Hepatitis C Antiviral Long-term Treatment against Cirrhosis

HALT-C Trial

End of Study Outcome Definitions – April 2005

1. Overview

The purpose of this document is to summarize current outcomes procedures and to propose end of study outcome definitions for the primary outcome of the trial.

2. HALT-C Randomization and Stratification

A total of 1050 patients were randomized. The first patient was randomized on January 17, 2001. The last patient was randomized on August 16, 2004 as a Relapse patient.

- 662 patients who were non-responders at the end of the Lead-in Phase;
- 151 Breakthrough or Relapse patients who were responders at the end of the Lead-In Phase but later became HCV RNA positive; and
- 237 Express patients.

Randomization was stratified based on the Central Pathology Committee reading of the screening biopsy. For the 1,050 randomized patients, 622 biopsies were read as fibrosis (59%) and 428 as cirrhosis (41%).

3. Timing of Month 48 Study Visits and Liver Biopsies

Liver biopsies during the Randomized Phase are collected at Month 24 and Month 48. In November 2004, the Steering Committee approved that the window for liver biopsies was 3 months previous and 6 months after Month 24 and Month 48. The biopsy window is calculated using the "target" liver biopsy date, which is the midpoint of the Month 24 or Month 48 visit (identified on the Visit Control Sheet).

- A biopsy taken from 3 months previous to the Month 24 "target" date or 6 months after Month 24 "target" date will be called a Month 24 Biopsy.
- A biopsy taken from 3 months previous to the Month 48 "target" date or 6 months after the Month 48 "target" date will be called a Month 48 Biopsy.

For patients randomized at the end of the Lead-in Phase, the M48 visit and biopsy windows are calculated from Form #8 Question B1: the date the patient entered the Lead-in and received the initial supply of Trial medications (trial_init).

M48 window = (trial_init + 48 months) ± 21 days

M48 Biopsy Window: (trial_init + 48 months – 3 months) to (trial_init + 48 months + 6 months)

For Express, Breakthrough, and Relapse patients, the Month 48 visit and biopsy windows are calculated from Form #98 Question B1: the date the patient came in for Randomization Visit (rand_visit).

M48 window = (rand_visit + 42 months) ± 21 days

M48 Biopsy Window: (rand_visit + 42 months – 3 months) to (rand_visit + 42 months + 6 months)

There were 50 patients randomized after July 2003 who will be followed until April 30, 2007 rather than until Month 48. All 50 of these patients will have a Month 48 type visit as their final HALT-C visit. The Steering Committee determined in March 2007 that all biopsies and endoscopies must be completed by March 31, 2007. All Trial medication treatment will be stopped on January 31, 2007.

4. Definition of the Primary Outcome for the HALT-C Trial

The major outcome variable for the HALT-C trial is the progression of liver disease as judged by any of the following eight outcomes. Type #1 of the eight outcomes is relevant only for the patients who had a baseline biopsy centrally read as fibrosis. It is expected that most of the primary clinical outcomes (Types #2 – #8) will occur in patients with a baseline biopsy centrally read as cirrhosis.

1. Increase in fibrosis score by 2 points or more at year 2 or year 4 biopsy (determined by Central Pathology Review).

2. Death from any cause.

3. Development of hepatocellular carcinoma (HCC) based on *either*:
   a. Histology showing HCC (from a biopsy, surgery, or autopsy), *or*
   b. A new hepatic defect on imaging with an AFP rising to > 1,000 ng/ml.

4. CTP score of 7 or higher at two consecutive study visits (i.e., two visits where completion of CTP Score Form #15 is required).

5. Variceal hemorrhage defined as gastrointestinal hemorrhage that is due to bleeding esophageal or gastric varices, based on an endoscopy showing *either*:
   a. Direct evidence of variceal bleeding (bleeding varix, red wale sign), *or*
   b. Moderate varices with no other site of bleeding identified, plus historical evidence for clinically significant upper gastrointestinal bleeding.

6. Ascites defined as any abdominal fluid that is *either*:
   a. "Mild", "moderate", or "marked" on ultrasound. (Abdominal fluid that is "mild" or "barely detectable" on physical examination requires ultrasound confirmation of "mild", "moderate", or "marked" ascites. An ultrasound report of "minimal" fluid around the liver does not meet the definition), *or*
   b. Progressive on serial physical examinations, *or*
   c. Requires diuretic therapy.

7. Spontaneous bacterial peritonitis (SBP) defined as any episode of spontaneous ascitic infection diagnosed on the basis of *either:*
   a. Elevated neutrophil count (> 250/ml) in paracentesis fluid, *or*
   b. Positive bacterial cultures and clinical diagnosis, in the absence of WBC availability.

8. Hepatic encephalopathy defined as any mental status alteration that is due to portosystemic encephalopathy *either*:
   a. Occurring during a provoked episode (GI bleeding, diuretics, usual sedative doses), *or*
   b. Occurring spontaneously (without apparent cause).

All possible clinical outcomes are reviewed by the Outcome Review Board, which consists of three of the clinical PIs, with membership changing every three months. Dr. Leonard Seeff chairs the board. Each possible outcome is masked and then sent to two members for review. If they do not agree, then Dr. Seeff reviews the outcome. Members do not review information from their own sites.

If an Outcome Review Board Member decides the event met the clinical outcome criteria, he or she reviews the required source documentation regarding the event and determines when the event first fulfilled Clinical Outcome criteria. [See Attachment A from Section I.2 of the Manual of Operations for primary clinical outcome definitions and required source documentation.]

