTION	1 (5)	6 (5)	10 (5)	30 (5)	4 (10)
HYPOAESTHESIA	2 (10)	3 (3)	9 (4)	31 (5)	1 (3)
WEIGHT DECREASE	0	4 (3)	9 (4)	29 (5)	4 (10)
DYSPNOEA	0	3 (3)	6 (3)	31 (5)	1 (3)
URINARY TRACT INFECTION	1 (5)	2 (2)	6 (3)	28 (5)	2 (5)

NOTE: Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.
AE13 16DEC1999:11:31:27

Appendix 5 Treatment-Related (Remotely, Possibly, or Probably Related) Serious Adverse Events during Treatment and within 56 Days after Treatment in Studies NV15489, NV15495, NV15496, and NV15497 in Patients with Hepatitis C

Body System/ Adverse Event	IFN 3 MIU/ 6 MIU N = 584 No. (%)	PEG-IFN 45 ug N = 20 No. (%)	PEG-IFN 90 ug N = 116 No. (%)	PEG-IFN 135 ug N = 215 No. (%)	PEG-IFN 180 ug N = 604 No. (%)	PEG-IFN 270 ug N = 40 No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	12 (2)	-	3 (3)	7 (3)	34 (6)	2 (5)
Total Number of AEs	17	-	4	8	44	2
PSYCHIATRIC DISORDERS						
Total Pts With at Least one AE	5 (1)	-	1 (1)	-	9 (1)	-
DEPRESSION NOS	1 (<1)	-	-	-	6 (1)	-
SUICIDAL IDEATION	1 (<1)	-	-	-	2 (<1)	-
SUICIDE ATTEMPT	1 (<1)	-	1 (1)	-	1 (<1)	-
PSYCHOSIS NOS	1 (<1)	-	-	-	1 (<1)	-
DEPRESSED MOOD	1 (<1)	-	-	-	-	-
DEPRESSION AGGRAVATED	1 (<1)	-	-	-	-	-
DRUG ABUSE	-	-	1 (1)	-	-	-
HYSTERIA	-	-	-	-	1 (<1)	-
MANIA	-	-	-	-	1 (<1)	-
Total Number of AEs	6	-	2	-	12	-
INFECTIONS & INFESTATIONS						
Total Pts With at Least one AE	-	-	1 (1)	2 (1)	6 (1)	-
PNEUMONIA NOS	-	-	-	2 (1)	-	-
CHOLANGITIS ACUTE NOS	-	-	-	-	1 (<1)	-
GASTROENTERITIS NOS	-	-	-	-	1 (<1)	-
LOWER RESPIRATORY TRACT INFECTION NOS	-	-	1 (1)	-	-	-
STREPTOCOCCAL INFECTION NOS	-	-	-	-	1 (<1)	-
TOOTH ABSCESS	-	-	-	-	1 (<1)	-
URINARY TRACT INFECTION NOS	-	-	-	-	1 (<1)	-
VIRAL INFECTION NOS	-	-	-	-	1 (<1)	-
Total Number of AEs	-	-	1	2	6	-
GASTROINTESTINAL DISORDERS						
Total Pts With at Least one AE	4 (1)	-	1 (1)	-	3 (<1)	-
ABDOMINAL PAIN NOS	1 (<1)	-	-	-	2 (<1)	-
ENTERITIS	1 (<1)	-	-	-	-	-
HAEMATEMESIS	-	-	-	-	1 (<1)	-
NAUSEA	1 (<1)	-	-	-	-	-
OESOPHAGEAL VARICES HAEMORRHAGE	-	-	1 (1)	-	-	-
PANCREATITIS NOS	1 (<1)	-	-	-	-	-
Total Number of AEs	4	-	1	-	3	-

AE11 08DEC1999:10:37:38

(continued)

Appendix 5 Treatment-Related (Remotely, Possibly, or Probably Related) Serious Adverse Events during Treatment and within 56 Days after Treatment in Studies NV15489, NV15495, NV15496, and NV15497 in Patients with Hepatitis C (Cont.)

Body System/ Adverse Event	IFN 3 MIU/ 6 MIU N = 584 No. (%)	PEG-IFN 45 ug N = 20 No. (%)	PEG-IFN 90 ug N = 116 No. (%)	PEG-IFN 135 ug N = 215 No. (%)	PEG-IFN 180 ug N = 604 No. (%)	PEG-IFN 270 ug N = 40 No. (%)
GENERAL DISORDERS						
Total Pts With at Least one AE	3 (1)	-	-	1 (<1)	2 (<1)	-
CHEST PAIN NOS	-	-	-	1 (<1)	1 (<1)	-
HERNIA NOS	1 (<1)	-	-	-	-	-
INTERMITTENT PYREXIA	1 (<1)	-	-	-	-	-
PYREXIA	-	-	-	-	1 (<1)	-
RIGORS	1 (<1)	-	-	-	-	-
Total Number of AEs	3	-	-	1	2	-
DISORDERS OF BLOOD & THE LYMPHATIC SYSTEM						
Total Pts With at Least one AE	1 (<1)	-	-	-	4 (1)	-
IDIOPATHIC THROMBOCYTOPENIC PURPURA	1 (<1)	-	-	-	1 (<1)	-
THROMBOCYTOPENIA	-	-	-	-	2 (<1)	-
NEUTROPENIA	-	-	-	-	1 (<1)	-
Total Number of AEs	1	-	-	-	4	-
NEUROLOGICAL DISORDERS						
Total Pts With at Least one AE	1 (<1)	-	-	1 (<1)	2 (<1)	1 (3)
COMA NOS	-	-	-	-	1 (<1)	-
HEADACHE NOS	1 (<1)	-	-	-	-	-
PERIPHERAL NEUROPATHY NOS	-	-	-	1 (<1)	-	-
POLYNEUROPATHY NOS	-	-	-	-	-	1 (3)
SYNCOPE	-	-	-	-	1 (<1)	-
Total Number of AEs	1	-	-	1	2	1
HEPATO-BILIARY DISORDERS						
Total Pts With at Least one AE	-	-	-	-	4 (1)	-
HEPATIC FUNCTION ABNORMAL NOS	-	-	-	-	1 (<1)	-
HEPATITIS NOS	-	-	-	-	1 (<1)	-
LIVER FATTY	-	-	-	-	1 (<1)	-
TRANSAMINASE NOS INCREASED	-	-	-	-	1 (<1)	-
Total Number of AEs	-	-	-	-	4	-
CARDIAC DISORDERS						
Total Pts With at Least one AE	1 (<1)	-	-	-	2 (<1)	-
ATRIAL FLUTTER	-	-	-	-	1 (<1)	-
CORONARY ARTERY DISEASE NOS	1 (<1)	-	-	-	-	-
ENDOCARDITIS NOS	-	-	-	-	1 (<1)	-
Total Number of AEs	1	-	-	-	2	-

AE11 08DEC1999:10:37:38

(continued)

Appendix 5 Treatment-Related (Remotely, Possibly, or Probably Related) Serious Adverse Events during Treatment and within 56 Days after Treatment in Studies NV15489, NV15495, NV15496, and NV15497 in Patients with Hepatitis C (Cont.)

