HALT-C Lead-In Phase

Lead-in Group patients who met the eligibility criteria and completed the required testing during the Screening Phase can be enrolled in the Lead in phase of the HALT-C Trial. During this phase, patients will receive combination therapy of peginterferon alfa-2a 180 μg sc once weekly plus 1000-1200 mg of ribavirin by mouth, daily in two divided doses. There are special safety measures for patients who enter the trial with platelet count under 75,000/mm^3 and/or neutrophils under1,500/$mm^{3:}$ The ribavirin should be unchanged, but may be lowered at the PI's discretion. Patients will start at a reduced dose of 90 μg of peginterferon alfa-2a once weekly. More information on the Lead-in Phase can be found in section H of the HALT-C protocol.

Baseline Visit (W00)
This visit must be conducted within 14 weeks of Screening Visit 1. The patient should be fasting for required lab tests. The following must be performed:

Visit Control Sheet
The Visit control sheet (VCS) should be printed prior to each study visit, regardless of the phase of the trial the patient is in. This is a computer generated form, recording the patients ID number, initials and study visit number, as well as the forms to be completed, labs to be drawn and tests to be done at that particular visit. The form will also indicate any non-trial medications the patient was taking, and any ongoing adverse events.

Patient administered questionnaires
- Alcohol Use (#42)
- Symptoms (Form #43)
- Physical Activity (Form #140)
- Analgesics Medications History (Form #141)

Interviews
- Baseline Medication Interview (Form #7)
- Life Events (Form #45)

Local lab test (Forms #30, #34)
- Fasting serum chemistries (BUN, creatinine, glucose, uric acid, triglycerides)
- Liver chemistries ((AST, ALT, alkaline phosphatase, total bilirubin, albumin, and globulin [or total protein])
- Complete blood count with diff (WBC, neutrophils, hematocrit, hemoglobin, platelets)
- Prothrombin time (INR)
- Alfa-fetoprotein (AFP)
- Pregnancy test (for women of child bearing potential)

Central lab tests (Forms #31, 72)
- HCV-RNA (sent to central repository for shipping to the central virology lab. See Section E, Specimen Collection, Processing, and Shipping for more information).

Forms
- Form #8: Baseline visit date. This form should be completed on the date that the patient receives the first dose of trial medication. This is the patient's official date of entry into the HALT-C Trial. This form should be data entered first.
- Form #7, Baseline Medication Interview
- Form #15, CTP Score

- Form #26, Pegasys accountability log
- Form #27, Ribavirin accountability log
- Form #30, Local Lab
- Form #31, Central Lab (results sent via email to clinical center; data form entered at the Central Virology Lab).
- Form #34 AFP
- Form #42, Alcohol Use Questionnaire
- Form #43, Symptoms
- Form #45, Live Events Status Form
- Form #72, Lead In Phase Aliquot Form
- Physical Activity (Form #140)
- Analgesics Medications History (Form #141)

Dispensation of trial medications

Trial medications should be dispensed to the patient for the first time at this visit. It is recommended that the patient take the first dose of each medication in front of the study coordinator/nurse. The patient should also receive medication instructions and follow up information at this time. Remind the patient to bring in all empty or unused vials and bottles.

Drug Accountability Logs and Dose Adjustments

Drug Accountability Logs (Forms #26 & #27) should be filled out for each individual patient when they receive and return medications. Drug Dose Adjustments (Forms #28 & #29) must be completed when s/he has a dose adjustment. If for some reason the patient is not started on ribavirin, complete Form #29 as indicated in the QxQ. Please see Section H, Trial Medication for further details in the dispensation of trial medications.

Patient diaries

Review with the patient the use of the patient diary, which will be used to record the administration of trial medications; any missed doses of trial medications; other medications; and patient visits to a health care provider; emergency room, hospital, or urgent care facility. Review the diary with the patient at each visit and use it as a guide in filling out the appropriate data forms.

Scheduling visits in the computer

The appointment date of the next visit can be printed on the visit control sheet if it is data entered into the system. See section C, Data Management, for instructions.

Week 2, 4, 8, 12, and 16 Visits W02, W04, W08, W12, W16

Follow the visit schedule provided in Section B5 for required tests, labs, questionnaires and forms. Dispense medications at each visit. See Section I, Adverse Events, for questions regarding dose modifications that may be required during the Lead-in Phase.