5. Proposed Primary Outcome Cut-off Dates

The plan for the final analysis of the primary outcome has been described in Section B.2 of the HALT-C Trial Manual of Operations (6/15/2000) and in the Data Monitoring Plan approved by the Steering Committee (03/18/2004). The primary analysis will be an intent-to-treat analysis and all randomized patients will be included.

We propose the following guidelines for "cut-off" dates at the end of the HALT-C Trial for the eight primary outcome types:

1. Increase in Ishak fibrosis score by 2 points or more on a biopsy taken up to 3 months after the Month 48 "target" date.
2. Death from any cause occurring up to 3 months after the Month 48 "target" date.
3. Development of definite HCC that met the clinical outcome criteria up to 3 months after the Month 48 "target" date.
4. CTP score of 7 or higher at two consecutive at least three months apart visits, with the second CTP score of 7 or higher calculated up to 3 months after the Month 48 "target" date.
5. Variceal hemorrhage that met the clinical outcome criteria up to 3 months after the Month 48 "target" date.
6. Ascites that met the clinical outcome criteria up to 3 months after the Month 48 "target" date.
7. Spontaneous bacterial peritonitis that met the clinical outcome criteria up to 3 months after the Month 48 "target" date.
8. Hepatic encephalopathy that met the clinical outcome criteria up to 3 months after the Month 48 "target" date.

Attachment A. PRIMARY CLINICAL OUTCOMES: Definitions, Forms to Complete, Required and Supportive Source Documentation

CLINICAL OUTCOME	PROTOCOL DEFINITION	FORMS TO COMPLETE	REQUIRED SOURCE DOCUMENTATION	SUPPORTIVE DATA / DOCUMENTATION
Death from any cause	Death from any cause. Death may or may not be related to liver disease.	Form #60 required Form #61 required Form #64 required Form #63 required if Screening Phase complete	Must have one of the following: ▪ Death certificate ▪ Autopsy report ▪ Notation in any medical record reporting details of death	Attempt to obtain medical record notations or written information from outside sources. Notation may pronounce date and time of death, details of death, signed by medical practitioner.
Development of hepatocellular carcinoma	Defined as *EITHER*: ▪ Histology showing HCC (from a biopsy, surgery, or autopsy) *OR* ▪ A new hepatic defect on imaging with AFP rising to >1000 ng/ml	Form #60 required Form #63 required if Screening Phase complete	Must have *EITHER*: Histology (one of the following): ▪ Liver biopsy report ▪ Pathology report ▪ Autopsy report *OR* AFP result *AND* one of the following showing new defect or abnormality: ▪ Liver U/S report ▪ Liver CT report ▪ Liver MRI report	

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CTP score of 7 or higher at two consecutive study visits where Form #15 is required	Follow CTP Scoring Protocol	Form #60 required (unless PI determines that the elevated CTP score does not qualify as an adverse event) Form #63 required if Screening Phase complete	Must have all of the following: ▪ Chemistry lab reports for two visits (albumin, serum total bilirubin, prothrombin time) ▪ Ascites documents if applicable (see below) ▪ Encephalopathy documents if applicable (see below)	Copy of two Form #15s
Variceal hemorrhage	Gastrointestinal hemorrhage that is due to bleeding esophageal or gastric varices, based on an endoscopy showing *EITHER*: Direct evidence of variceal bleeding (bleeding varix, red wale sign), *OR* Moderate varices with no other site of bleeding identified, *AND* historical evidence for clinically significant upper GI bleeding.	Form #60 required Form #63 required if Screening Phase complete	Must have the following: ▪ Endoscopy report showing evidence of active or recurrent bleed within 48 hours of episode	May have: ▪ Medical record notation documenting episode of hemoptysis or rectal bleeding ▪ CBC report showing decline in Hgb

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CLINICAL OUTCOME	PROTOCOL DEFINITION	FORMS TO COMPLETE	REQUIRED SOURCE DOCUMENTATION	SUPPORTIVE DATA / DOCUMENTATION
Ascites	Any abdominal fluid that is *EITHER*:Is mild, moderate, or marked on U/S. (An U/S report of minimal fluid around the liver does not meet the definition) *OR* Is progressive on serial physical examinations, *OR* Requires diuretic therapy.	Form #60 required Form #63 required if Screening Phase complete	Must have physical exam note *AND* one of the following: ▪ Paracentesis lab report ▪ Liver U/S report ▪ Liver CT report ▪ Liver MRI report	May have: ▪ Medical record notation of fluid volume removed
Spontaneous bacterial peritonitis	Any episode of spontaneous ascitic infection diagnosed on the basis of *EITHER:* Elevated neutrophil count (>250/ml) in paracentesis fluid, *OR* Positive bacterial cultures and clinical diagnosis, in the absence of WBC availability.	Form #60 required Form #63 required if Screening Phase complete	Must have paracentesis fluid lab report indicating one of the following: ▪ Elevated neutrophil count (>250/ml) ▪ (+) bacterial cultures	May have: ▪ Lab report of (+) blood culture ▪ Medical record notation ▪ Lab report of CBC showing an elevated WBC
Hepatic encephalopathy	Any mental status alteration that is due to portosystemic encephalopathy *EITHER*: Occurring during a provoked episode (GI bleeding, diuretics, usual sedative doses), *OR* Occurring spontaneously	Form #60 required Form #63 required if Screening Phase complete	Must have Medical record notation indicating one of the following: ▪ Asterixis ▪ Clinical alteration in mental status with reversibility with therapy ▪ Two or more episodes of confusion consistent with encephalopathy	May have: ▪ Elevated ammonia level ▪ Prolonged Trails test