TITLE:	A Phase 2, Open Label Pilot Study of the Safety, Tolerability Pharmacokinetic and Pharmacodynamic Activity of EBP-994 Given Orally in Subjects Chronically Infected with HDV
PROTOCOL NO.	EIG-300
INVESTIGATIONAL DRUG:	EBP-994
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MEDICAL MONITOR:	Eduardo B. Martins, MD, DPhil
ORIGINAL VERSION DATE:	April 16, 2013

AMENDMENT 1: December 1, 2014
AMENDMENT 2: October 2, 2015
AMENDMENT 3: May 10, 2016

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LIST OF ABBREVIATIONS

ALT	alanine transaminase (or serum glutamic-pyruvic transaminase)
ANC	absolute neutrophil count
Anti-HIV AB	Anti-human immunodeficiency virus antibody
AST	aspartate transaminase (or serum glutamic-oxaloacetic transaminase)
AUC	area under the time-concentration curve
AUC_{0-t}	area under the time-concentration curve from time 0 to the last measurable concentration
$AUC_{0-\tau}$	area under the time-concentration curve over the dosing interval at steady-state
BP	blood pressure
BUN	blood urea nitrogen
CAS	chemical abstracts service
CBC	complete blood count
CFR	Code of Federal Regulations
Cl	clearance
CL/F	apparent total body clearance after extravascular administration
C_{max}	maximum concentration
C_{min}	minimum concentration at steady state
CRF	case report form
CTP	Child-Turcotte-Pugh
ECG	electrocardiogram
EC	Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HERG	human–ether-a-go-go
HIV	human immunodeficiency virus
HCV	hepatitis C virus
ICH	International Conference on Harmonisation
IgM AB	immunoglobulin M antibody
IM	intramuscular
INR	international normalized ratio

IRB	Institutional Review Board
IU	international unit
IUPAC	International Union of Pure and Applied Chemistry
Kel	apparent first-order terminal elimination constant
IV	intravenous
LFTs	liver function tests
ms	millisecond
PCR	polymerase chain reaction
PD	pharmacodynamics
PK	pharmacokinetics
PO	per orum (by mouth)
rDNA	recombinant deoxyribonucleic acid
RNA	ribonucleic acid
SAE	serious adverse event
t_{max}	time to peak concentration
$t_{1/2}$	apparent elimination half life
SOC	standard of care
TSH	thyroid stimulating hormone
UA	urinalysis
ULN	upper limit of normal
USP	United States Pharmacopeia
$V_{area/F}$	apparent volume of distribution
WBC	white blood cell

PROTOCOL SIGNATURE SHEET

The undersigned have reviewed the format and content of this protocol and have approved Protocol No. EIG-300 (Amendment 3 dated May 10, 2016) for issuance.

Eiger BioPharmaceuticals, Inc.

May 10, 2016

INVESTIGATOR SIGNATURE SHEET

I have read the attached protocol and agree that it contains all the necessary details for performing the study.

I will provide copies of the protocol and of the preclinical information on the test article, which was furnished to me by the sponsor, to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the test article and the conduct of the study.

Once the protocol has been approved by the IRB/ethics committee, I will not modify this protocol without obtaining the prior approval of the sponsor and of the IRB/ethics committee. I will submit the protocol modifications and/or any informed consent modifications to the sponsor and the IRB/ethics committee, and approval will be obtained before any modifications are implemented.

I understand the protocol and will work according to it, the principles of Good Clinical Practice (current ICH guidelines), and the Declaration of Helsinki (1964) (Appendix 3) including all amendments up to and including the Scotland revision (2000).

_____

Investigator's Signature Date

(EIG-300 protocol Amendment 3 dated May 10, 2016)

PROTOCOL SUMMARY

Study Title
A Phase II, Open Label Pilot Study of the Safety, Tolerability Pharmacokinetic and Pharmacodynamic Activity of EBP-994 Given Orally in Subjects Chronically Infected with HDV

Sponsor
Eiger BioPharmaceuticals, Inc. (United States)
Sigma CRO. (Turkey)

Study Objectives
The primary objectives of the study are to:

- Evaluate the safety and tolerability of 12 weeks of treatment with a 200 vs. 300 mg PO BID dose of EBP-994 in subjects chronically infected with HDV
- Evaluate the pharmacodynamic (PD) activity of a 200 vs. 300 mg PO BID dose of EBP-994 on HDV viral load
- Evaluate the pharmacokinetic (PK) activity of a 200 vs. 300 mg PO BID dose of EBP-994
- Evaluate the safety, tolerability, PK, and HDV viral load of a treatment up to 48 weeks with EBP-994 alone and in combination with Norvir® and/or Pegasys® in subjects chronically infected with HDV

Study Design
This study is a phase II, randomized, open-label study up to 48 weeks of treatment with EBP-994 alone, or in combination with Norvir® and/or Pegasys® in subjects chronically infected with HDV genotype 1. The duration of the study for each subject will last approximately 11-55 weeks (up to three week screening period, 4-48 week treatment period and four week safety follow-up period. The duration of the entire study is anticipated to be approximately 45 months (first subject in to last subject out). The investigator is free to initiate licensed medications at any time point and decrease the dose of EBP-994 if deemed warranted for GI side effects.

This study will explore EBP-994 in four groups of treatments:

Group 1: EBP-994 (up to 600 mg daily dose) monotherapy
Group 2: EBP-994 (up to 200 mg daily dose) in combination with Norvir®
Group 3: EBP-994 (up to 600 mg daily dose) in combination with Pegasys®

Group 4: EBP-994 (up to 150 mg daily dose) in combination with Norvir® and Pegasys®

Study Population and Number of Subjects
Up to 75 subjects chronically infected with HDV genotype 1 will be enrolled at a single study sites.

