TITLE: The impact of peginterferon alfa-2a maintenance therapy on portal hypertension in patients with chronic hepatitis C virus infection and advanced fibrosis and cirrhosis enrolled in the HALT-C trial.

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INTRODUCTION, BACKGROUND AND RATIONALE:

Chronic hepatitis C virus (HCV) infection is one of the most common causes of chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC) in the USA (**1**). Nearly half of all patients who undergo liver transplantation in the USA have cirrhosis secondary to chronic HCV. Although peginterferon alfa-2a and ribavirin is highly effective for treatment of chronic HCV more than half of patients with HCV genotype 1 do not achieve a sustained virologic response (SVR) and are at risk for fibrosis progression and may develop cirrhosis (**2**). Improvements in hepatic histology and a reduced risk for developing HCC have been observed in patients who achieve an SVR following interferon therapy (**3,4,5**). It remains controversial whether patients who have not become HCV RNA undetectable during interferon treatment, non-response (NR), have benefited from this treatment. Some data has suggested that patients with NR also exhibit improvements in hepatic histology and may have a reduced risk for the development of HCC (**3,4,5**). A randomized controlled trial has demonstrated that continuing interferon as a maintenance therapy in a sub-set of patients with NR is associated with a lack of fibrosis progression (**6**). These preliminary data formed the basis for the National Institute of Health to sponsor the HALT-C clinical trial.

1. Portal hypertension, morbidity and mortality:
   Portal hypertension develops in patients with advanced fibrosis and cirrhosis and is the primary driving force leading to complications of cirrhosis, hepatic decompensation and mortality in patients with chronic liver disease (**8**). None of the three major complications of advanced liver disease variceal hemmorhage, ascites and hepatic encephalopathy occur in the absence of portal hypertension. As a result, measuring portal pressure and treating

portal hypertension is an important part in the management of patients with advanced liver disease. A sub-study to measure portal pressure was initially proposed as part of the HALT-C clinical trial. Unfortunately, only 2/10 centers elected to participate in this sub-study and as a result, this was eventually dropped as a sub-study within the HALT-C trial.

2. The effect of interferon on portal pressure:
   Recent data has suggested that interferon therapy may selectively reduce portal hypertension in patients with cirrhosis. In an abstract presented at the 2004 annual meeting of the European Association for the Study of the Liver (EASL), portal pressure declined significantly in patients with NR after 6 months of treatment with peginterferon and ribavirin (**9**). At the time portal pressure was measured in this study, a transjugular liver biopsy was also performed to assess the effects of treatment on hepatic histology. Despite a reduction in portal pressure, no reduction in hepatic fibrosis score was observed. This suggested that interferon may reduce portal pressure through a direct affect on the hepatic vasculature; and suggests that interferon may prevent complications of cirrhosis regardless of its effects on HCV RNA and hepatic inflammation. Since portal pressure is the primary factor responsible for complications of cirrhosis including variceal hemorrhage, ascites and hepatic encephalopathy, these preliminary results suggest that maintenance interferon therapy could possibly prevent these complications.

   Preliminary results form a randomized, controlled trial of maintenance interferon therapy (Co-Pilot) presented at the 2004 annual meeting of the American Association of the study of Liver Disease (AASLD) did in fact demonstrate that patients with advanced fibrosis or cirrhosis who received maintenance peginterferon maintenance therapy over a two year period had a significant reduction in the incidence of variceal hemorrhage compared to that observed in the control group (**10**). The HALT-C trial provides an ideal patient population in which to further assess the effects of maintenance interferon therapy on portal hypertension.

3. Overview of the HALT-C trial:
   The HALT-C trial is a randomized, controlled study designed to determine if maintenance therapy utilizing peginterferon alfa-2a can prevent fibrosis progression, hepatic decompensation, reduce the risk of HCC, the need for liver transplantation and death in patients with advanced fibrosis or cirrhosis (**7**). The study is being conducted at 10 clinical sites in the USA and is funded by the National Institute of Diabetes, Digestive and Kidney Disease (NIDDK). Approximately 1,100 patients were enrolled in the HALT-C study over two years. Half of these patients are being treated with peginterferon alfa-2a 90 mcg/week. The other half are in an untreated control group. Both groups of patients are followed at 3 month intervals and monitored for the above noted end-points. The two sites with the largest enrollment in HALT-C are Virginia Commonwealth University with 223 patients and the University of Colorado with 163 patients. Together, these two sites account for close to 40% of all patients enrolled in the HALT-C trial.