Body System/ Adverse Event	IFN 3 MIU/ 6 MIU N = 584 No. (%)	PEG-IFN 45 ug N = 20 No. (%)	PEG-IFN 90 ug N = 116 No. (%)	PEG-IFN 135 ug N = 215 No. (%)	PEG-IFN 180 ug N = 604 No. (%)	PEG-IFN 270 ug N = 40 No. (%)
MUSCULOSKELETAL, CONNECTIVE TISSUE & BONE DISORDERS						
Total Pts With at Least one AE	-	-	-	-	2 (<1)	1 (3)
ARTHRITIS NOS	-	-	-	-	1 (<1)	-
MYOSITIS	-	-	-	-	1 (<1)	-
SYNOVITIS	-	-	-	-	-	1 (3)
Total Number of AEs	-	-	-	-	2	1
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS						
Total Pts With at Least one AE	-	-	-	1 (<1)	1 (<1)	-
LUNG DISORDER NOS	-	-	-	1 (<1)	-	-
PNEUMONITIS ASPIRATION	-	-	-	-	1 (<1)	-
RESPIRATORY ARREST (EXC NEONATAL)	-	-	-	-	1 (<1)	-
Total Number of AEs	-	-	-	1	2	-
SKIN & SUBCUTANEOUS TISSUE DISORDERS						
Total Pts With at Least one AE	-	-	-	1 (<1)	1 (<1)	-
ALOPECIA	-	-	-	1 (<1)	-	-
URTICARIA AGGRAVATED	-	-	-	-	1 (<1)	-
Total Number of AEs	-	-	-	1	1	-
VASCULAR DISORDERS						
Total Pts With at Least one AE	-	-	-	-	2 (<1)	-
CEREBRAL HAEMORRHAGE	-	-	-	-	1 (<1)	-
PULMONARY EMBOLISM	-	-	-	-	1 (<1)	-
Total Number of AEs	-	-	-	-	2	-
DISORDERS OF METABOLISM & NUTRITION						
Total Pts With at Least one AE	-	-	-	-	1 (<1)	-
DIABETIC CONTROL IMPAIRED	-	-	-	-	1 (<1)	-
Total Number of AEs	-	-	-	-	1	-
DISORDERS OF THE EYE						
Total Pts With at Least one AE	-	-	-	-	1 (<1)	-
CORNEAL ULCER	-	-	-	-	1 (<1)	-
Total Number of AEs	-	-	-	-	1	-

AE11 08DEC1999:10:37:38

(continued)

Appendix 5 Treatment-Related (Remotely, Possibly, or Probably Related) Serious Adverse Events during Treatment and within 56 Days after Treatment in Studies NV15489, NV15495, NV15496, and NV15497 in Patients with Hepatitis C (Cont.)

Body System/ Adverse Event	IFN 3 MIU/ 6 MIU N = 584 No. (%)	PEG-IFN 45 ug N = 20 No. (%)	PEG-IFN 90 ug N = 116 No. (%)	PEG-IFN 135 ug N = 215 No. (%)	PEG-IFN 180 ug N = 604 No. (%)	PEG-IFN 270 ug N = 40 No. (%)
DISORDERS OF THE REPRODUCTIVE SYSTEM AND BREAST						
Total Pts With at Least one AE	-	-	-	1 (<1)	-	-
DYSFUNCTIONAL UTERINE BLEEDING	-	-	-	1 (<1)	-	-
Total Number of AEs	-	-	-	1	-	-
ENDOCRINE DISORDERS						
Total Pts With at Least one AE	-	-	-	1 (<1)	-	-
HYPERTHYROIDISM	-	-	-	1 (<1)	-	-
Total Number of AEs	-	-	-	1	-	-
INJURY & POISONING						
Total Pts With at Least one AE	1 (<1)	-	-	-	-	-
OVERDOSE NOS	1 (<1)	-	-	-	-	-
Total Number of AEs	1	-	-	-	-	-

AE11 08DEC1999:10:37:38

Appendix 6 Summary of Adverse Events by Body System during Treatment and for 8 Weeks Posttreatment in Study NV16037 in Patients with Hepatitis B

Body System/ Adverse Event	ROFERON-A 4.5 MIU N = 50 No. (%)	PEGYLATED INTERFERON 90mcg N = 48 No. (%)	PEGYLATED INTERFERON 180mcg N = 45 No. (%)	PEGYLATED INTERFERON 270mcg N = 48 No. (%)
ALL BODY SYSTEMS				
Total Pts with at Least one AE	48 (96)	45 (94)	44 (98)	48 (100)
Total Number of AEs	224	215	239	276
GENERAL DISORDERS				
Total Pts With at Least one AE	45 (90)	34 (71)	37 (82)	42 (88)
PYREXIA	36 (72)	25 (52)	26 (58)	34 (71)
FATIGUE	14 (28)	14 (29)	10 (22)	13 (27)
ASTHENIA	5 (10)	1 (2)	4 (9)	4 (8)
FEELING COLD	4 (8)	1 (2)	2 (4)	4 (8)
MALAISE	4 (8)	-	5 (11)	1 (2)
PAIN NOS	2 (4)	-	2 (4)	4 (8)
RIGORS	4 (8)	-	1 (2)	3 (6)
INJECTION SITE INFLAMMATION	1 (2)	2 (4)	2 (4)	1 (2)
INJECTION SITE PAIN	-	2 (4)	2 (4)	2 (4)
LETHARGY	1 (2)	1 (2)	2 (4)	1 (2)
INJECTION SITE IRRITATION	1 (2)	-	-	1 (2)
CHEST PRESSURE SENSATION	1 (2)	-	-	-
FEELING HOT AND COLD	-	-	1 (2)	-
INFLAMMATION LOCALISED	-	1 (2)	-	-
INJECTION SITE OEDEMA	-	1 (2)	-	-
PAIN IN LIMB	-	1 (2)	-	-
VESICLE	-	1 (2)	-	-
Total Number of AEs	73	50	57	68

Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.
AE11 23NOV2001:10:27:44

(continued)

Appendix 6 Summary of Adverse Events by Body System during Treatment and for 8 Weeks Posttreatment in Study NV16037 in Patients with Hepatitis B (Cont.)

Body System/ Adverse Event	ROFERON-A 4.5 MIU N = 50 No. (%)	PEGYLATED INTERFERON 90mcg N = 48 No. (%)	PEGYLATED INTERFERON 180mcg N = 45 No. (%)	PEGYLATED INTERFERON 270mcg N = 48 No. (%)
NEUROLOGICAL DISORDERS				
Total Pts With at Least one AE	19 (38)	30 (63)	26 (58)	24 (50)
HEADACHE NOS	13 (26)	22 (46)	17 (38)	22 (46)
INSOMNIA	8 (16)	8 (17)	9 (20)	5 (10)
DIZZINESS (EXC VERTIGO)	5 (10)	9 (19)	7 (16)	7 (15)
WEAKNESS	-	-	4 (9)	3 (6)
CONCENTRATION IMPAIRMENT	1 (2)	-	2 (4)	1 (2)
PARAESTHESIA	-	1 (2)	1 (2)	-
SYNCOPE	-	1 (2)	1 (2)	-
FACIAL PALSY	-	1 (2)	-	-
MEMORY IMPAIRMENT	-	-	1 (2)	-
MIGRAINE	-	-	-	1 (2)
PERIPHERAL NEUROPATHY NOS	-	-	-	1 (2)
PHOTOPHOBIA	-	-	-	1 (2)
POLYNEUROPATHY NOS	-	1 (2)	-	-
TASTE DISTURBANCE	-	-	-	1 (2)
Total Number of AEs	27	43	42	42
MUSCULOSKELETAL, CONNECTIVE TISSUE & BONE DISORDERS				
Total Pts With at Least one AE	27 (54)	20 (42)	18 (40)	25 (52)
MYALGIA	21 (42)	18 (38)	16 (36)	22 (46)
ARTHRALGIA	6 (12)	1 (2)	2 (4)	3 (6)
BACK PAIN	1 (2)	1 (2)	2 (4)	2 (4)
BONE PAIN	-	-	1 (2)	2 (4)
MUSCLE SPASMS	1 (2)	-	-	-
TENDONITIS	1 (2)	-	-	-
Total Number of AEs	30	20	21	29

Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.
AE11 23NOV2001:10:27:44

(continued)

Appendix 6 Summary of Adverse Events by Body System during Treatment and for 8 Weeks Posttreatment in Study NV16037 in Patients with Hepatitis B (Cont.)