Inclusion Criteria
A subject may be included in this study if he/she meets all of the following criteria:

1. Males or females, 18 to 65 years of age who are diagnosed with HDV by PCR
2. Chronic hepatitis D infection, genotype 1, documented by a positive anti-HDV Ab test of at least 6 months duration and detectable HDV RNA by PCR within 3 months to study entry
3. Liver biopsy within the last two (2) years or consent of having a liver biopsy which can be done at the Screening Visit
4. Electrocardiogram (ECG) shows no acute ischemia or clinically significant abnormality and a QT/QTc interval <450 milliseconds using Bazett's correction: QTc $=QT/RR^{0.5}$ (ICH Guidance E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs)
5. Females of childbearing potential (intact uterus and within one year since the last menstrual period) should be non-lactating and have a negative serum pregnancy test. In addition, these subjects should agree to use one of the following acceptable birth control methods throughout the study:
    a. abstinence
    b. surgical sterilization (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) six month minimum
    c. IUD in place for at least three months
    d. barrier methods (condom or diaphragm) with spermicide
    e. surgical sterilization of the partner (vasectomy for six months)
    f. hormonal contraceptives for at least three months prior to the first dose of study drug
6. Willing and able to comply with study procedures and provide written informed consent

Exclusion Criteria
A subject will be excluded from this study if he/she meets any of the following criteria:

1. Participation in a clinical trial with or use of any investigational agent within 30 days of Study Visit 1
2. Patients co-infected with HIV or HCV (if HCV RNA is positive)
3. Patients with screening tests positive for anti-HIV Ab
4. Active jaundice defined by total bilirubin >2.0 and known not to have Gilbert's disease

5. INR ≥ 1.5
6. Eating disorder or alcohol abuse within the past two years, excessive alcohol intake (>20 g per day for females (1.5 standard alcohol drinks) or >30 g per day for males (2.0 standard alcohol drinks) (a standard drink contains 14 g of alcohol: 12 oz of beer, 5 oz of wine or 1.5 oz of spirits) (1.0 fluid oz (US) = 29.57 mL) or if in the opinion of the investigator, an alcohol use pattern that will interfere with study conduct
7. Drug abuse within the last six months with the exception of cannabinoids and their derivatives
8. Patients with absolute neutrophil count (ANC) <1500 cells/mm^3; platelet count <100,000 cells/mm^3; hemoglobin <12 g/dL for women and <13 g/dL for men; abnormal TSH, T_4 or T_3 or thyroid function not adequately controlled; or serum creatinine concentration ≥1.5 times upper limit of normal (ULN).
9. History or clinical evidence of any of the following:
    a. variceal bleeding, ascites, hepatic encephalopathy, CTP score >6, decompensated liver disease or any other form of non-viral hepatitis
    b. immunologically mediated disease (e.g, rheumatoid arthritis, inflammatory bowel disease, severe psoriasis, systemic lupus erythematosus) requiring more than intermittent non-steroidal anti-inflammatory medications for management or that requires frequent or prolonged use of corticosteroids (inhaled asthma medications are allowed)
    c. any malignancy within 5 years except for basal cell skin cancer
    d. significant or unstable cardiac disease (e.g, angina, congestive heart failure, uncontrolled hypertension, history of arrhythmia)
    e. chronic pulmonary disease (e.g, chronic obstructive pulmonary disease) associated with functional impairment
    f. severe or uncontrolled psychiatric disease, including severe depression, history of suicidal ideation, suicidal attempts or psychosis requiring medication and/or hospitalization
10. Patients with a body mass index of >30 kg/m^2
11. Concomitant drugs known to prolong the QT interval
12. Concomitant use of immunosuppressive or immune modulating agents
13. Patients with any serious condition that, in the opinion of the investigator, would preclude evaluation of response or make it unlikely that the contemplated course of therapy and follow-up could be completed or increase the risk to the subject of participation in the trial

Summary of Dosing Plan/Treatment Plan/Schema

At the Screening Visit, subjects giving written informed consent will have all required evaluations to determine their eligibility to participate in the study. The outpatient Screening Visit must occur within 21 days of first Study Visit.

Each eligible subject will undergo 8-19 Treatment Study Visits; Screening, Day 1, Day 2, Day 3, Day 7, Day 14, Day 28, then every 4 weeks (total treatment duration depends on assigned treatment group), followed by a Safety Follow-up Visit, 4 weeks post-treatment. Moreover, the investigator is free to initiate licensed medications at any time point and decrease the dose of EBP-994 if deemed warranted for GI side effects.

During the intervals between Study Visits, subjects will be free to carry on their usual activities of daily living. Subjects should be instructed to take the study medication at 24 (QD dosing), 12 (BID dosing) or 8 (TID dosing) hour intervals ±2 hours. Efforts should be made to schedule Study Visits according to the study protocol; however the window for consecutive Study Visits will be ±2 days with the exception of Days 2 and 3 for which a visit window is not allowed.

Criteria for Evaluation

Statistical Plan
The sample size has not been determined by strict statistical considerations. From a safety, pharmacokinetic and pharmacodynamic perspective, no a-priori assumptions are made as to the expected treatment effect and associated variability.

General
Demographics of subjects will be described. All reported adverse events will be mapped to standard coding terms (MedDRA) and grouped by system organ class and preferred terms. The incidence of adverse events will be tabulated by seriousness, severity, and relationship to study drug. If an adverse event is reported more than once during the study period, the greatest severity and worst-case attribution will be presented in tables. Adverse events will also be listed for individual subjects, along with information regarding onset, duration, severity, and relationship to study drug. Adverse events that lead to withdrawal from the study will be listed and summarized by treatment group separately. Summary tables and listings of serious adverse events will also be generated. Pharmacodynamic data will be presented in listings and will display viral load data at each period/timepoint collected by subject. These data will also be presented graphically. Mean and median levels of the viral load will be calculated at each period/timepoint.

Safety
Safety will be monitored by assessing vital signs, adverse events, concomitant medications and laboratory and ECG results. ECGs will be conducted in triplicate and vital signs assessed at each Study Visit.

The most common side effects seen with lonafarnib (the active ingredient of EBP-994) are gastrointestinal (diarrhea, nausea, and vomiting). There were no serious adverse events (SAEs) observed in the studies conducted in healthy volunteers. The SAEs reported in at least 2% of subjects in the Phase 1 and Phase 2 studies conducted in subjects with solid tumors or hematologic malignancies included fever (6%), diarrhea (6%), dehydration (6%), febrile neutropenia (4%) and sepsis (4%).

As with any anti-viral medication, a possible effect of EBP-994 is viral resistance. Hepatitis D viral load levels will be measured through quantitative PCR at all Study Visits. Viral mutation analysis and resistance phenotyping will be conducted to assess viral resistance to the study medication. The investigator may terminate the subject from the trial if, in his/her opinion, there is an unacceptable increase in HDV viral load. Moreover, the investigator is free to initiate standard of care (SOC) medications and doses (i.e. Pegasys®) at any time point.