4. Measuring portal pressure at the conclusion of the HALT-C trial:
   The first patients who were enrolled into the HALT-C trial are scheduled to complete four years of maintenance therapy near the end of 2004. This provides an optimal time point at which to assess the impact of maintenance interferon therapy on portal pressure. Although an ideal study design would have been to measure portal pressure at baseline and then again after 4 years in both the control and treatment groups, measuring portal pressure at the completion of the study will still provide significant information regarding the impact of maintenance interferon therapy on portal hypertension. The number of patients enrolled into HALT-C at these two sites is substantial (nearly 400 patients) and since the control and maintenance therapy groups were well matched at the start of the study we can assume that baseline portal pressure at the time of randomization was not significantly different in the two groups. Thus, if 4 years of maintenance interferon therapy does indeed reduce portal pressure a significant difference in mean portal pressure should be observed between the two groups at the completion of the HALT-C trial.

Patients who were randomized to the control arm of HALT-C during the past four years have received no treatment for chronic HCV during the past 4 years. Such patients will be offered the opportunity to receive peginterferon maintenance therapy for 6 months as part of this protocol and then undergo repeat measurement of portal pressure to determine if they could potentially benefit from remaining on peginterferon maintenance therapy long term.

HYPOTHESIS:

1. Peginterferon alfa-2a maintenance therapy (90 mcg/week) will reduce portal pressure in patients with advanced fibrosis or cirrhosis.

2. Peginterferon alfa-2a maintenance therapy (90 mcg/week) will reduce the incidence of complications in patients with advanced fibrosis or cirrhosis.

OBJECTIVES:

The study will be divided into two phases with the following objectives.

A. Phase 1:

Phase 1 of this study will assess portal pressure at the completion of the HALT-C trial. The study objectives for this phase 1 are as follows:

1. To determine if patients who received peginterferon alfa-2a maintenance therapy (90 mcg/week) during the HALT-C trial have a significantly lower portal pressure than patients randomized to the control (no-treatment) group.

2. To determine if patients who developed complications of cirrhosis (variceal bleeding, ascites and hepatic encephalopathy) during the HALT-C trial had a higher portal pressure at the end of this trail than patients who did not develop complications of cirrhosis.

B. Phase 2:

Phase 2 will consist of a randomized trial of peginterferon alfa-2a maintenance therapy versus no treatment for patients who were in the control arm of the HALT-C trial and did not receive peginterferon alfa-2a maintenance therapy. The study objectives for phase 2 are as follows:

1. To determine if 6 months of treatment with peginterferon alfa-2a maintenance therapy (90 mcg/week) will reduce portal pressure.

RESEARCH AND DESIGN METHODOLOGY:

A. Study Design - Phase 1:

Phase 1 of this study is an observational assessment of portal pressure in patients at the end of the HALT-C trial; a randomized controlled trial comparing peginterferon alfa-2a maintenance therapy (90 mcg/week) administered over 3.5 years to a control receiving no treatment group. The goals of the HALT-C trial are to determine if maintenance therapy with peginterferon alfa-2a fibrosis can reduce complications of cirrhosis, hepoatocellular carcinoma, the need for liver transplantation and improve survival.

Phase 1 of this study will be submitted as a formal ancillary study to the HALT-C steering committee. If approved, all data collected in this trial could then be entered into the HALT-C trial database and correlations between portal pressure measurements obtained at the completion of the HALT-C trial and end-points in the HALT-C trial could then be made.

Approximately 400 patients were enrolled in the HALT-C trial at the two Centers (VCU Medical Center, Richmond, VA and University of Colorado Health Science Center, Denver, CO) where this portal pressure study will be conducted. Patients are currently completing 4 years of participation in the HALT-C trial at these two Centers. It is anticipated that a total of 200 patients will be enrolled into this ancillary study at these two Centers.

1. After completing 3.5 years in the maintenance phase of the HALT-C Trial the possibility of participating in the portal hypertension study will be discussed with all eligible patients. Informed consent will be obtained from all patients who agree to enter this study at this time.