Body System/ Adverse Event	ROFERON-A 4.5 MIU N = 50 No. (%)	PEGYLATED INTERFERON 90mcg N = 48 No. (%)	PEGYLATED INTERFERON 180mcg N = 45 No. (%)	PEGYLATED INTERFERON 270mcg N = 48 No. (%)
GASTROINTESTINAL DISORDERS				
Total Pts With at Least one AE	18 (36)	24 (50)	25 (56)	22 (46)
DIARRHOEA NOS	4 (8)	4 (8)	8 (18)	8 (17)
NAUSEA	4 (8)	5 (10)	8 (18)	7 (15)
ABDOMINAL PAIN UPPER	7 (14)	5 (10)	4 (9)	2 (4)
ABDOMINAL PAIN NOS	4 (8)	3 (6)	2 (4)	3 (6)
VOMITING NOS	1 (2)	1 (2)	3 (7)	6 (13)
DRY MOUTH	3 (6)	1 (2)	3 (7)	3 (6)
DYSPEPSIA	3 (6)	3 (6)	2 (4)	1 (2)
CONSTIPATION	1 (2)	-	4 (9)	2 (4)
FEELING OF GASTROINTESTINAL FULLNESS	-	3 (6)	3 (7)	-
MOUTH ULCERATION	1 (2)	-	-	4 (8)
GINGIVAL BLEEDING	2 (4)	1 (2)	-	1 (2)
ABDOMINAL DISTENSION	-	-	1 (2)	1 (2)
DYSPEPSIA AGGRAVATED	-	1 (2)	-	1 (2)
GASTRITIS	-	1 (2)	-	1 (2)
HAEMORRHOIDS	1 (2)	-	1 (2)	-
NAUSEA AND VOMITING	2 (4)	-	-	-
APPENDICITIS	-	-	1 (2)	-
DUODENAL ULCER	-	1 (2)	-	-
ENTERITIS	-	1 (2)	-	-
IRRITABLE BOWEL SYNDROME	-	-	1 (2)	-
LOOSE STOOLS	1 (2)	-	-	-
TOOTHACHE	-	1 (2)	-	-
Total Number of AEs	34	31	41	40

Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.
AE11 23NOV2001:10:27:44

(continued)

Appendix 6 Summary of Adverse Events by Body System during Treatment and for 8 Weeks Posttreatment in Study NV16037 in Patients with Hepatitis B (Cont.)

Body System/ Adverse Event	ROFERON-A 4.5 MIU N = 50 No. (%)	PEGYLATED INTERFERON 90mcg N = 48 No. (%)	PEGYLATED INTERFERON 180mcg N = 45 No. (%)	PEGYLATED INTERFERON 270mcg N = 48 No. (%)
SKIN & SUBCUTANEOUS TISSUE DISORDERS				
Total Pts With at Least one AE	17 (34)	14 (29)	21 (47)	25 (52)
ALOPECIA	12 (24)	8 (17)	15 (33)	21 (44)
DERMATITIS NOS	5 (10)	2 (4)	3 (7)	6 (13)
PRURITUS	2 (4)	3 (6)	1 (2)	4 (8)
URTICARIA NOS	-	2 (4)	1 (2)	2 (4)
ECZEMA NOS	-	1 (2)	1 (2)	-
BRITTLE NAILS	1 (2)	-	-	-
DERMATITIS ATOPIC	-	1 (2)	-	-
GENITAL PRURITUS FEMALE	-	-	1 (2)	-
PHOTOSENSITIVITY REACTION NOS	-	1 (2)	-	-
PRURIGO	-	-	-	1 (2)
RASH GENERALISED	-	1 (2)	-	-
SCALP TENDERNESS	1 (2)	-	-	-
SEBACEOUS CYST	-	-	1 (2)	-
SKIN HYPERPIGMENTATION	-	1 (2)	-	-
SUBCUTANEOUS NODULE	-	1 (2)	-	-
SWEATING INCREASED	-	-	1 (2)	-
Total Number of AEs	21	21	24	34
DISORDERS OF METABOLISM & NUTRITION				
Total Pts With at Least one AE	17 (34)	8 (17)	12 (27)	13 (27)
ANOREXIA	10 (20)	4 (8)	8 (18)	9 (19)
APPETITE DECREASED	5 (10)	4 (8)	3 (7)	3 (6)
WEIGHT DECREASE	1 (2)	-	2 (4)	1 (2)
DIABETES MELLITUS AGGRAVATED	1 (2)	-	-	-
DIABETES MELLITUS NOS	1 (2)	-	-	-
HYPERTRIGLYCERIDAEMIA	-	-	-	1 (2)
Total Number of AEs	18	8	13	14

Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.
AE11 23NOV2001:10:27:44

(continued)

Appendix 6 Summary of Adverse Events by Body System during Treatment and for 8 Weeks Posttreatment in Study NV16037 in Patients with Hepatitis B (Cont.)

Body System/ Adverse Event	ROFERON-A 4.5 MIU N = 50 No. (%)	PEGYLATED INTERFERON 90mcg N = 48 No. (%)	PEGYLATED INTERFERON 180mcg N = 45 No. (%)	PEGYLATED INTERFERON 270mcg N = 48 No. (%)
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS				
Total Pts With at Least one AE	8 (16)	12 (25)	14 (31)	13 (27)
COUGH	3 (6)	7 (15)	3 (7)	4 (8)
SORE THROAT NOS	2 (4)	2 (4)	3 (7)	6 (13)
NASOPHARYNGITIS	-	1 (2)	3 (7)	1 (2)
NASAL CONGESTION	-	1 (2)	2 (4)	1 (2)
POSTNASAL DRIP	1 (2)	1 (2)	-	2 (4)
RHINORRHOEA	1 (2)	1 (2)	1 (2)	1 (2)
EPISTAXIS	1 (2)	-	2 (4)	-
SPUTUM INCREASED	1 (2)	-	1 (2)	-
ASTHMA	-	1 (2)	-	-
CHEST TIGHTNESS	-	-	-	1 (2)
DYSPNOEA	-	-	1 (2)	-
TONSILLAR HYPERTROPHY	-	-	1 (2)	-
Total Number of AEs	9	14	17	16

Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.
AE11 23NOV2001:10:27:44

(continued)

Appendix 6 Summary of Adverse Events by Body System during Treatment and for 8 Weeks Posttreatment in Study NV16037 in Patients with Hepatitis B (Cont.)

Body System/ Adverse Event	ROFERON-A 4.5 MIU N = 50 No. (%)	PEGYLATED INTERFERON 90mcg N = 48 No. (%)	PEGYLATED INTERFERON 180mcg N = 45 No. (%)	PEGYLATED INTERFERON 270mcg N = 48 No. (%)
INFECTIONS & INFESTATIONS				
Total Pts With at Least one AE	4 (8)	14 (29)	8 (18)	12 (25)
UPPER RESPIRATORY TRACT INFECTION NOS	4 (8)	11 (23)	6 (13)	4 (8)
PHARYNGITIS NOS	-	2 (4)	1 (2)	1 (2)
FOLLICULITIS	-	-	1 (2)	1 (2)
PERIODONTITIS	-	-	1 (2)	1 (2)
SINUSITIS NOS	-	1 (2)	-	1 (2)
VAGINITIS	-	-	1 (2)	1 (2)
BLEPHARITIS	-	-	1 (2)	-
CELLULITIS	-	-	-	1 (2)
CYSTITIS NOS	-	-	1 (2)	-
HERPES SIMPLEX OPHTHALMIC	-	-	-	1 (2)
PYELONEPHRITIS ACUTE NOS	-	-	-	1 (2)
SEPSIS NOS	-	-	1 (2)	-
STYE	-	-	-	1 (2)
TINEA NOS	-	1 (2)	-	-
TOOTH ABSCESS	-	-	1 (2)	-
URINARY TRACT INFECTION NOS	-	1 (2)	-	-
Total Number of AEs	4	16	14	13
DISORDERS OF THE EYE				
Total Pts With at Least one AE	2 (4)	3 (6)	1 (2)	4 (8)
VISION BLURRED	-	-	-	2 (4)
XEROPHTHALMIA	1 (2)	-	-	1 (2)
ASTIGMATISM	-	1 (2)	-	-
CONJUNCTIVAL HAEMORRHAGE	-	1 (2)	-	-
CONJUNCTIVITIS NOS	1 (2)	-	-	-
EYE PAIN	-	-	-	1 (2)
PINGUECULA	-	1 (2)	-	-
RED EYE	-	-	1 (2)	-
RETINAL HAEMORRHAGE	-	-	-	1 (2)
Total Number of AEs	2	3	1	5

Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.
AE11 23NOV2001:10:27:44

(continued)

Appendix 6 Summary of Adverse Events by Body System during Treatment and for 8 Weeks Posttreatment in Study NV16037 in Patients with Hepatitis B (Cont.)