Week 20 Visit (W20)
Lead-in Group patients are assessed at Week 20 (W20) for virologic response and eligibility for randomization. The patient should be fasting for required lab tests and ultrasound.

Data collected to assess the eligibility of the Lead-in Group patients for randomization is recorded on Form #21: Randomization Checklist. This form triggers the DMS to randomize patients to the Treatment or Control Arm; to place the patient in the Week 20 Responder protocol, or to schedule no further visits if the patient is no longer able, willing or eligible to participate. This form should be data entered in the patient's W20 visit.

The following testing and interviews are required at Week 20:

W20 Patient administered Interviews
- Symptoms (Form #43)
- Beck Depression Inventory (Form #44)

W20 Interviews
- Study Visit (Form #10)
- Medications Interview (Form #12)

W20 Tests
- Physical exam (Form #11)
- Ultrasound, MRI, CT evaluation of the liver (Form #22)

W20 Local lab tests (Form #30)
- Fasting serum chemistries (BUN, creatinine, glucose, uric acid, triglycerides)
- Liver chemistries (AST, ALT, alkaline phosphatase, total bilirubin, albumin, and globulin [or total protein])
- Complete blood count with diff (WBC, neutrophils, hematocrit, hemoglobin, platelets)
- Prothrombin time (INR)
- Thyroid stimulating hormone (TSH)
- Alfa-fetoprotein (AFP)
- Pregnancy test (for women of child bearing potential)

W20 Central lab tests (Forms #31, 32, 72)
- HCV-RNA sent to central repository for shipping for the central virology lab

W20 Forms
- Form #10, Study Visit
- Form #11, Physical Exam
- Form #12, Medications Interview
- Form #15, CTP Score
- Form #21, Randomization Checklist (see below for further details)
- Form #22, Ultrasound (MRI, CT)
- Form #30, Local Lab
- Form #31, Central Lab (results sent via email to clinical center; data form entered at the Central Virology Lab)
- Form #34, AFP
- Form #43, Symptoms
- Form #44, Beck Depression Inventory
- Form #72, Lead In Phase Aliquot Form

Week 24 Visit (W24)
Week 24 is the last visit in the Lead-in Phase. See the appropriate section, according to whether the patient enters the Randomized Phase or Week 20 Responder Phase.

Patients with undetectable HCV RNA at Week 20 will be considered to have a virological response and can enter the Responder Phase.

If the patient is a non-responder and is not eligible for randomization, Week 24 will be her/his final visit in the HALT-C Trial.
Patients who meet any of the following conditions are not eligible for continuation in the HALT-C trial and Week 24 will be the final visit:

- The AFP level is equal to or above 1000 ng/ml.
- There is evidence of HCC on the ultrasound.
- Both CTP scores are 7 or greater at Week 12 and Week 20.
- There is evidence of a clinical outcome.
- The patient is unwilling to be randomized.
- The patient is unwilling to be followed for the duration of the study.
- The patient is non-compliant with medications or study visits.

If the patient is not eligible and/or not willing to be randomized, complete Form #5: Trial Ineligibility, thus closing the patient in the DMS.

<u>W24 Instructions to Patients entering Responder Phase</u>
- Collect returned ribavirin and Peginterferon alfa-2a 180 μg.
- Dispense trial medications. Patients will continue to receive their current dose of Peginterferon alfa-2a (180 μg sc weekly or adjusted dose) and ribavirin (1000 mg or 1200 mg/day depending on weight or adjusted dose).
- Give medication instructions and follow up information regarding Week 30 visit.
- Record return and dispensation of Peginterferon on Form #26: Peginterferon Accountability Log.
- Record return and dispensation of ribavirin on Form #27: Ribavirin Accountability Log.

<u>W24 Instructions to Patients who are non-responders and not eligible or not willing to be randomized</u>
- If the patient is not willing or ineligible to be randomized for any reason, Week 24 will be the last visit in the HALT-C Trial. After all the forms for W24 are completed and data entered in the DMS, no other form need be completed.
- Collect all vials of Peginterferon alfa-2a 180 μg and record return on Form #26: Peginterferon Accountability Log.
- Collect all ribavirin and record return on Form #27: Ribavirin Accountability Log.
- Record Peginterferon dose discontinuation on Form #28: Peginterferon Dose Adjustment.
- Record ribavirin dose discontinuation on Form #29: Ribavirin Dose Adjustment.