2. All portal pressure measurements will be performed by a Radiologist trained to measure hepatic venous pressure and who will be blinded as to the treatment that the patient received. Prior to the measurement of hepatic venous pressure the transducer will be calibrated against the same pressure standard.

    a. The left neck in the area of the jugular vein will be prepped and draped according to sterile conditions.

    b. The jugular vein will be cannulated and the cannula connected to a calibrated pressure transducer. The pressure of the right atriam and inferior vena cava will be obtained.

    c. The cannula will be advanced into the hepatic vein under flouroscopic guidance. The pressure of hepatic vein pressure will be measured.

    d. The cannula will then be advanced to the wedge position within the hepatic veins and the pressure again measured.

5. Patients who have provided informed consent to enter this portal hypertension study will then undergo hepatic venous catheterization and the following measurements will be obtained:
    a. Right atrial pressure
    b. IVC pressure
    c. Free hepatic vein pressure (FHVP)
    d. Wedged hepatic vein pressure (WHVP)
    e. The hepatic venous pressure gradient (HVPG) will then be calculated as follows: (FHVP) - (WHVP)

6. All laboratory studies and procedures obtained on these patients during their last visit in the HALT-C trial will be recorded. No additional laboratory studies need be obtained specifically for this study. The following laboratory studies will be recorded:
    a. Liver chemistries
    b. Complete blood count (WBC, hemoglobin, platelet count)
    c. INR
    d. Serum HCV RNA level
    e. Alpha-feto protein

7. Liver biopsy will be performed on all patients at the end of the HALT-C trial.

8. Upper endoscopy with standardized measurement of variceal size is performed on all patients at the end of the HALT-C trial.

9. Liver ultrasound is performed on all patients at the end of the HALT-C trial.

10. Patients who received peginterferon maintenance therapy as part of the HALT-C trial will receive no additional follow-up in this portal hypertension study after they recover from the hepatic vein catheterization procedure.

11. Patients who were randomized to the "Control-No Treatment Arm" of the HALT-C trial and had not received peginterferon alfa-2a maintenance therapy will be eligible to enter phase 2 of this portal hypertension study.

B. Study Design - Phase 2:

Phase 2 of this study will directly assess the effects of peginterferon alfa-2a maintenance therapy administered for 6 months on portal pressure. This will be accomplished by performing a randomized, controlled trial of peginterferon alfa-2a (90 mcg/week) maintenance therapy versus no treatment. Portal pressure will be measured at baseline and after 6 months in both the control and peginterferon alfa-2a maintenance therapy groups. Patients randomized to receive no treatment in Phase 2 will be treated with peginterferon alfa-2a (90 mcg/week) maintenance therapy for 6 months (after completing 6 months in the control-no treatment arm) and then undergo one final measurement of portal pressure.

1. After completing 3.5 years in the maintenance phase of the HALT-C Trial the possibility of participating in the portal hypertension study will be discussed with all eligible patients. Informed consent will be obtained from all patients who agree to enter this study at this time. Only patients who were randomized to the Control-No Treatment arm of the HALT-C Trial will be eligible to enter Phase 2 of this portal pressure study.

2. All portal pressure measurements will be performed by a Radiologist trained to measure hepatic venous pressure and who will be blinded as to the treatment that the patient received. Prior to the measurement of hepatic venous pressure the transducer will be calibrated against the same pressure standard. The specific procedure to measure portal pressure was described above (see section A.2 and A.3).

3. Patients entering phase 2 of this trial will be randomized to enter either Group A (peginterferon alfa-2a maintenance therapy) or Group B (no treatment) and stratified for presence of cirrhosis or no cirrhosis based upon the final biopsy performed at the completion of the HALT-C trial.

    a. Group A will treated with peginterferon alfa-2a at a dose of 90 mcg/week (the same dose as utilized for maintenance therapy in the HALT-C trial) for the next 6 months. These patients will be monitored at the following time intervals:
        i. 2 weeks
        ii. 1 month
        iii. 3 months
        iv. 6 months

    b. Group B patients will not receive peginterferon alfa-2a at this time. These patients will be followed at 3 month intervals (the same interval they had been followed in HALT-C) for an additional 6 months.