Pharmacokinetics
Blood samples will be obtained for pharmacokinetics of EBP-994 at Study Visit 1 (Day 1) and Study Visit 6 (Day 28). Pharmacokinetic parameters for EBP-994 such as maximum concentration (C_{max}), area under the time-concentration curve (AUC), time to peak concentration (t_{max}), elimination half life ($t_{1/2}$), volume of distribution ($V_{area/F}$) and clearance (CL/F)] will be calculated and tabulated with descriptive statistics. Geometric mean and geometric CV% will be provided for AUC and C_{max} values.

Pharmacodynamics
Mean and median levels of the viral load will be calculated.

Estimated Start and Completion Dates
July 2013 through July 2017.

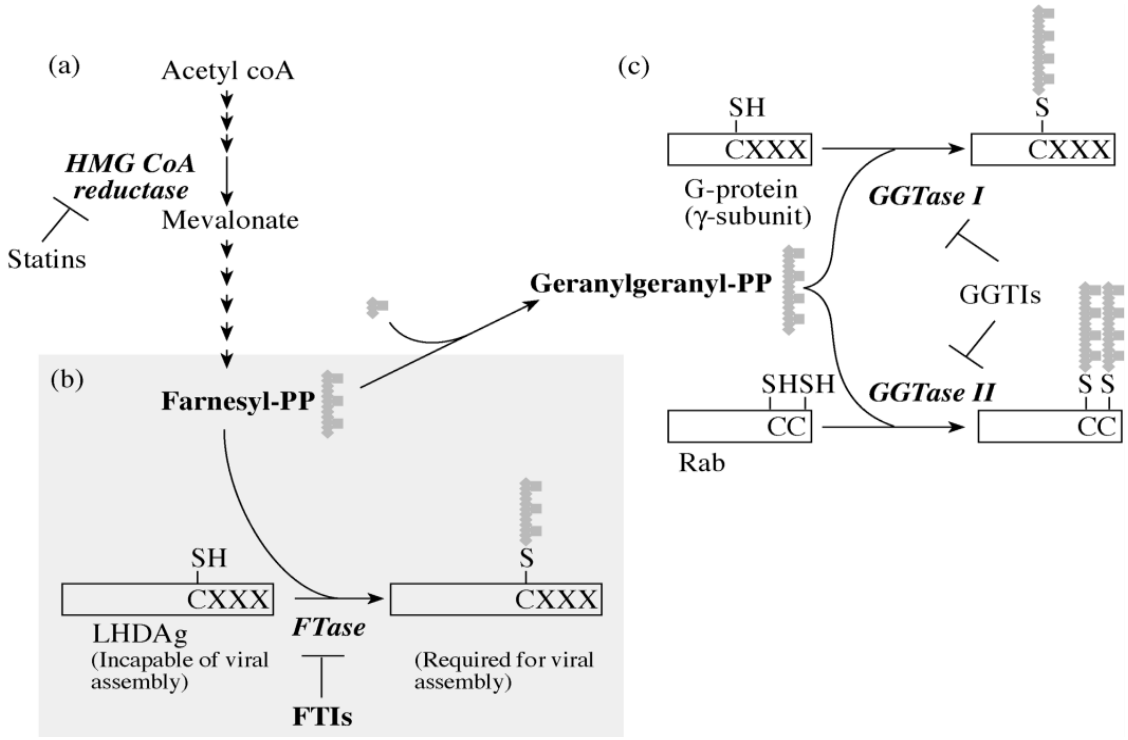
1 BACKGROUND

Hepatitis D virus (HDV) was first described as a novel antigen in the nucleus of hepatocytes derived from patients infected with hepatitis B (HBV) and antibodies to this "delta antigen" were detected in patients with severe cases of HBV infection. HDV was subsequently identified as the infectious agent causing viral hepatitis in the presence of HBV (1,2). While HDV can replicate autonomously (3), the virus does require co-infection with HBV to complete virion assembly and to facilitate transmission. HDV uses the hepatitis B surface antigen (HBsAg) proteins L, M, and S, as its envelope protein which is pivotal for HDV exit from host cells and transmission to other hepatocytes (4). Therefore, HDV can be considered a superinfection among patients chronically infected with HBV or as a simultaneous acute co-infection with HBV (5).

The HDV genome is a small circular single-stranded RNA molecule which can be classified into eight different genotypes (6). HDV genotype 1 is the most prevalent globally and is the most common in Europe and North America. The main route of transmission is parenteral exposure, like that observed with HBV. In the United States, the number of cases of HDV is projected to be roughly 40,000 to 75,000, or 5% of the estimated 750,000 to 1.5 million persons infected with HBV (14). Multiple studies have revealed that chronic HDV infection leads to more severe liver disease than HBV mono-infection, is associated with accelerated fibrosis progression, as well as a higher risk of developing hepatocellular carcinoma (7,8,9). HDV is the only form of chronic viral hepatitis for which there is no established highly successful treatment. Despite multiple direct antiviral agents directed against HBV, these have not proven effective against HDV, nor has ribavirin alone, or in combination with interferon (10,11,12,13)

Given the aggressive nature of the hepatitis seen in HDV infection, agents are needed that can help mitigate the disease by directly interfering with the virus life-cycle. An important interaction between HDV and HBV proteins has been shown to depend on the presence of the last four amino acids of the large delta antigen, comprising a CXXX box motif, where C represents cysteine and X denotes any other amino acid. This amino acid sequence is required for the protein to be post-translationally modified by farnesyltransferase (FT), an enzyme which covalently attaches a prenyl lipid (farnesyl) to the cysteine of the CXXX box as depicted in Figure 1 (15,16) . Prenylation of HDV results in the addition of farnesyl to the delta antigen. Inhibiting the action of FT could result in compromised HDV particle production since the unprenylated large delta antigen of HDV cannot associate with HBV antigens to form an infective HDV virion. In addition, the use of FT inhibitors (FTIs) could subvert the ability of the virus to develop resistance since the drug targeted locus does not lie within the viral genome but is a host function. Most importantly, host cells display a tolerance in the presence of prenylation inhibition by FTIs through the use of alternative prenylation pathways while HDV cannot use alternative pathways (17,18).

