Hepatitis C Antiviral Long-term Treatment against Cirrhosis

HALT-C Trial
Data Coordinating Center

To: FDA, IRBs and DSMB Members
From: HALT-C Trial Steering Committee
Re: Amendment # 7 to HALT-C Trial protocol
Date: July 24, 2006

The HALT-C Trial Steering Committee has recommended that the changes detailed below be made to the HALT-C Trial protocol (Version: 01/20/2004). This amendment is to allow for extended surveillance follow up of patients through October 2009.These changes have been incorporated into the protocol (Version: 07/21/2006) and are submitted for your review.

1.) Title, Title page (page 1):

The underlined phrase has been added to reflect the amendment regarding the Extension of HALT-C.

Extension of the **H**epatitis C **A**ntiviral **L**ong-term **T**reatment against **C**irrhosis (HALT-C) Trial: A randomized controlled trial to evaluate the safety and efficacy of long-term peginterferon alfa-2a for treatment of chronic hepatitis C in patients who failed to respond to previous interferon therapy.

2.) Principal Investigators, Title page (page 1):

The underlined names of Principal Investigators at HCV Treatment Center and Data Coordinating Center have been changed to reflect personnel changes.

HCV Treatment Centers:
Gyongyi Szabo, M.D.
University of Massachusetts
Worcester, MA

Data Coordinating Center:
Kristin K. Snow, Sc.D.
New England Research Institutes
Watertown, MA

3.) Section A: Purpose and Overview, A2 Overview (page 4):

The underlined phrases define the end date of follow-up for all patients entering the HALT-C Trial. Those patients who are currently being followed will be offered up to five visits at 6-month intervals through October 2009.

In August, 2001, to increase enrollment two modifications were made to the study design: Those Week 20 Responder patients with virologic breakthrough or relapse documented by detection of HCV RNA at weeks 36, 48, 60 or 72, and those patients who are adequately treated with pegylated interferon and ribavirin combination therapy outside of the HALT-C Lead-in (Express Group) will be considered for randomization into the maintenance phase. These patients will be followed for an additional 48 months and their biopsies performed 18 months and 42 months after randomization.

All treatment in the randomized phase will end in January 2007. A small number of patients may not have completed 48 months at that time. Every patient will stop treatment at that time point, regardless of what month of randomization they are in.

Those patients who have completed Month 54 visit will be offered "extended follow-up" visits at Month 60 and Month 72 through April 2007. These visits will primarily be to identify outcome events, and to provide information to patients concerning the current status of the trial. Some questionnaires, blood tests, and an ultrasonogram will be performed. This visit is not to take the place of patients establishing a relationship with a primary care or liver specialist once the Month 54 visit is completed.

Those patients who are currently being followed will be offered visits at 6 month intervals through October 2009. Depending on when the patient was randomized this visit will be a Month 54, Month 60, Month 66, Month 72, Month 78, Month 84, Month 90, Month 96, Month 102 and Month 108. Each of these visits will be similar. These visits will primarily be to identify outcome events, and to provide information to patients concerning the current status of the trial. Some questionnaires, blood tests, and an ultrasonogram will be performed. This visit is not to take the place of patients establishing a relationship with a primary care or liver specialist after April 2007 visit is completed.

4.) Section B: Summary and Study Rationale B.6. (page 12):

The underlined phrase was added at the end of this section to define the aim of the Extension of HALT-C through October 2009.

The purpose of the continued observation in this long-term follow-up phase of the HALT-C Trial is to determine the outcome of patients enrolled in this study over a longer time interval.

5.) Section E: Inclusion Criteria E.8. (page 14):

The underlined phrase was added and phrase crossed out to clarify the use of adequate contraception in the Extension of HALT-C through October 2009.

E. 8. A willingness by all women of child bearing potential to utilize adequate contraception during the ~~entire 4 years of this~~ Main Trial study. Use of adequate contraception is not mandated during the extension trial since no medication is being offered.

6.) Section F: Exclusion Criteria F32. (page 19):

The underlined phrase was added to clarify the exclusion of patients who have had a liver transplantation from the Extension of HALT-C through October 2009.

F32. Patients who have undergone liver transplantation.

7.) Section J: Randomized Phase J.4. (page 25.)

The underlined phrase was added to define the addition of Extension of HALT-C visits for those patients who are currently being followed..