4. During each visit all patients (Groups A and B) will undergo the following evaluation:
    a. Physical examination
    b. Hepatic panel
    c. Complete blood count
    d. Pro-thrombin time
    e. Alfa-fetoprotein (performed at months 3 and 6 only)

f. Liver ultrasound to screen for HCC (performed at months 3 and 6 only)

5. Hepatic venous pressure measurements will be repeated in all patients (both Groups A and B) as described above (section A.2 and A.3) after 6 months of treatment with peginterferon alfa-2a (Group A) or 6 months of additional follow-up (Group B). Participation in this portal hypertension study will then be complete for patients who received treatment with peginterferon alfa-2a (Group A).

6. Patients randomized to Group B (not treated with peginterferon alfa-2a in the HALT-C trial or in this portal hypertension study) will then receive treatment with peginterferon alfa-2a at a dose of 90 mcg/week for the next 6 months. These patients will be monitored at the identical time intervals as outlined in section B.3.a.i-iv. During each of these visits the same laboratory studies as listed in section B.4.a-f will be obtained.

7. Hepatic venous pressure measurements will then be repeated one final time for patients in Group B as described above (section A.2 and A.3). Participation in this portal hypertension study will then be complete.

8. The dose of peginterferon alfa-2a will be reduced by 50% (45 mcg/week) for the following hematologic abnormalities:
   a. Decline in absolute neutrophil count below 500/mm (same criteria utilized for the HALT-C trial).
   b. Decline in platelet count below 30,000/mm (same criteria utlized for HALT-C trial).
   c. Significant psychiatric abnormalities as judged by the principle or co-investigator. No formal measurement of depression or fatigue will be utilized.
   d. If patients cannot tolerate the lower dose of peginterferon maintenance therapy they will be discontinued from the trial.

C. PHARMACOLOGY:

1. The starting dose of peginterferon alfa-2a for patients entering phase 2 of this study will be 90 mcg/week. This is the same dose as utilized in the HALT-C clinical trial.

2. The dose of peginterferon alfa-2a will be reduced by 50% to 45 mcg/week when patients develop adverse events as noted above. If this lower dose of peginterferon cannot be tolerated treatment will be discontinued and patients removed from the trial.

D. POPULATION CHARACTERISTICS:

1. Entry Criteria:
   a. All patents enrolled in the HALT-C trial at the Virginia Commonwealth University and the University of Colorado who have remained on peginterferon alfa-2a 90 mcg/week as maintenance therapy for the past 3.5 years.

   b. All patients enrolled in the HALT-C trial who were randomized to the control arm of the HALT-C trial and did not receive peginterferon alfa-2a 90 mcg/week as maintenance therapy for the past 3.5 years.

   c. The characteristics of these patients are as follows:
      1. Adults greater than 18 years of age.
      2. Male and female or all races
      3. Well defined chronic HCV with anti-HCV (+) and HCV RNA (+)
      4. Non-responders (HCV RNA positive after 20 weeks of treatment) to peginterferon alfa-2a or 2b and ribavirin.

d. Willingness of women with childbearing potential to utilize two forms of contraception at least one of which is a barrier method.

2. Exclusion criteria:
   a. Patients randomized to receive peginterferon alfa-2a 90 mcg/week as maintenance therapy but who could not tolerate this treatment for any reason and failed to remain on this treatment for the past 3.5 years. Patients with only brief interruptions in treatment will not be excluded as long as they have remained on treatment for the last 6 months before completing this trial.

   b. Patients randomized to the control group of HALT-C who do not wish to be treated with peginterferon maintenance therapy after the initial portal pressure measurement.

   c. Patients with any other co-existent liver disease were previously excluded from enrolling in the HALT-C trial. These disorders included:
      i. Chronic hepatitis B infection
      ii Alpha-1-antitrypsin deficiency
      iii. Wilson's disease
      iv. Non-alcoholic fatty liver disease
      v. Autoimmune liver diseases
      vi. Hemochromatosis (carriers of 1 HFE mutation may be enrolled as long as there is less than 3+ iron on the HALT-C entry liver biopsy).
      vii. Drug induced liver injury

   d. Patients who developed hepatocellular carcinoma while in the HALT-C trial.

   e. Patients with any underlying autoimmune disorder.

   f. Patients who require treatment with any immune suppressive agent.

   g. Patients who are actively utilizing illicit drugs.

   h. Patients who are consuming more than 6 grams of alcohol/day.

   i. Patients who are unwilling or unable to sign informed consent.

   j. Patients with advanced cardiopulmonary disease.

   k. Patients with uncontrolled diabetes mellitus.

   l. Patients who in the opinion of the principle or co-investigators should not be enrolled in this trial.