Figure 1 The Mevalonate Pathway



Eiger BioPharmaceuticals, Inc. (Eiger BioPharmaceuticals) is developing EBP-994 as an investigational new drug for the treatment of hepatitis D virus (HDV) in patients chronically infected with HDV. EBP-994 is an orally active tricyclic farnesyltransferase inhibitor (FTI) initially developed as lonafarnib (aka SCH 66336) by Schering-Plough, now Merck. It has been studied in over 2000 patients within the context of over a dozen clinical studies, including three Phase I (pharmacokinetic, metabolic distribution, drug-drug interaction) healthy volunteer studies and nine Phase I, II and III studies in patients with advanced malignancies in an attempt to inhibit farnesylated ras-mediated cancers. In patients with advanced cancers (blast crisis and acute leukemia), EBP-994 has been given for up to 120 days with the MTD determined to be 200-300 mg PO BID, with TEAEs being diarrhea and nausea.

The drug was generally well tolerated, although insufficient anti-tumor efficacy was observed, likely because such malignancies can be driven by additional factors beyond farnesylated ras. EBP-994 offers a valuable repurposing opportunity, however, for inhibiting the HDV life cycle where a critical dependence on farnesylation of large delta antigen has been demonstrated, and thereby treating hepatitis D infections.

1.1 Rationale

The IC50 for EBP-994 (formerly lonafarnib) in the H-ras farnesyl transferase inhibition assay is 2.4 nM. Because HDV particle production is dependent on the farnesylation of HDV large delta antigen, EBP-994 is expected to be an inhibitor of the HDV life cycle at the stage of

particle production. Indeed, the EC50 for EBP-994 in the HDV virus-like particle (VLP) production assay is 34 pM, consistent with the fact that multiple large delta antigen proteins are contained in a virus or virus—like particle and the hypothesis that inhibiting the farnesylation of only a fraction of the delta antigens can have a trans-dominant effect on particle production. These data suggest that EBP-994 can be a potent inhibitor of the HDV life cycle in vivo. Combined with EBP-994's favorable safety and tolerability profile demonstrated to date in Phase I through III testing for oncology indications, EBP-994 was therefore hypothesized to be a useful novel way of treating hepatitis delta infections.

Recently, a Phase Ib study of EBP-994 in patient chronically infected with HDV was initiated at the National Institutes of Health (NIH). In the first phase of the study, 8 patients were randomly assigned to drug (6 patients; 100 mg PO BID) vs. placebo (2 patients) for 28 days of treatment. In the second phase, 8 patients will receive either EBP-994 (6 patients; 200 mg PO BID) or placebo for 28 days of treatment. Data on the first seven patients from the first phase of the study is currently available. EBP-994 was well tolerated in all subjects with no SAEs. All patients receiving EBP-994 experienced reductions in HDV viral load during the treatment period, with rebound observed upon cessation of drug treatment (see Figure 2). Three of the 5 patients treated with EBP-994 experienced an approximate 1 log drop or greater in HDV viral load during the 28 day treatment period (Note: patients # 3 and # 7 received placebo).

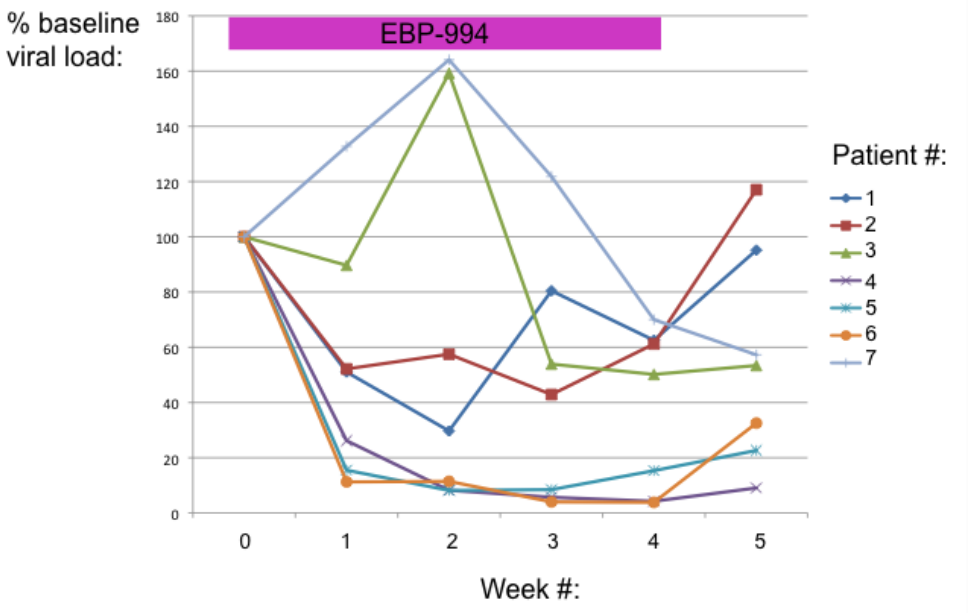


Figure 2. Interim analysis of changes in HDV viral load during treatment with 100 mg PO BID EBP-994. Bar indicates period of treatment with EBP-994 (or placebo).

The mean change in viral load from baseline was directly proportional to the mean drug levels measured in individual patients.