J.4. Post-treatment follow-up:

Patients in both groups will be followed but not treated for an additional 6 months after study visit Month 48 (Table 2, visit Month 54). Additional follow-up visits will be offered to patients at Month 60 and Month 72 until April 2007. After April 2007 follow-up visits every six months will be offered to all patients who are being currently followed except for those patients who have undergone liver transplantation.

8.) Section N: Adverse Events N.2. Data collection procedures for adverse events (page 28):

The underlined phrase has been added to clarify the data collection of adverse events in the Extension of HALT-C visits.

N.2.a. At each follow-up visit through Month 54, patients will be interviewed regarding medical conditions, medical changes and symptoms that have occurred since the last visit. All adverse events and Serious Adverse Events as of May 1, 2007 will not be reported to the DCC.

9.) Section N: Adverse Events N.3.b. Reporting procedures for deaths (page 28):

The underlined phrase has been added to clarify the data collection of death reporting.

N.3.b. All deaths, in both the treated and in the control group will be reported to the DCC within 24 hours by telephone. The Death Report will be faxed to the DCC within 24 hours. This reporting begins at the time the patient has signed the Trial informed consent up to the last scheduled patient visit (through October 2009). The report will include the relationship of the death to trial medications. A Clinical Outcome form will also be completed and sent to DCC for distribution and review by the Outcome Review Board (ORB). Deaths will be reported immediately to NIDDK and the DSMB. A death will be reported in an expedited report only if it is unexpected and drug related. A death must also be reported in accordance with local law and regulations.

10.) Section Q: Policies and Procedures. Central Repository Q.1.e. (page 35):

The underlined phrase has been added and words deleted to reflect the change in the name of the Central Repository.
Q.1.e. Central Repository (CR)

SeraCare Bio Services, formerly BBI-Biotech Research Laboratories, Inc, will serve as the Central Repository for the trial. This repository will be responsible for receipt, storage and distribution of serum, plasma, peripheral blood mononuclear cells (PBMC) and frozen liver tissue.

11.) Section Q: Data and Safety Monitoring Board. Q.1.i. (page 37):

The underlined phrase has been added to reflect the continued monitoring of the Extension of HALT-C by a DSMB.

Q.1.i. Data and Safety Monitoring Board
The primary purpose of this Board will be to monitor and provide independent ethical oversight for the trial. The DSMB will provide advice to NIDDK, as needed. This board will review the protocol developed during Phase 1, plans for recruitment and follow-up, and any other questions pertinent to the ethical conduct of the trial. It will review protocol changes and might suggest changes as needed. During Phase 2, it will monitor the data at regular intervals to determine whether significant benefit or harm has been demonstrated in either treatment group or whether there is other compelling need to stop the trial.

If the DSMB finds the treatment to be effective all patients enrolled into HALT-C will be notified. However, funds are not currently available to provide treatment to all study participants. Every effort will be made to assist all patients in obtaining treatment with peginterferon alfa-2a.

During the extension, a DSMB will continue to monitor the study.

12.) Tables and Figures: Figure 1: Design of the HALT-C Trial (page 39):

The following underlined phrases have been added and phrases deleted to reflect the addition of study visits every 6 months after Study Visit Month 54.

Study visit month 60 ~~& Month 72~~ and every 6 months through 10/31/09.

13.) Tables and Figures: Table 5: Trial Flow Chart – Extension of the HALT-C Trial (page 45):

All Month 60 through Month 108 Study Visits performed after April 2007 will consist of the following as outlined in the table: PE, LFT, Creatinine, CBC, PT, AFP, 5 serum aliquots and U/S.

14.) Template Consent Form: Title of Research (page 1)

The following phrases have been added to identify the consent for the Extension of HALT-C.

Title of Research: Extension of the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial: A randomized controlled trial to evaluate the safety and efficacy of long-term Peginterferon alfa-2a for treatment of chronic hepatitis C in patients who failed to respond to previous interferon therapy

15.) Template Consent Form: Invitation (page 1)

The following phrases have been added to invite patients for the Extension of HALT-C.

INVITATION: You are invited to continue participation in an observational trial to study the outcomes of effectiveness of long term antiviral therapy for your chronic hepatitis C. You are considered eligible to participate if you completed the HALT-C Trial. The present study is an extension through October 31, 2009; you are being offered further follow-up for your hepatitis C condition.