Body System/ Adverse Event	ROFERON-A 4.5 MIU N = 50 No. (%)	PEGYLATED INTERFERON 90mcg N = 48 No. (%)	PEGYLATED INTERFERON 180mcg N = 45 No. (%)	PEGYLATED INTERFERON 270mcg N = 48 No. (%)
PSYCHIATRIC DISORDERS				
Total Pts With at Least one AE	3 (6)	2 (4)	3 (7)	1 (2)
ANXIETY	1 (2)	2 (4)	1 (2)	-
IRRITABILITY	2 (4)	-	1 (2)	1 (2)
AGITATION	-	1 (2)	1 (2)	-
Total Number of AEs	3	3	3	1
DISORDERS OF THE REPRODUCTIVE SYSTEM AND BREAST				
Total Pts With at Least one AE	2 (4)	1 (2)	2 (4)	2 (4)
VAGINAL DISCHARGE	1 (2)	1 (2)	1 (2)	-
MENSES DELAYED	-	-	1 (2)	1 (2)
IMPOTENCE	1 (2)	-	-	-
MENORRHAGIA	-	1 (2)	-	-
VAGINAL HAEMORRHAGE	-	-	-	1 (2)
Total Number of AEs	2	2	2	2
INJURY & POISONING				
Total Pts With at Least one AE	-	1 (2)	-	2 (4)
ELECTRIC SHOCK	-	-	-	1 (2)
MUSCLE SPRAIN	-	1 (2)	-	-
ROAD TRAFFIC ACCIDENT	-	-	-	1 (2)
TENDON RUPTURE	-	-	-	1 (2)
Total Number of AEs	-	1	-	3
DISORDERS OF THE EAR & LABYRINTH				
Total Pts With at Least one AE	-	-	1 (2)	2 (4)
TINNITUS	-	-	1 (2)	1 (2)
EARACHE	-	-	-	1 (2)
Total Number of AEs	-	-	1	2

Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.
AE11 23NOV2001:10:27:44

(continued)

Appendix 6 Summary of Adverse Events by Body System during Treatment and for 8 Weeks Posttreatment in Study NV16037 in Patients with Hepatitis B (Cont.)

Body System/ Adverse Event	ROFERON-A 4.5 MIU N = 50 No. (%)	PEGYLATED INTERFERON 90mcg N = 48 No. (%)	PEGYLATED INTERFERON 180mcg N = 45 No. (%)	PEGYLATED INTERFERON 270mcg N = 48 No. (%)
CARDIAC DISORDERS				
Total Pts With at Least one AE	-	1 (2)	1 (2)	-
PALPITATIONS	-	1 (2)	1 (2)	-
Total Number of AEs	-	1	1	-
DISORDERS OF BLOOD & THE LYMPHATIC SYSTEM				
Total Pts With at Least one AE	-	1 (2)	-	1 (2)
ANAEMIA NOS	-	1 (2)	-	1 (2)
Total Number of AEs	-	1	-	1
ENDOCRINE DISORDERS				
Total Pts With at Least one AE	-	-	1 (2)	1 (2)
HYPERTHYROIDISM	-	-	-	1 (2)
THYROID NODULE	-	-	1 (2)	-
Total Number of AEs	-	-	1	1
HEPATO-BILIARY DISORDERS				
Total Pts With at Least one AE	1 (2)	-	1 (2)	-
CHOLELITHIASIS	1 (2)	-	-	-
HEPATIC PAIN	-	-	1 (2)	-
Total Number of AEs	1	-	1	-
VASCULAR DISORDERS				
Total Pts With at Least one AE	-	-	-	2 (4)
LYMPHANGITIS	-	-	-	1 (2)
POSTURAL HYPOTENSION	-	-	-	1 (2)
Total Number of AEs	-	-	-	2
BENIGN & MALIGNANT NEOPLASMS (INCLUDING CYSTS AND POLYPS)				
Total Pts With at Least one AE	-	-	-	1 (2)
UTERINE FIBROIDS	-	-	-	1 (2)
Total Number of AEs	-	-	-	1

Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.
AE11 23NOV2001:10:27:44

(continued)

Appendix 6 Summary of Adverse Events by Body System during Treatment and for 8 Weeks Posttreatment in Study NV16037 in Patients with Hepatitis B (Cont.)

Body System/ Adverse Event	ROFERON-A 4.5 MIU N = 50 No. (%)	PEGYLATED INTERFERON 90mcg N = 48 No. (%)	PEGYLATED INTERFERON 180mcg N = 45 No. (%)	PEGYLATED INTERFERON 270mcg N = 48 No. (%)
DISORDERS OF THE IMMUNE SYSTEM				
Total Pts With at Least one AE	-	-	-	1 (2)
ANAPHYLACTIC SHOCK	-	-	-	1 (2)
Total Number of AEs	-	-	-	1
RENAL & URINARY DISORDERS				
Total Pts With at Least one AE	-	1 (2)	-	-
DYSURIA	-	1 (2)	-	-
Total Number of AEs	-	1	-	-
SURGICAL & MEDICAL PROCEDURES				
Total Pts With at Least one AE	-	-	-	1 (2)
POST-OPERATIVE WOUND INFECTION	-	-	-	1 (2)
Total Number of AEs	-	-	-	1

Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once.
AE11 23NOV2001:10:27:44

Appendix 7 Toxicology Studies with Ribavirin Alone or PEG-IFN α-2a Plus Ribavirin

Study Type	Species	Duration and Design	Dose, Route and Regimen
Chronic toxicity (Ribavirin)	Crl:BR rat	26 weeks with a 6-week recovery	10, 35, 70 mg/kg po (gavage) once/day
Chronic toxicity (Ribavirin)	Beagle dog	26 weeks with a 6-week recovery	5, 10, 20 mg/kg po (gavage) once/day
Mutagenicity (Ribavirin)	in vitro	Ames test	Up to 5000 µg/plate with and without S9 for both *Salmonella typhimurium* tester strains and *E. coli* strain WP2*uvr*A
Mutagenicity (Ribavirin)	in vitro	Mouse lymphoma	Up to 2500 µg/mL with and without S9 (10 mM)
Genotoxicity (Ribavirin)	CD-1 mouse	Mouse micronucleus	500, 1500, 2000 mg/kg po (gavage) (3 consecutive doses, once/day)
Subacute toxicity (Ribavirin)	C57BL/6 mice	4 weeks	30, 100, 200, 400 mg/kg po (gavage) once/day
Carcinogenicity (Ribavirin)	p53 knockout mouse	26 weeks	10, 50, 100 mg/kg po (gavage) once/day
Fertility and Early Embryonic Development (Ribavirin)	Crl:BR rat	Part 1. Female Rats Part 1A: Dosed for 4 weeks through mating and gestation day 7. Part 1B: Dosed for 4 weeks, bled for TK on the first and last day of dosing. Part 1C: Dosed for 4 weeks, held off treatment for 6 weeks, and then mated. Part 2. Male Rats Part 2A: Dosed for 9 weeks prior to mating plus 2-week mating period. Part 2B: Dosed for 9 weeks, bled for TK on the first and last day of dosing. Part 2C: Dosed for 11 weeks, held off treatment for 9, 18 or 27 weeks, and then mated.	10, 30, 100 mg/kg po (gavage) once/day

(Continued)

Appendix 7 Toxicology Studies with Ribavirin Alone or PEG-IFN α-2a Plus Ribavirin (Cont.)

Study Type	Species	Duration and Design	Dose, Route and Regimen
Subchronic toxicity (Ribavirin)	Crl:BR rat	13 weeks	10, 40, 80, 160 mg/kg po (gavage) once/day
Carcinogenicity (Ribavirin)	Crl:BR rat	2 years	10, 30, 60 mg/kg po (gavage), once/day
Subacute toxicity (PEG-IFN alfa-2a and Ribavirin)	Cynomolgus monkeys	4 weeks with a 6-week recovery	Group 1: 0 mg/kg PEG-IFN alfa-2a sc twice weekly, 0 mg/kg ribavirin po (gavage), once/day. Group 2: 0 mg/kg PEG-IFN alfa-2a sc twice weekly, 50 mg/kg ribavirin po (gavage), once/day. Group 3: 0 mg/kg PEG-IFN alfa-2a sc twice weekly, 100 mg/kg ribavirin po (gavage), once/day. Group 4: 600 µg/kg PEG-IFN alfa-2a sc twice weekly, 0 mg/kg ribavirin po (gavage), once/day. Group 5: 600 µg/kg PEG-IFN alfa-2a sc twice weekly, 50 mg/kg ribavirin po (gavage), once/day. Group 6: 600 µg/kg PEG-IFN alfa-2a sc twice weekly, 100 mg/kg ribavirin po (gavage), once/day

Depression

and

QOL

Questionnaires

PEDS-C
Physical Activity Assessment Form

PDC 13
Rev 0
12/23/2004
Page 1 of 1

5890

Please Use Black Pen To Fill Out Form.