E. OUTCOMES:

1. HVPG and the WHVP (portal pressure) at the end of the HALT-C Trial:
   It is anticipated that patients who received peginterferon alfa-2a maintenance therapy in the HALT-C Trial will have a significantly lower HVPG and WHVP compared to patients who were in the control-no treatment arm of the HALT-C Trial.

   a. Linking of portal pressure to data obtained in the HALT-C trial:
      It is anticipated that patients who developed the following complications of cirrhosis while in the HALT-C trial with have a significantly higher portal pressure at the end of HALT-C than patients who did not develop these complications:

i. Development of varicies
ii. Development of portal gastropathy
iii. Variceal hemorrhage
iv. Development of ascites or use of diuretics to prevent ascites
v. Hepatic encephalopathy
vi. Thrombocytopenia
vii. Neutropenia

2. HVPG and WHVP (portal pressure) 6 months after completing the HALT-C trial:
It is anticipated that patients who were in the Control-No Treatment arm of HALT-C, who then receive peginterferon alfa-2a will have a significant decline in HVPG and WHVP. In contrast, it is anticipated that patients who remain in the Control-No Treatment group will have either no change or a small increase in HVPG and WHVP.

3. HVPG and WHVP (portal pressure) in Group 2 patients who received delayed treatment with peginterferon alfa-2a:
It is anticipated that these patients would have no significant decline in portal pressure after being followed for 6 months with no additional treatment after completing he HALT-C trial. However, it is expected that these patients would then have a decline in portal pressure after receiving 6 months of treatment with peginterferon alfa-2a.

F. DATA ANALYSIS:

1. Sample size for Phase 1:
No formal sample size calculations were performed for Phase 1 of this study. The clinical outcomes observed in patients during for the HALT-C trial will be compared to the portal pressure measurements. It is anticipated that patiens who developed complications of cirrhosis during HALT-C will have a higher mean portal pressure.

Portal pressure was not measured during the HALT-C trial. As such, no baseline measurement of portal pressure is available for comparison with the portal pressure measurements observed at the completion of the HALT-C trial (Phase 1 of this study). Mean portal pressure at the completion of HALT-C (phase 1 of this study) will be compared in patients who had received peginterferon alfa-2a or no treatment while in the HALT-C trial. In a small previous trial, treatment of cirrhotic HCV patients with peginterferon and ribavirin was associated with a reduction in portal pressure by about 20-25% from the pre-treatment baseline (**9**). It is therefore possible that a significant decline in portal pressure may be observed patients who received peginterferon alfa-2a (90 mcg/week) maintenance therapy in the HALT-C trial when compared to the no-treatment control group.

To date in the HALT-C trial, approximately 33% of patients found to have bridging fibrosis on liver biopsy were also found to have esophageal varicies, thrombocytopenia, spenomegally and other findings consistent with cirrhosis. As a result, the HVPG is likely to be a better measure of cirrhosis than liver biopsy and confining portal pressure measurements only to patients with histologically confirmed cirrhosis is likely to exclude many patients who developed complications of cirrhosis and who have elevated portal pressure from this analysis. For these reasons, we propose to measure portal pressure in all patients who complete the HALT-C trial at these two Centers. By the time this study is initiated, we estimate that this will be approximately 200 patients.

2. Sample size for Phase 2:
Patients who were treated in the control-no treatment arm of the HALT-C trial will be randomized to treatment with peginterferon alfa-2a or no treatment for 6 months. It is anticipated that 100 patients will be eligible for randomization, 50 in each group. It is anticipated that a 10-20% mean decline in portal pressure from the pre-treatment baseline will be observed in patients treated with peginterferon alfa-2a and that no net

change in portal pressure will be observed in the control-no treatment group. Assuming a standard deviation of 15% in portal pressure measurements in each group, an alpha (type I) error of 0.05 and beta (type II) error of 0.1; then 15-58 patients will be required to demonstrate that peginterferon alfa-2a contributes to a significant reduction in portal pressure.