16.) Template Consent Form: Complications (page 2)

The following phrases have been deleted because there is no study drug being used in the Extension of HALT-C.

~~**COMPLICATIONS:** Every effort will be made to prevent any injury or other complication that can result from your participation in this research. The medical doctors listed in the heading of this consent form can recommend treatment in case of injury or any other complication, which you should report to them promptly. Emergency medical treatment will be provided by this Medical Center. Provision of subsequent medical care will be determined by XX. **Telephone numbers where they may be reached are listed above.**~~

~~Compensation for a physical injury or any other complication that results from participating in this research is not available from this Medical Center. However, you retain your legal rights during your participation in this research.~~

17.) Template Consent Form: Study Procedures (page 3)

The following phrases have been deleted to reflect that there will be no virus counts or further genetic testing in the Extension of HALT-C.

At each visit during the maintenance phase of the study, approximately 70 cc of blood will be collected for laboratory tests. Blood samples will be used to monitor progress of your liver disease. These tests include: blood counts, liver enzyme, ~~virus counts,~~ and alpha fetoprotein (a marker that is used to detect liver cancer). A small portion of your blood sample will be stored in a repository for future testing to identify factors that affect progression of liver disease and development of liver cancer. ~~These tests could include but are not limited to genetic testing. Your specimens may be used to develop commercially valuable medical products. By signing this form you agree not to seek share of any proceeds that might result; that is, you waive any claim to share in the commercialization of products developed from your DNA samples.~~

18.) Template Consent Form: Study Procedures (page 3)

The following phrase has been added to clarify that there will be ultrasound testing every six months in the Extension of HALT-C.

All patients will undergo ultrasound examinations of the liver at every six months to screen for liver cancer.

19.) Template Consent Form: Study Procedures (page 3)

The following underlined phrases have been added to clarify the nature of the study visits and have the participant agree or disagree to continue with the Extension of HALT-C.

If you have continued in the HALT-C Trial you will be offered follow-up visit(s) through October 2009, at which time the study will be officially closed. These observational visits are to provide us with additional data on your progress after your study participation is completed. The visit(s) will include questionnaires about your overall health status, a physical examination, blood tests, and an ultrasonogram. You will not be receiving additional care or asked to have a biopsy at these visits.

I agree to participate in the above-mentioned follow-up visits through October 2009.

☐ Yes ☐ NO

Patient's signature

_____

Witness' signature (if applicable)

_____
Date

20.) Template Consent Form: Medications under Investigation (page 3)

The following phrases have been added to clarify that there are no medications under investigation in the Extension of HALT-C.

No medications are under investigation in this portion of the study. You may take any medications that you or your doctor choose to use for your hepatitis C at this point in the study. At some point in the future, other medications may be offered through the HALT-C Trial but this present study does not include such medications.

21.) Template Consent Form: Discontinuation of Participation (page 4)

The following phrases have been deleted to clarify that the Extension of HALT-C is an observational study and patients will not discontinue participation related to liver failure or liver cancer.

DISCONTINUATION OF PARTICIPATION: The investigator may discontinue your participation in this study if you fail to follow study instructions, if it is considered to be in your best interest or if the entire study is canceled by the sponsor. ~~The investigator will also discontinue your participation in this study if there is evidence that you have developed liver failure or liver cancer.~~

22.) Template Consent Form: Consent for Testing (page 5)

The following phrases have been deleted because there is no genetic testing in the Extension of HALT-C.

~~A. CONSENT FOR TESTING~~
~~I consent to have my blood, cell lines and tissues used for genetic testing. You can participate in this study and NOT have your blood, cell lines, or tissues used for genetic testing.~~

_____ _____
~~Name~~ ~~Date~~

~~B. CONSENT FOR INFORMATION~~
~~I consent to be informed of any genetic information that is found from any blood, cells, or tissues taken from me during any part of this study. I understand the risks that this information may imply.~~

~~_____ _____~~
~~Name Date~~

~~* By not signing your name you consent to~~ not be informed ~~of any genetic information that is found using your blood, cells, or tissue during the course of this study.~~

23.) Template Consent Form: Design of HALT-C (page 6)

The following underlined phrases have been added and phrases deleted to reflect the addition of study visits every 6 months after Study Visit Month 54.

Study visit month 60 ~~& Month 72~~ and every 6 months through 10/31/09.