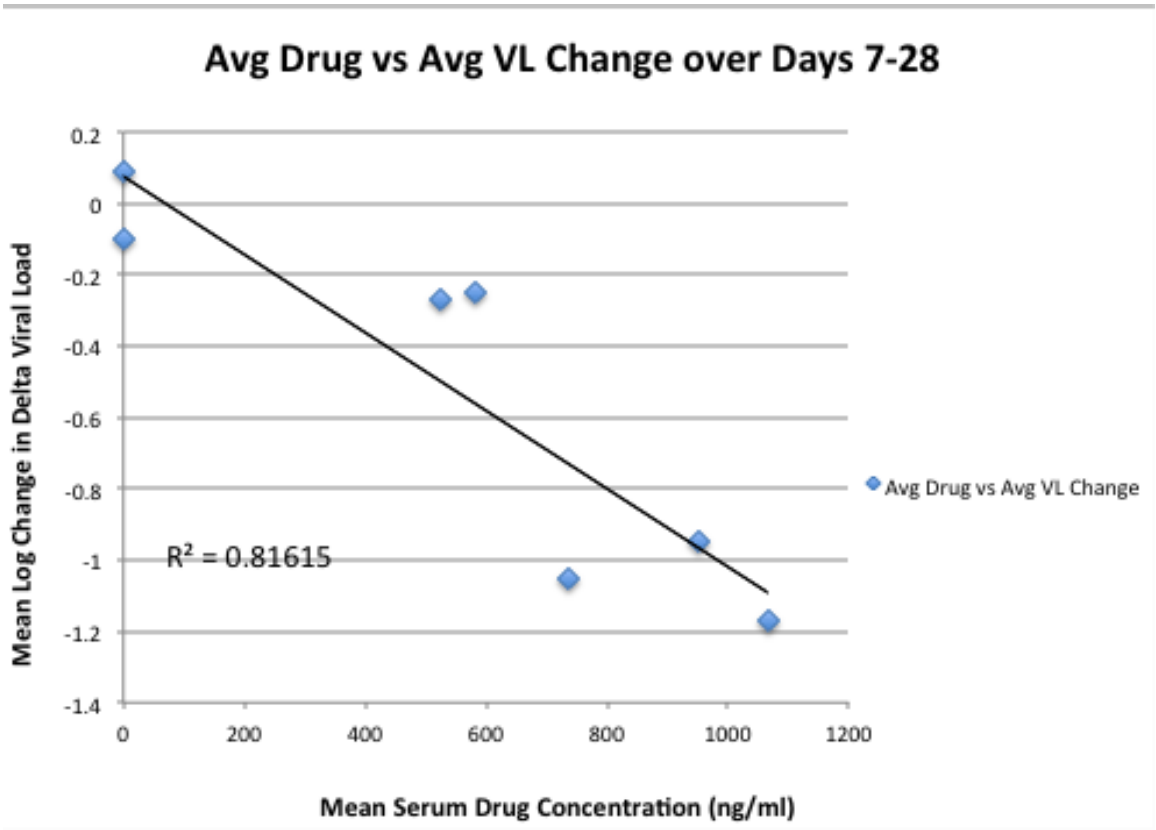


Figure 3. Average serum EBP-994 concentration vs. average change in HDV viral load over days 7-28 of treatment.

These data demonstrate: 1) EBP-994 is well-tolerated in patients with chronic hepatitis D infection; 2) a direct antiviral effect of EBP-994 against HDV; 3) a dose dependence of EBP-994's anti-HDV efficacy; 4) suboptimal levels of drug appear to be achieved in this patient population at the relatively low dose (100 mg PO BID) used in this first phase of the study; 5) a strong rationale exists for progressing to the planned higher dose of EBP-994. In addition to using the higher doses of EBP-994 that were previously used and tolerated in generally sicker patients (i.e with advanced malignancies, including metastatic disease and blast crisis), a duration of treatment longer than 28 days is expected to be needed to achieve more profound suppression of HDV viral loads (including to undetectability) that will be maintained upon cessation of treatment (indicative of cure). These are exactly the interventions to be explored in the current study that aims to determine the safety and efficacy of EBP-994 alone, or in combination with Norvir® and/or Pegasys® in chronically infected HDV patients for up to 6 months.

1.2 Anticipated Risks To Subjects

Preclinical Safety Summary

Toxicokinetic data to support the toxicology program for the development of EBP-994 were obtained from three- and six-month toxicity studies in rats (19, 20), three-month and 12-month toxicity studies in cynomolgus monkeys (21, 22), and an embryo-fetal developmental toxicity and toxicokinetic study in rabbits (23). Additionally, a single-dose (SD) oral vs IV pharmacokinetic study in monkeys was conducted (24). Data on the distribution of EBP-994 are available from a single dose tissue distribution study in pigmented rats (25), a pilot whole body autoradiography (WBA) study in monkeys (26), and in vitro plasma protein binding studies (27, 28). The metabolism of EBP-994 was studied in vitro using liver microsomes, hepatocytes, and recombinant human cytochrome P450 (CYP) isozymes (29, 30, 31, 32). Additional information about the metabolism of EBP-994 was obtained from profiling in rats, monkeys, and humans (33, 34, 35, 36, 37, 38). The routes and extent of excretion of EBP-994 were evaluated in rats, monkeys, and humans (26, 33, 34, 35, 36, 37, 39, 40). The effects of EBP-994 on enzyme induction and enzyme inhibition were studied in vitro (41, 42) and in vivo (19, 21), and the potential for EBP-994 interactions related to transport proteins was also assessed (43, 44, 45).

Pharmacokinetic/toxicokinetic studies in rats, rabbits and monkeys given single and repeated oral doses of EBP-994 suggested slow absorption, with mean T_{max} = 2-8 hr. The compound had good bioavailability, with a mean absolute oral bioavailability of greater than 65% in rats and monkeys. In both species, increases in plasma AUC with increasing dose were observed but there were also cross-study and cross-species differences in exposure (e.g., sex-dependence) and accumulation patterns.

EBP-994 distributed rapidly into tissues, with liver, adrenal gland, pancreas, bile duct, and kidney reaching maximum concentrations of radioactivity by 4 hr post-dose; the tissue-to-plasma ratios of drug-derived radiocarbon in these tissues at 4 hr ranged from 3.90-14.7. Plasma protein binding to ^{3}H-EBP-994 was ≥99% in all species over a 0.5-40.0 µg/mL concentration range and binding to purified serum proteins (HSA, AAG, HSA-AAG) ranged from 94-98%.

CYP 3A (3A4 and 3A5) is responsible for the oxidative metabolism of EBP-994 (29, 31). Studies of CYP inhibition indicate that the CYP3A4 IC50 = 10.2 µg/mL and CYP2C9 IC50= 16 µg/mL (24), showing that the one-half maximal inhibition is achieved at three to five times the mean human plasma C_{max} (2.8 µg/mL) at 200 mg BID (46, 47, 48). Preincubation of human liver microsomes for 15 min with EBP-994 decreased the IC50 for inhibition of CYP3A4, suggesting a metabolism-based inhibition. In vitro inhibition of activity of other CYP enzymes (1A2, 2C19, 2D6) by EBP-994, however, does not appear to occur to an extent likely to suggest a risk of adverse events in humans.