Week # | Date of Assessment (mm / dd / yyyy) | Patient ID | Patient Letter Code | ○ Correction

1. In comparison to other children the same age and sex, is the patient :

A lot less active	A little less active	About average	A little more active	A lot more active
○	○	○	○	○

2. **Instructions:** The interviewer, parent / guardian, and patient should work together to complete this item. The total for each day should add up to 24 hours. Time should be filled out to the nearest half (0.5) hour.

On a usual weekday and a usual weekend day during the past month, how much time did the patient spend at each activity level listed below?

	1. Weekday (hours/day)	2. Weekend day (hours/day)
A. **Sleeping:**	.	.
B. **Sedentary or seated activities:**	.	.
Eating		
TV, radio, music,,videos, etc.		
Reading		
Cards, board games		
Playing musical instruments		
Computer activities		
Other seated activies		
C. **Light or casual activities:**	.	.
Household chores		
Standing, walking, activities which require standing or walking		
Volleyball, ping pong, boating, sailing, bowling, fishing, horseback riding, archery		
Easy bike riding		
Playing on swings or jungle gym		
General play		
D. **Moderate or stop / start activities:**	.	.
Heavy yard chores		
Calisthenics		
Skate boarding		
Fast walking, hiking, hard bike riding, carrying heavy objects		
Frisbee, playing catch, softball, golf, recreational skating, recreational swimming, dancing, aerobics, ballet, gymnastics, cheerleading, surfing, water skiing, weight lifting, shooting baskets or basketball half-court, doubles tennis		
All sports participation with start/stop rather than sustained activity level		
E. **Intense or sustained activities** (for entire time):	.	.
Running, swimming laps, jogging, jump rope, cross country or downhill skiing, basketball full court, soccer, field hockey, ice hockey, singles tennis, raquetball, figure skating, paddle ball, lacrosse, touch football, rowing		

CRA Use Only

Signature: _____ **Certif. #:** ___ - ___

PEDS-C
Manual for Completing Case Report Forms (CRF's)

Prepared by:
Maryland Medical Research Institute MMRI)
600 Wyndhurst Ave, 3rd floor
Baltimore, MD 21210
410-435-4200

PURPOSE OF THIS MANUAL

- To assist PEDS-C Site coordinators in completing PEDS-C CRF's in an legible, accurate, and clear manner

- To provide a comprehensive set of guidelines for the PEDS-C staff who are responsible for completing PEDS-C CRF's to the Data Coordinating Center (DCC) utilizing the Teleform System

- To provide a picture of what actually transpires when a CRF is received by the DC C

Appendix J

Completing and Reviewing PEDS-C Study Forms

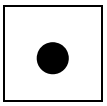
Only certified PEDS-C trained staff members should complete study forms

- Black ink should be used for completing PEDS-C forms
- A black gel-writer is ideal for filling in bubbles
- Responses should be printed clearly in the spaces provided for write-in items
- A PEDS-C staff certification number is required for CRF completion
- A PEDS-C staff certification number will be provided after the DCC receives a certification number request form
- The PEDS-C staff member who completes a CRF form will enter his/her certification number in the appropriate boxes at the bottom of the form and sign the CRF. CRF's received without a valid certification number are considered invalid and will be returned to the site primary contact for correction
- Completed forms should be reviewed while the patient is still in the clinic and again before the site monitor arrives to assure that all required information has been recorded in a legible, consistent and unambiguous manner
- Missing or incomplete data should be reviewed with the individual staff members who completed that particular section of the form
- Missing or incomplete data that has been received by the DCC will be returned to the site primary contact to be corrected

Easy and Effective Guidelines for Completing PEDS-C Forms

- **Filling in Bubbles – Circles are called Bubbles**

  Bubbles must be completely darkened. Bubbles should **NEVER** be circled because Teleform does not look outside the circle for marking information

  Bubbles must be filled in like this: 

- **Filling in Letters and Numbers**

  When printing letters and numbers, use capital block letters. **Be sure to print only one character per box** keeping the character's line **completely inside the box**. Zero, Seven, and "Z" should not be crossed.

  Write zeros, sevens, and "Z" like this: 

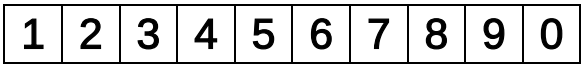
  Not like this: 

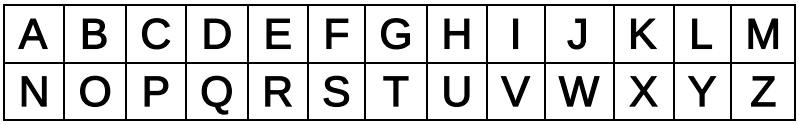
- **Use the Right Pen**
  A black gel-type pen works well

- **Press Firmly**
  The printing must go through 3 pages

- **Print Neatly in Block Capital Letters**

  Examples:





Completing the Header Information

- The "Header Information" contains the 3-Digit Week Number, 6-Digit Patient Identification Number, 3-Letter Patient Letter Code and Date of Assessment (mm/dd/yyyy)
- A correction box is included in the header but will only be completed when a CRF requires changes after the original CRF was collected
- The "Header Information" will vary depending on what type of PEDS-C form is completed but the items mentioned above will remain consistent
- At each CRF submission, the Patient Identification Number and Patient Letter Code and are compared against the same data that was entered into the ATRS (Automated Telephone Response System) when the patient entered the PEDS-C Study
- If any inconsistency is found in the Patient Identification Number and Patient Letter Code, the form is rejected during the validation process and returned to the site primary contact and a new form must be completed with the correct identifying information
- For every page of every form collected, all header information boxes (except for the Correction box) must be completed.

Additional Notes About Letter Codes

- Once a patient's Letter Code and ID Number are entered into the ATRS, they cannot be changed.
- The same Letter Code and ID Number must be entered on all forms and correspondence about the patient's data
- The Letter Code will not have any relationship to the patient's initials
- If the Letter Code is entered into the ATRS incorrectly, a note should be entered in the source document(s) explaining the discrepancy

Completing the Visit Week Number

- The Week # for Screening Forms will be pre-filled with **"ELG"**
- The Week # for the Baseline Assessment Form will be pre-filled with **"000."** Other forms completed at Baseline will also be labeled with Week # 000.
- The Week # for follow-up weeks will be entered as **"001", "003", "005",** …. etc. per the Tables of Assessments in the Study Protocol
- The Annual Visit Form will use week numbers as outlined in the following chart:

Annual Visit Chart	**Annual Visit 1 at Week:**	**Annual Visit 2 at Week:**
Mono/Combo Therapy Group		
Path 1	104	156
Path 2	128	180
Original Mono Group		
Path 3	100	152
Original Combo Group		
Path 4	76	128
Path 5	100	152

- Visit windows allow +/- one day for the 2 week visits (001, 003, 005), +/- one week for monthly visits (008, 012 …) and +/- one month for annual visits (as per Annual Visit chart above)
- If a visit occurs outside the visit window (early or late), the Week # must be entered for the week # the visit was scheduled
- Visits made outside the visit window will receive queries
- All scheduled visits must be accounted for
- Example: If a Week 24 Visit occurs late, for example in the 26th week, Week number **"024"** must still be entered in the Week # box.
- Any form not pre-printed with a week number, will need to have the appropriate week number completed
- Missed visits will be documented using the Missed Forms Report for each form that was missed and should have been completed at that visit
- Forms missed but not accounted for will be considered delinquent and receive a query

Header Information Form Types (Continued)

Sequence Box:

- Some forms will have a Sequence Box in the header
- When present, the Sequence Box must be completed
- For each version of a particular form at a particular visit, the sequence box will be numbered "01"
- If the continuation of any form is needed, a second form is used and given a sequence the appropriate sequence number
    - For example, the Concurrent Medication Form has space to list 2 drugs. If a patient is receiving more than 2 drugs, a second Concurrent Medication Form is used with the sequence number '02' entered into the sequence box. All other information in the sequential header box will be identical to the header of the initial form