3. Data analysis:
   Portal pressure measurements at the end of HALT-C will be entered into the HALT-C database if this study protocol is approved as a formal HALT-C ancillary study. This data can then be linked with other outcomes of portal hypertension such as esophageal varicies, variceal hemorrhage, ascites, hepatic encephalopathy, thrombocytopenia and neutropenia. Absolute measurements of portal pressure will also be available to the investigators in order to determine if maintenance therapy led to lower net value for portal pressure in patients treated with maintenance peginterferon.

   Changes in portal pressure after 6 moths of treatment with peginterferon alfa-2a will be calculated by comparing portal pressure at the end of HALT-C to values obtained after 6 months of peginterferon. IT is anticipated that a 10-20% decline in portal pressure will be observed in this group. This will be compared to the change in portal pressure in patients in the control no treatment group. These changes in portal pressure will not be entered into the HALT-C trial database and tabulated and analyzed the investigators of this trial.

SAFETY:

1. The potential complications of obtaining hepatic venous pressure measurements will be discussed with each patient prior to their signing informed consent to participate in this protocol and undergoing hepatic venous pressure measurements. These potential complications include bleeding at the site of cannulation, soreness or hematoma in the left neck secondary to cannulation of the jugular vein and cardiac arrhythmia.

2. For patients entering phase 2 of this study:
   The potential complications of being treated with peginterferon alfa are well known to all patients since all were treated with this medication either as part of the HALT-C trial or just prior to entering ths trial. The major complications of peginterferon therapy in patients with advanced fibrosis or cirrhosis include thrombocytopenia and neutropenia. These laboratory studies will be monitored on a regular basis and dose adjustments of peginterferon will be made as noted above. Patients will also be monitored at monthly intervals for possible psychiatric side effects of treatment including depression and irritability.

3. All concomitant medications will be recorded at each study visit in the data collection forms.

4. Reporting of Severe Adverse Events:
   a. Definition of a serious adverse event (SAE):
      An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any Adverse Event that at any dose fulfils at least one of the following criteria:
      i. Is fatal (i.e., where death is the outcome of the event, report the event).
      ii. Is life-threatening (i.e., the patient was at immediate risk of death at the time of the event; not hypothetically at risk of death had the event been more severe).
      iii. Requires in-patient hospitalization or prolongation of existing hospitalization.
      iv. Results in persistent or significant disability/incapacity.
      v. Is a congenital anomaly/birth defect.

   b. Definition of an unexpected adverse events UAE):

An UAE is one the nature or severity of which is not consistent with the applicable package insert.

c. Reporting timelines:
Any SAE, UAE or seriously abnormal laboratory test value occurring during the study, irrespective of the patient's treatment, will be reported to Roche by the Principal Investigator within 7 calendar days of learning of the event. Preliminary reports will be followed later by detailed descriptions which include copies of hospital case records, autopsy reports and other documents when requested and applicable. The definition and reporting requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, will be adhered to. The investigator will also notify the Institutional Review Board (IRB) of such an event in writing as soon as is practical and in accordance with international and local laws and regulations.

d. Pregnancy Reporting:
Female patients will be instructed to immediately inform the investigator of any pregnancy. When notified of a pregnancy, the investigator will instruct the patient to stop taking study medication. The investigator will counsel the patient; discuss the risks of continuing the pregnancy and the possible effects on the fetus. The patient will be monitored until the pregnancy is concluded.

The Principal Investigator will report all pregnancies, including those occurring up to 6 months after study completion, to Roche within 15 days of discovery. Pregnancy occurring in the partner of a patient participating in the study will also be reported to Roche by the Principal Investigator.

Reports of pregnancies will be sent via facsimile to Roche's Pharma Development Medical Safety - Central Operations (PDMS-COps) in Welwyn, U.K. at 011.44.170.737.3793 using Form FDA 3500 (i.e., a MedWatch form). Reports of pregnancies will not be sent to the FDA.

e. Expedited Reporting (Immediate Reporting to Roche):
Each SAE and UAE will be reported using Form FDA 3500 (i.e., a MedWatch form) within 15 calendar days of discovery or within seven calendar days if the event was life-threatening or fatal. Each time a Form FDA 3500 is submitted to the FDA, the Principal Investigator will simultaneously forward a copy via facsimile to Roche's Pharma Development Medical Safety - Central Operations (PDMS-COps) in Welwyn, U.K. at 011.44.170.737.3793. If Roche PDMS determines a medical assessment of the SAE is necessary, the Principal Investigator will provide the additional information upon Roche's request.

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