In ancillary pharmacology studies in rats, EBP-994 was well tolerated over the oral dose range of 30 to 300 mg/kg. It was devoid of gastric ulcerogenicity and adverse effects on CNS function, but exhibited moderate inhibition of GI motility at high doses (≥100 mg/kg). Clinical findings consistent with a decrease in GI motility have not been observed with EBP-994. Urine chemistry parameters showed a decrease in sodium and potassium excretion at 300 and 500 mg/kg and a reduction in creatinine clearance at 500 mg/kg. At doses of 500 mg/kg orally, rats were moribund and displayed a variety of adverse effects. Repeated oral

dosing of EBP-994 to monkeys at 60 mg/kg for 7 days caused diarrhea, emesis, weight loss, thrombocytopenia and an elevation of AST.

Inhibition of the hERG current by EBP-994 occurred at an IC_{50} of 1.3 μM (representing an approximately 59-fold multiple over the mean free C_{max} plasma concentration achieved at a clinical dose of 200 mg BID). This relatively large safety margin between the IC50 for SCH 66336 in the hERG assay and the free C_{max} at a clinical dose of 200 mg BID, together with the absence of effects on isolated Purkinje fibers up to 1.1 μM, is consistent with the absence of effects of EBP-994 on QT or QTc interval in vivo in anesthetized guinea pigs (total C_{max} of 30 μM) and in conscious monkeys (repeated-dose toxicity studies) administered EBP-994 for three-months and one year at doses up to 60 and 40 mg/kg, respectively. Metabolism studies conducted in vitro (30, 31, 32) and in vivo (rat, monkey, human) (33, 34, 35, 36, 37, 38) provided no evidence for the formation of human-specific EBP-994 metabolites. EBP-994 was shown to be extensively metabolized following SD administration of 14C-EBP-994 to rats (PO, IV), monkeys (PO,IV), and humans (PO) (33, 34, 36, 37); only small amounts of unchanged EBP-994 were detected in urine, bile or feces. LC-MS analyses indicated that the most common metabolic conversions involved oxidation (+O or +16) or dehydrogenation (-2H or -2) and were associated with changes in the pendant piperidine ring (33, 34, 36, 37).

Biliary and/or fecal excretion was the major route of elimination for administered drug and its metabolites following administration of 14C-EBP-994 to rats; urinary excretion (<1%) played a minor role (33, 39, 40). The available data likewise showed excretion patterns in monkeys and humans that were similar to those in rat.

Renal excretion in humans is not a major elimination pathway for EBP-994 and its metabolites. Mean urinary recovery of EBP-994 ranged from 0.001 to 0.5% of the dose over a 12-hr collection interval (46, 47, 48), and mean urinary radioactivity accounted for only ~0.7% of the dose following oral administration (37). After administration of 14C-EBP-994 to bile duct-cannulated rats, 16.5%-55.0% of the administered dose was collected in bile (up to 48-hr post-dose) of individual rats (33, 39). Evaluation of enterohepatic circulation by intraduodenal (ID) dosing of bile from 14C-EBP-994 PO-dosed donor rats to recipient rats suggested that <5% of the EBP-994 dose undergoes enterohepatic circulation (39).

Thus, the nonclinical pharmacokinetics and metabolism of EBP-994 supported further development of the compound.

Clinical Safety Summary

There are currently no HDV-specific therapies. EBP-994 could be the first direct acting anti-HDV agent by disrupting the HDV life cycle through inhibition of prenylation at the level of host cell farnesyl-transferase. EBP-994 has been dosed in human studies examining PK and PD and has exhibited inhibition of farnesyl transferase at levels below the maximally tolerated dose (MTD; 300 mg BID). A risk associated with the use of direct acting antiviral agents would be the development of resistance by the virus. However, because prenylation is a host function not coded for by the HDV genome, the risk of resistance development could be mitigated. Viral surveillance will be conducted throughout the conduct of the study to assess the risk of viral resistance. Two doses of EBP-994 alone, or in combination with Norvir® and/or Pegasys® will be examined in this proof-of-concept study, 200 vs. 300 mg

(PO BID), and the adverse profile will be correlated to the clinical benefit of viral suppression.

Other risks that may be encountered with the treatment of HDV include an increase in liver function tests during and after therapy, the risk of a flare in HBV (≥1 log increase in HBV viral load) as the HDV viral load goes down, and an increase in HDV viral load after therapy is ended. Flares in liver function tests are not uncommon with the start of treatment of HBV disease and necessitate a careful and frequent review of liver function studies. We will follow the same approach in this study unless there is a concomitant flare in HBV viral load. A flare of HBV viral load while on EBP-994 will be treated by starting specific anti-HBV therapy using one of the 5 approved drugs, the selection being made by the Investigator based on the subject's condition and history of prior anti-HBV therapy. A flare in HDV viral load after the termination of EBP-994 will be watched closely and interferon therapy may be started as determined by the investigator.

Finally, the known adverse event profile for EBP-994 (and all other prenylation inhibitors in clinic) is primarily gastrointestinal, primarily dose related diarrhea as well as nausea and vomiting.

2 STUDY OBJECTIVES

The primary objectives of the study are to:

- Evaluate the safety and tolerability of 12 weeks of treatment with either a 200 mg po BID dose of EBP-994, or a 300 mg po BID dose of EBP-994, in subjects chronically infected with HDV genotype 1
- Evaluate the pharmacodynamic (PD) activity of a 200 mg po BID dose of EBP-994, vs. a 300 mg po BID dose of EBP-994 on HDV viral load
- Evaluate the pharmacokinetic (PK) profile of a 200 mg po BID dose of EBP-994 vs. a 300 mg po BID dose of EBP-994 in subjects chronically infected with HDV genotype 1
- Evaluate the safety, tolerability, PK, and HDV viral load of a treatment up to 48 weeks with EBP-994 alone, or in combination with Norvir® and/or Pegasys® in subjects chronically infected with HDV

3 STUDY DESIGN

This study is a phase II, randomized, open label study of up to 48 weeks of treatment with EBP-994 alone, or in combination with Norvir® and/or Pegasys® in subjects chronically infected with HDV genotype 1. The investigator is free to initiate licensed medications at any time point and decrease the dose of EBP-994 if deemed warranted for GI side effects. The duration of the study for each subject will be approximately 11-55 weeks (up to three week screening period, up to 48 week treatment period and four week safety follow-up period).