Filling in the Correction Bubble

One of the most misunderstood parts of the header information is the purpose of the ***"Correction Bubble"***

- The filled in "Correction Bubble" indicates that a form is a correction of a ***previously submitted*** (pulled) CRF
- Forms may be corrected at any time
- The filled in "Correction Bubble' also indicates that form has been corrected in response to an ***edit query*** that was received from the DCC
- **DO NOT** fill in the "Correction Bubble" when ***initially*** filling in any CRF

How to use the Correction Bubble:

If you need to make a correction to a previously submitted CRF, you will do the following:

- Using a duplicate of the page that requires correction, fill in the header of the clean unused version of the same form with the EXACT header information as the original (incorrect) document, being sure to use the date of the original assessment
- Fill in the Correction Bubble
- ONLY enter the correct information that was found to be incorrect, leave the rest of the form blank
- Fax the CRF to the DCC

What a Correction Bubble cannot do:

- Mistakes made in filling out the header information ***CANNOT Be Corrected*** by filling in the "Correction Bubble." If you need to make a correction on a header call the DCC/CRO

- A CRF image that contains errors in the header information will not be processed. The CRF image will be returned immediately to the site primary contact.

- A new original form must be completed and faxed

What transpires when a PEDS-C CRF is Received by the Data Coordinating Center?

- Certified PEDS-C staff members who complete a PEDS-C CRF should review each CRF carefully making sure all required data is legible, clear, and unambiguous before it is reviewed by a site monitor

- CRF's are faxed to the DCC for Fax Data Entry

- The faxed CRF's go directly into the Fax Data Form System and are automatically read using Teleform optical scanning recognition software

- All CRF's are then saved as Form images on the DCC server and related to the data records

- The PEDS-C data coordinator manually validates each legible CRF for completeness, accuracy, and legibility

- PEDS-C CRF's that are successfully validated or processed are exported to the PEDS-C database

- Editing programs are run on the CRF's which may generate 'edit messages' which are sent to the clinical center for review

- Any CRF image that does not meet the criteria for legibility, accuracy, or unambiguous data is scanned into a Non-Forms file and cannot be processed or validated

- Non-Forms are returned to the appropriate PEDS-C staff member by the PEDS-C data coordinator to be corrected

Appendix J

Abbreviations Used in this Document

PEDS-C	Pegylated Interferon +/- Ribavirin for Children with HCV
DCC	Data Coordinating Center
CRO	Contract Research Organization
CRF	Case Report Form
ATRS	Automated Telephone Response System
ELG	Eligibility Visit

PP - Abstract/Publication/Presentation Proposal

Purpose: To describe the subject matter, authorship, presentation/publication plans, and resources needed for the proposed abstract/publication and provide a basis for approval or rejection.

When: Whenever an investigator is seeking approval for preparation of :

1. a proposed abstract that requires access to PEDS-C data
2. a proposed publication that describes PEDS-C design, rationale or methods; involves PEDS-C data; or involves other PEDS-C resources.
3. a proposed presentation that describes PEDS-C design, rationale or methods; involves PEDS-C data; or involves other PEDS-C resources.

Instructions: The form should be sent (along with any supporting materials) to the PEDS-C Data Coordinating Center for distribution to the Presentations and Publications Committee for review.

A. Administrative information

1. Proposing investigator(s): _____

2. Center(s) or agencies: Children's Hospital and Regional Medical Center_____

3. Date received at DCC *(to be completed by the DCC)*: _____ _____-_____ _____ _____-
day mon year

4. Is this proposal for:
( ) an abstract
( ) a publication (*MS#[supplied by DCC]:* _____)
( ) a presentation
( ) other (review, etc)

B. Abstract/publication/presentation proposal information

5. Proposed title or topic: PEDS-C, Evolution of the pediatric hepatitis C treatment study with integrated study of the impact of pegylated interferon and ribavirin treatment on quality of life and growth in children.

6. General content of abstract/publication/presentation:

( )PEDS-C design and methods
( ) PEDS-C baseline data
( ) PEDS-C primary outcomes
( ) PEDS-C secondary outcomes
( ) PEDS-C substudy report
( ) Ancillary study data *(specify ancillary study)*

_____

( ) Other _____

7. Proposed writing committee members *(specify name, center)*: Dr. Kathleen Schwarz, Johns Hopkins Medical Center (overall study concept); Dr. Regino Gonzalez-Peralta, University of Florida (quality of life); Dr. Maureen Jonas, Children's Hospital of Boston (body composition and growth); Dr. Kathleen Brown, MMRI (statistics, DCC)

Due to conflict of interest incurred by my role as chairman of the Publications and Presentation Committee (P&P), I would request that for the P&P committee review of this proposal that Dr. Jean Molleston assume the role of Chair of the P&P Committee.

8. Proposed format for authorship:

( ) Modified corporate (e.g., PEDS-C CRN Research Group; writing committee listed in credits section)
( ) Modified conventional (e.g., John Doe and Jane Smith for the PEDS-C CRN Research Group)
( ) Conventional (e.g., John Doe, Jane Smith)
( ) Other, please describe

_____

9. Planned society meeting for presentation/journal for submission:

Clinical Trials

10. Description: Write a brief description of the abstract/publication/presentation being proposed, specifying the objective and rationale for the abstract/publication. **DO NOT EXCEED THE SPACE PROVIDED.**

To describe the background and rationale in the design of the PEDS-C study, and changes in the design with time due to industry pressures. To discuss the considerations taken in including the ribavirin placebo control and ethical implementation of such a study with pediatric study subjects. To review the background for the inclusion of growth and body composition and quality of life analyses in the basic protocol.

The methods section of the manuscript would include: planning and management- the establishment of the PEDS-C CRN, and selection of MMRI as the DCC; the treatment portion of the study design and rationale for the changes that occurred in reaching the final protocol including inclusion of the ribavirin control; body composition and growth; QOL; study hypotheses; outcome measures and study endpoints; inclusion and exclusion criteria; statistics.

C. NASH CRN resources

11. Does preparation of this abstract/publication/presentation require any DCC resources *(check all that apply; specify resources in each category)*?

(X) None (Go to question #12)

( ) Staff *(specify)*: _____

( ) Other *(specify)*: _____

12. What PEDS-C CRN data will be required to prepare this abstract/publication/presentation? *(check all that apply)*

(X)None (Go to question #13)

( )PEDS-C treatment database *(list required forms and visits below; attach copies of relevant forms with required items circled)*

_____

_____

_____

_____

( )Growth and body composition database

_____

_____

( )QOL and functioning database

_____

_____

( )Ancillary study database *(specify ancillary study)*

_____

_____

( )Other *(specify data and where the data are located)*: _____

_____

D. Data analysis

13. Which of the following is required for preparation of this abstract/publication/presentation? *(check all that apply)*

( )Analysis of PEDS-C CRN data by DCC staff

( )Provision of PEDS-C CRN dataset to clinic staff for clinic staff to analyze

( )Other *(specify)*: _____

_____

(X)None (Go to question #15)

14. Briefly describe the proposed analysis **(DO NOT EXCEED THE SPACE PROVIDED):**

E. Author assurance and sign off

- ❑ I understand that any abstracts/manuscripts/presentations resulting from this effort must be approved by the PEDS-C CRN- Steering Committee (SC) prior to submission to any journal or meeting.
- ❑ I understand that verification of data analyses may be required by the DCC prior to submission to any journal.
- ❑ I understand that the DCC is the archive for PEDS-C CRN and that a copy of any draft circulated to any person or entity external to the PEDS-C CRN Research Group must be sent to the DCC for their records.
- ❑ I understand that the PEDS-C CRN SC will make the final decision regarding authorship format.
- ❑ I understand that reviewers may be appointed from the PEDS-C CRN Research Group to provide internal review of this abstract/manuscript/presentation prior to submission to any society/journal.
- ❑ I will adhere to the confidentiality policies of PEDS-C CRN and its IRBs, which require that no identifying personal information be included in any abstract/publication/presentation.