The duration of the entire study is anticipated to be approximately 36 months (first subject in to last subject out). Pharmacokinetic sampling will be done at Day 1 and Day 28 of dosing. PK sampling will be conducted only on subjects who have consented to participate in the PK portion of this study. Participation in PK sampling is optional for each subject.

At the Screening Visit, subjects giving written informed consent will have all required evaluations to determine their eligibility to participate in the study. The outpatient screening visit must occur within 21 days of Study Visit 1.

Each eligible subject will undergo 8-16 Study Visits; Screening, Day 1, Day 2, Day 3, Day 7, Day 14, Day 28, then every 4 weeks (total duration depends on assigned treatment group), followed by a Safety Follow-Up Visit, 4 weeks post-treatment. Study drug will consist of EBP-994 alone or in combination with either Norvir® and/or Pegasys®, depending on which group the subject has been randomized to on the Day 1 visit. Moreover, the investigator is free to initiate licensed medications at any time point and decrease the dose of EBP-994 if deemed warranted for GI side effects.

During the intervals between Study Visits, subjects will be free to carry on their usual activities of daily living. Subjects will be instructed to take their study medication at appropriate dosing intervals. Efforts should be made to schedule Study Visits according to the study protocol; however the window for consecutive Study Visits will be ±2 days with the exception of Day 2 and Day 3 for which a visit window is not allowed.

Safety will be monitored by assessing vital signs, adverse events, concomitant medications, laboratory and ECG results. ECGs will be conducted and vital signs assessed at each Study Visit.

As with all antiviral medications, a possible effect of EBP-994 is viral resistance. Hepatitis D viral load levels will be measured through quantitative PCR at all Study Visits. Viral mutation analysis and resistance phenotyping will be conducted to assess viral resistance to the study medication. The investigator may terminate the subject from the trial if, in his/her opinion, there is an unacceptable increase in HDV viral load.

4 ELIGIBILITY CRITERIA

Up to 75 subjects chronically infected with HDV genotype 1 will be enrolled at a single University study site.

4.1 Inclusion Criteria

A subject may be included in this study if he/she meets all of the following criteria:

1. Males or females, 18 to 65 years of age who are diagnosed with HDV by PCR

2. Chronic hepatitis D infection, genotype 1, documented by a positive anti-HDV Ab test at least of 6 months duration and detectable HDV RNA by PCR within 3 months to study entry

3. Liver biopsy within the last two (2) years (biopsy can be done at the Screening Visit)

4. Positive viral load of >100,000 copies/mL as measured by quantitative PCR

5. Electrocardiogram (ECG) shows no acute ischemia or clinically significant abnormality and a QT/QTc interval <450 milliseconds - using Bazett's correction: QTc =$QT/RR^{0.5}$ (ICH Guidance E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs)

6. Females of childbearing potential (intact uterus and within 1 year since the last menstrual period) should be non-lactating and have a negative serum pregnancy test. In addition, these subjects should agree to use one of the following acceptable birth control methods throughout the study:
    a. abstinence
    b. surgical sterilization (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) six months minimum
    c. IUD in place for at least six months
    d. barrier methods (condom or diaphragm) with spermicide
    e. surgical sterilization of the partner (vasectomy for six months)
    f. hormonal contraceptives for at least three months prior to the first dose of study drug

7. Willing and able to comply with study procedures and provide written informed consent

4.2 Exclusion Criteria

A subject will be excluded from this study if he/she meets any of the following criteria:

1. Participation in a clinical trial with or use of any investigational agent within 30 days of Study Visit 1

2. Patients co-infected with HIV

3. Patients with screening tests positive for HCV, or anti-HIV Ab

4. History of decompensated cirrhosis within the past year.

5. Active jaundice defined by total bilirubin >2.0 excluding Gilbert’s

6. INR ≥ 1.5

7. Eating disorder or alcohol abuse within the past 2 years, excessive alcohol intake (>20 g per day for females (1.5 standard alcohol drinks) or >30 g per day for males (2.0 standard alcohol drinks) (a standard drink contains 14 g of alcohol: 12 oz of beer, 5 oz of wine or 1.5 oz of spirits) (1.0 fluid oz (US) = 29.57 ml), or if in the opinion of the investigator, an alcohol use pattern that will interfere with the study conduct

8. Drug abuse within the last six months with the exception of cannabinoids and their derivatives

9. Patients with absolute neutrophil count (ANC) <1500 cells/mm^3; platelet count <100,000 cells/mm^3; hemoglobin <12 g/dL for women and <13 g/dL for men; abnormal TSH,T_4, or T_3or thyroid function not adequately controlled; or serum creatinine concentration ≥1.5 times upper limit of normal (ULN)

10. History or clinical evidence of any of the following:
    a. variceal bleeding, ascites, hepatic encephalopathy, CTP score >6, decompensated liver disease or any other form of non-viral hepatitis
    b. immunologically mediated disease (e.g., rheumatoid arthritis, inflammatory bowel disease, severe psoriasis, systemic lupus erythematosus) requiring more than intermittent nonsteroidal anti-inflammatory medications for management or that requires frequent or prolonged use of corticosteroids (inhaled asthma medications are allowed)
    c. any malignancy within 3 years except for basal cell skin cancer
    d. significant or unstable cardiac disease (e.g., angina, congestive heart failure, uncontrolled hypertension, history of arrhythmia)
    e. chronic pulmonary disease (e.g., chronic obstructive pulmonary disease) associated with functional impairment
    f. severe or uncontrolled psychiatric disease, including severe depression, history of suicidal ideation, suicidal attempts or psychosis requiring medication and/or hospitalization

11. Patients with a body mass index >30 kg/m^2

12. Concomitant drugs known to prolong the QT interval

13. Concomitant use of immunosuppressive or immune modulating agents

14. Patients with any serious or condition that, in the opinion of the investigator, would preclude evaluation of response or make it unlikely that the contemplated course of therapy and follow-up could be completed or increase the risk to the subject of participation in the trial

4.3 Withdrawal Of Subjects

At any time during the study, a subject may discontinue (i.e., withdraws consent or is no longer willing to participate) or a subject may be withdrawn by the Investigator because of a safety risk, adverse event, or noncompliance. The reason for early withdrawal shall be noted in the appropriate CRF.

The Sponsor has the option to enroll additional subjects to replace subjects who discontinue prematurely.