15. Signature(s) of individual(s) proposing abstract/publication: _____

_____

_____

16. Signature of Principal Investigator of center submitting this proposal:

_____

Acknowledgment:

PEDS-C **Appendix K**

In drafting the PEDS-C CRN Publication Proposal Form, we reference the NASH CRN Publication Proposal Form- Draft version.

PEDS-C CRN
Presentations and Publications Policy

Contents

PEDS-C CRN Presentations and Publications Policy

1. Charge of the Presentations and Publications Committee

The purpose of the Presentations and Publications (P&P) Committee is to oversee and provide guidance relative to reporting study data and to assure that study reports have expert input, a high standard of scientific quality, responsible conclusions, and sound interpretations and fulfill the overall objectives of the Pediatric HCV PEG-IFN +/- Ribavirin Clinical Research Network (PEDS-C CRN). The charge of the P&P Committee is to:

- Develop the policy for publications in regards to proposal of manuscripts, review and approval of manuscript proposals, assignment of tasks in analysis and writing, review of manuscripts, authorship policy, and other issues related to publications.
- Develop the policy for presentations in regards to proposal of presentations, review and approval or presentation proposals, assignment of tasks in analysis and writing, review of presentations, authorship policy, and other issues related to presentations.
- Make recommendations to the Steering Committee about topics for publications
- Make recommendations to the Steering Committee about topics for presentations at national and international meetings
- Make recommendations concerning the priority of manuscripts and presentations.
- Review proposals for publications and presentations and make recommendations for approval or disapproval to the Steering Committee
- Review manuscripts prior to journal submission and review presentations prior to presentation
- Mediate and settle all disputes and conflicts among study investigators over publication or presentation priorities, authorship, and any other issues related to publications or presentations. Investigators who perceive inequities in authorship or other problems relating to authorship should discuss these concerns with the P&P Committee chairperson; if the difficulty cannot be settled in this informal manner, the concerned investigator should submit a letter to the P&P Committee chairperson outlining the problem. The document will be reviewed and discussed by the P&P Committee, and a written reply will be made to the investigator. If P&P Committee deliberations fail to resolve such a dispute, the dispute will be submitted for resolution to the full Steering Committee, excepting those with a conflict of interest.
- Prepare and maintain a list of concepts for publications and prepare and maintain a list of approved PEDS-C CRN publications, which shows the status of each manuscript from initiation through publication

The purview of the P&P Committee includes publications and presentations arising from PEDS-C CRN main studies, substudies, pilot and feasibility studies, and ancillary studies.

2. Goals

- To promote timely, scientifically accurate, and high-quality presentation and publication of findings from PEDS-C CRN studies.
- To support broad and equitable participation by PEDS-C CRN investigators in presentations and publications.
- To define a set of equitable policy and procedures to determine authorship and the order in which authors are listed.
- To review and select topics for publications and presentations, assign authors to writing groups, set priorities for publications and presentations, and monitor progress of publications and presentations.
- To provide editorial support and timely review for presentations and publications.
- To defend the academic freedom of PEDS-C CRN investigators collectively to publish results emanating from the PEDS-C CRN studies, while providing limitations on publication of results from any one center that could threaten the integrity of collective data.

3. Scope

- These policy and procedures apply to original manuscripts (including methodology, validation, laboratory approaches), abstracts, oral and poster presentations, letters to the editor, meeting proceedings, and extended abstracts that include data collected as part of the PEDS-C CRN. The policy and procedures also apply to review articles that include original PEDS-C CRN data not previously published.
- These policy and procedures apply to publications and presentations arising from PEDS-C CRN main studies, substudies, pilot and feasibility studies, and ancillary studies.
- The P&P Committee reserves the right to amend the presentation and publication policy and procedures as necessary to clarify their intent.

4. Presentations and Publications Committee membership

- Consists of a chairperson (initially appointed by the NIDDK and, thereafter, elected by the Steering Committee) and 5 clinical center principal investigators (initially appointed by the NIDDK and, thereafter, elected by the Steering Committee), an investigator from the Data Coordinating Center, and an NIDDK representative, and a Roche representative.
- The chairperson serves for a 1-year term and 5 clinical center principal investigators serve for 2-year terms.
- The members from the Data Coordinating Center and NIDDK serve for the duration of the PEDS-C CRN.
- The number of consecutive or interrupted terms that a chairperson or other elected member may serve will not be limited.
- Each member has one vote.
- If a member is an author on a presentation or manuscript or otherwise has a conflict of interest, the member will recuse himself/herself from review of the proposal or manuscript or presentation.

5. Types of publications

- **Main reports** arise from main studies and address the main objectives of main studies or report primary outcome data or design and methods of main studies. Examples of main reports are those that address the efficacy in the treatment trial, and design and methods of PEDS-C CRN studies.
- **Secondary reports** arise from main studies and address secondary objectives of main studies or report data or design issues or methods that are more peripheral to the main studies than those addressed in main reports.
- **Substudy reports** arise from substudies of the PEDS-C CRN.
- **Ancillary study reports** arise from an ancillary study of the PEDS-C CRN.
- **Pilot and feasibility reports** arise from a pilot or feasibility study of the PEDS-C CRN.
- Abstracts, meeting proceedings, extended abstracts, oral and poster presentations.
- Letters to the editor.
- Press releases.

6. Writing groups and authorship issues

6.1. Writing groups

- Writing groups: The writing of manuscripts will be assigned to a writing group consisting of PEDS-C CRN investigators, one of whom will be designated the Chair. The P&P Committee will nominate the writing group chair and members and send the selection to the Steering Committee for final approval. Investigators proposing manuscripts may suggest writing group membership to the P&P.

6.2. Authorship criteria

- Authors should participate in the writing of the paper according to guidelines of the International Committee of Medical Journal Editors (N Engl J Med 1997; 336:309-315). Those who participated in conception and design, analysis and interpretation of data, drafting the manuscript, critical revision of the manuscript relating to important intellectual content, and final approval of the manuscript should be included as authors. Expertise (eg, statistical, virology, or pathology) that relates directly to the conduct of the study is additional criterion for authorship. Provision of study material or patients; data collection and assembly; administrative, technical, or logistic support; and obtaining funding do not necessarily merit authorship but should be considered on a case-by-case basis, especially when other contributions are included. Honorary authorship will not be considered.

6.3. Authorship format by type of report

- Main reports will have authorship "The PEDS-C CRN Research Group". An appendix listing all investigators in the PEDS-C CRN will be included, and the writing group will be designated in a footnote to the title page. The writing group will include one to three clinical center investigators, one investigator from the DCC, and one investigator from the NIDDK.
- Secondary or lesser reports of main PEDS-C CRN studies will have modified conventional authorship (Name1, name2, ... and the PEDS-C CRN Research Group) or conventional authorship. An appendix listing all investigators in the PEDS-C CRN will be included, journal permitting.
- Substudy reports will have modified conventional authorship (Name1, name2, ... and the PEDS-C CRN Research Group) or conventional authorship. An appendix listing all investigators in the PEDS-C CRN will be included, journal permitting.
- Pilot and feasibility study reports will have modified conventional authorship (Name1, name2, ... and the PEDS-C CRN Research Group) or conventional authorship. An appendix listing all investigators in the PEDS-C CRN will be included, journal permitting.
- Ancillary study reports will request of the primary authors modified conventional authorship when stored samples are used. An appendix listing all investigators in the PEDS-C CRN will be included, journal permitting. The PEDS-C CRN does not control authorship of ancillary study papers when data only is used. Ancillary study reports should acknowledge the role of the SC member who serves as the liaison for the ancillary study in this situation but the liaison does not necessarily need to be included as an author unless the SC member has materially participated in the ancillary study and meets the standard criteria for authorship.

6.4. General issues for naming authors

The following points apply when conventional or modified conventional authorship is used for a publication or presentation.

- The writing group, plus any ad hoc contributors who fulfill criteria for authorship, will be listed as authors.
- Order of authorship: The Chairperson of the writing group will propose authorship order to the P&P Committee based on the level of input into the manuscript. The P&P Committee may amend the order of authorship to recognize an exceptional contribution to the study or the manuscript by an individual. Upon P&P Committee approval, the order will be submitted to the Steering Committee for final approval. For all manuscripts, factors to be included in decisions about order of authorship are contribution to concept, design, and analysis; role in drafting the article or revising it critically for important intellectual content; completeness and integrity of the data and specimens from the investigator's site; and leadership role.
- For journals that limit the number of masthead authors, the following order of authorship will apply until the journal's limit is reached:
    - The writing group.
    - Other investigators identified by the writing group as having made special contributions to the concept, design, or analysis of the study.

- Other investigators identified by the writing group as having contributed special effort to the execution of the study.
- If the journal's limit of authors is reached before all writing group members are listed, all others in the writing group will be listed in an appendix section of the manuscript, and the masthead will include "PEDS-C CRN Writing Group".
- Unless he/she delegates otherwise, the Chairperson of the writing group will be the first author.

7. Proposal of topics and review of proposed topics

- The DCC will keep a list of topics proposed for manuscripts and will maintain a list of approved topics and their status.
- Any member of the Research Group may propose a manuscript. Non Steering Committee members should channel their requests through the Steering Committee member of their site who will forward the topic to the P&P Committee. Proposals must be submitted in writing to the P&P Committee by completion of the Publication Proposal (PP) form which is available on the PEDS-C CRN website. This form requires:
  - a brief description of the background, hypothesis, and purpose of the topic
  - a summary of the analysis plans
  - a description of the subjects to be included
  - a list of variables of interest
  - proposed writing group membership (including statistician) and proposed chair
  - for abstracts, the date of submission and date of the meeting
  - for manuscripts, target journals or book
- The DCC will distribute a copy of the proposals to members of the P&P with a deadline for return of comments (or will schedule a conference call). P&P members may propose additional or alternate writing group members. The P&P Committee will select the final writing group membership and appoint the writing group chair. The chair will usually be the person who proposed the project. The selection of writing groups and their Chairpersons will be submitted to the Steering Committee for final approval.
- Criteria for judging proposals:
  - scientific merit of the hypothesis or aim of the proposal
  - availability of appropriate data to address the hypothesis or aim
- If overlap in content exists between or among proposals, the P&P Committee will either eliminate overlap or consolidate the proposals.

8. Responsibilities of the writing group

- The chair of the writing group will be responsible for assigning tasks to other members of the writing group and for overseeing the completion of these tasks on schedule.
- Manuscripts will be prepared at the center of the writing group Chair.
- All data analysis will be done through the DCC (mainline papers) or appropriate statistician at a PEDS-C CRN site. Based upon their review of these requests, the statistician will provide an estimate of the time and resources required to be included in

the final proposal.

- When the manuscript is judged ready for internal review, the chair will submit the completed manuscript to the P&P Committee in care of the DCC.
- If a writing group does not complete its work or fails to meet timeline milestones, the P&P Committee may reassign the roles of chair or select new writing group members. This exigency may be exercised if no draft is produced within 3 months of the availability of a clean data set.
- If, during the course of work on a manuscript, the analysis is found to be too broad for a single manuscript, the writing group may suggest that the data would be more suitable for more than a single manuscript. The writing group must notify the P&P Committee that they plan to narrow the scope of the manuscript. The writing group may propose in writing the writing of an additional manuscript.

9. Acknowledgments to be included in publications and presentations

- All PEDS-C CRN manuscripts must include an acknowledgment of NIDDK funding, with specific grant numbers, as well as NIH funding numbers of participating General Clinical Research Centers. Acknowledgment of CRADA partners should be included as well. When appropriate, other institute or center support is to be acknowledged (e.g., National Institute of Child Health and Human Development, National Cancer Institute). Grant numbers do not have to be specified on acknowledgments for abstracts and presentations.

10. Review of manuscripts

- The P&P Committee will serve as the editorial review committee for all manuscripts.
- Manuscripts that are judged ready for P&P review should be submitted to the P&P Committee in care of the DCC.
- The DCC will send all manuscripts received for P&P review to the full Steering Committee for voluntary comment direct to the corresponding author. A deadline for comments will be specified.

- For each report (ancillary study reports are excluded), two P&P Committee members who did not write the paper or two PEDS-C CRN Research Group members with relevant expertise will be designated to provide a timely review (within two weeks) of the manuscript for editorial clarity and data integrity. The DCC will simultaneously do their own review of the analysis and statements about the PEDS-C CRN protocol. Ancillary study reports will be sent to one P&P Committee member for review for accuracy of statements about the PEDS-C CRN resources used in the ancillary study and for appropriate acknowledgment of PEDS-C CRN.
- The results of the P&P, and DCC reviews will be collated by the DCC and sent to the writing group chair.
- The result of the review may be that the manuscript is approved for submission to NIDDK or that the manuscript needs revision and rereview.
- The final step in the PEDS-C CRN review process is submission to NIDDK for review. All papers arising from the PEDS-C CRN, including ancillary study reports, must be reviewed by NIDDK prior to journal submission. The writing group chair will submit the manuscript to the NIDDK project officer after receiving approval from the P&P to do so. In the case of ancillary studies the P&P chair will submit the manuscript to the NIDDK project officer.
- The NIDDK project officer will notify the writing group chair (with a copy to the DCC) when the manuscript is approved for journal submission.
- If a dispute occurs between the authors and the P&P Committee, resolution of the dispute is the responsibility of the Steering Committee.
- Although approval by CRADA/CTA partners is not required, as a courtesy, manuscripts that relate to work carried out through the support of a CRADA/CTA will be submitted to the relevant CRADA/CTA partner at the same time as submission to the P&P. CRADA/CTA partners will not have authority to prevent or delay publication. CRADA/CTA partners will be given a 30 day deadline for return of comments. Their review will occur prior to review by NIDDK.

11. Publications priorities

- No investigator may jeopardize the publication of PEDS-C CRN study results in a peer-reviewed journal by releasing or presenting data prematurely. Local press releases are to be timed to coincide with publication of manuscripts and must respect any applicable publication embargoes.
- No individual site will be permitted to publish site-specific PEDS-C CRN results without the approval of the Steering Committee.

12. Presentations, abstracts, and letters to the editor

- Presentations of unpublished PEDS-C CRN data at national and international meetings must be approved. The approval process may entail review of slides and printed material by the same mechanism as that used to review abstracts. P&P Committee approval is not required for local presentations and accompanying syllabus material (eg, medical school lectures, continuing education courses, grand rounds lectures, research seminars, etc). Investigators are encouraged to consult the Committee chairperson when questions about the propriety of a local presentation arise. If the chair cannot address such questions readily, the issue will be considered by the entire P&P Committee (via conference call or written communication).
- Presentations and abstracts will use modified conventional authorship (name 1, name 2, etc, and the PEDS-C CRN Research Group) and will include acknowledgment of NIDDK funding.
- The DCC will be responsible for data analysis and final slide preparation for PEDS-C CRN corporate presentations.

- Investigator-initiated abstracts that require data analysis assistance from the DCC must be proposed to the P&P Committee at least 3 months prior to the submission deadline (use the same form used to propose a manuscript). The P&P Committee will review the proposal, and if approved will prioritize the analysis requests, in consultation with the DCC.
- Completed abstracts are to be submitted to the P&P Committee at least 10 days prior to submission to the organization sponsoring the meeting. The abstract will be circulated to the full P&P Committee with a ballot for approval as written, approval with revisions, or disapproval. A majority of the P&P Committee members responding must approve the abstract for it to be approved for submission.
- Letters to the editor are to be approved according to the same process as that used for abstracts.

13. Reprints and postings to the PEDS-C CRN website

- Reprints of mainline manuscripts authored by "The PEDS-C CRN Research Group" will be purchased by the DCC, and requests for reprints may be addressed to the DCC. Reprints for all other manuscripts are the responsibility of the writing group chair (who may determine that purchase of reprints is not feasible).
- Published PEDS-C CRN manuscripts will be posted on the PEDS-C CRN website. Slide material prepared for presentation at national or international meetings will also be posted to the PEDS-C CRN website after the presentation is delivered.

Acknowledgments:

In drafting the PEDS-C CRN Presentations and Publications Policy and Procedures, we referred to the following sources: Publication and Presentation guidelines of the NASH CRN study which in turn was drafted from the Virahep-C and HALT-C studies sponsored by the NIDDK, and the Presentation and Publication Policy and Procedures of the National Emphysema Treatment Trial sponsored by the NHLBI.