4.4 Study Termination

Eiger BioPharmaceuticals may terminate the study if new findings indicate that the study would be potentially dangerous or detrimental to subjects. Eiger BioPharmaceuticals may also terminate the study for administrative reasons unrelated to the purpose of the study. In addition, the regulatory agency or the site's IRB/EC has the authority to stop the study.

5 STUDY TREATMENT

5.1 EBP-994

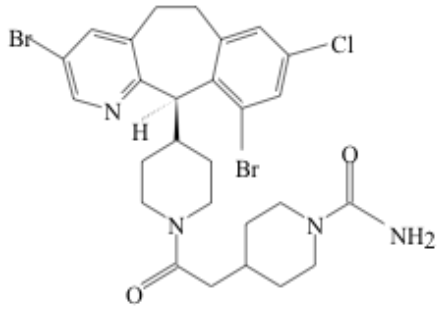
The drug to be utilized for this study is EBP-994 (previously developed as lonafarnib by Schering-Plough, now Merck). The EBP-994 active pharmaceutical ingredient (API) is manufactured by Schering Corporation located in 1011 Morris Avenue Union, NJ 07083. Each capsule contains 25 mg, 50 mg or 75 mg of EBP-994.

5.1.1 Description of EBP-994

IUPAC Name: 4-(2-4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5*H*benzo[5,6]cyclohepta[*b*]pyridin-11-yl]piperidino-2-oxoethyl)-1-piperidinecarboxamide
CAS Number: none
Molecular Formula: C27H31N4O2ClBr2

Molecular Weight: 638.7 g/mol

Figure 4: EBP-994



5.1.2 Description of Study Treatment

Study Visit 2 (Day 1) marks the initiation of the Treatment Period; all subjects will begin dosing with EBP-994 alone or in combination with Norvir® and/or Pegasys®, and continue dosing through Study Visit 7, 8, 9, 10, 11-47 (depending on treatment duration) morning dose.

5.1.2.1 Dosage Form of EBP-994

EBP-994 is formulated into hard gelatin, white opaque capsule shells. Each capsule contains 25 mg, 50 mg or 75 mg of EBP-994. The capsules are provided in white opaque high density polyethylene (HDPE) bottles with polypropylene twist off caps and desiccant. Each bottle contains 30 capsules. EBP-994 is stable if stored at 20°C - 25°C (68°F - 77°F). A "use by" date is included on the product label. EBP-994 should be stored at room temperature 20°C - 25°C (68°F - 77°F) in a locked, limited-access storage area prior to dispensing.

5.1.2.2 Dosage Form of Ritonavir

Commercial formulation of ritonavir (Norvir®) is supplied as 100-mg, white, film-coated, ovaloid tablets in white, opaque, HDPE bottles with polypropylene twist-off caps.

Ritonavir should be stored at or below 30 °C (86 °F).

5.1.2.3 Dosage Form of Pegylated Interferon

Commercial formulation of Pegasys® is supplied in vials. Each vial contains approximately 1.2 mL of solution to deliver 1.0 mL of drug product. Subcutaneous (SC) administration of 1.0 mL delivers 180 µg of drug product (expressed as the amount of interferon alfa-2a). The solution is colorless to light yellow.

5.2 Administration

Subjects will be instructed to self-administer EBP-994 at 8, 12 or 24 hour intervals ±2 hours. Norvir® at 12 or 24 hour intervals ±2 hours and/or Pegasys® at weekly intervals . If a dosing window is missed, the subject should skip the dose completely. Subjects should not "double up" at the next scheduled dose period.

5.3 Concomitant Medications

All drugs that are listed as excluded in the Exclusion Criteria should not be initiated during the study unless prior approval has been received from the Medical Monitor. Check the prescribing information of Norvir® and Pegasys® before initiating any concomitant medication.

5.4 Measuring Subject Compliance

Study drug is administered on an out-patient basis. Subjects will be instructed to return all study drug containers dispensed at the previous study visit (including empty ones) at each Study Visit in order to measure study drug compliance. The study coordinator will verify the subject has taken the correct amount of study medication prior to issuing the next supply of study medication.

5.5 Drug Accountability

All supplies of study drug will be accounted for by study personnel in accordance with current Good Clinical Practices (GCPs). Details of receipt, storage, administration, and return or destruction of study drug will be recorded in the study drug accountability record according to the standard operating procedure of the investigational site. Copies of the study drug accountability record will be provided to the Sponsor.

6 STUDY PROCEDURES

Refer to Appendix 1 for Schedule of Events.

6.1 Screening; Visit 1

The outpatient Screening Visit must occur no more than 21 days prior to Study Visit 1. Written informed consent must be given before any study related diagnostic or screening procedures. At the Screening Visit, subjects will have all required evaluations to determine their eligibility to participate in the study as follows:

1. Written informed consent

2. Medical history

3. Comprehensive physical examination (performed by a physician) including CTP scoring and encephalopathy assessment (see Appendix D)

4. Weight and height (BMI is based on these measures; see Appendix B)

5. Vital signs (BP after being seated for 5 minutes, pulse, respiratory rate and temperature)

6. List of concomitant medications

7. Serial 12-Lead ECG (x3) 2-3 minutes apart

8. Liver biopsy (if needed)

9. Laboratory studies (non-fasting):
    a. Serum chemistry panel, including liver function tests and albumin
    b. Thyroid function tests, T3, T4, TSH
    c. Complete blood count (CBC with differential and platelet count)
    d. Quantitative PCR for HCV viral load
    e. HCV genotype
    f. Blood samples (plasma and serum) for viral mutation analysis and resistance phenotyping
    g. Serologies (HCV, and anti-HIV Ab)
    h. INR
    i. Urinalysis
    j. Urine drug screen for opiates, amphetamines, barbiturates, benzodiazepines, cocaine
    k. Serum pregnancy test (child bearing females only)
    l. Blood sample for monitoring immunologic changes in peripheral blood mononuclear cells (PBMC).

Subjects meeting all of the inclusion criteria and none of the exclusion criteria and giving written informed consent will return within 21 days after screening for Study Visit 1 when randomization one of the treatment groups will occur.

6.2 Study Visit 2 (Day 1) – Treatment Period

This Study Visit marks the beginning of the twenty-four weeks treatment Period in which subjects will receive EBP-994 treatments (EBP-994 alone or in combination with Norvir® and/or Pegasys®). Subjects will be admitted to the unit on the morning of Day 1 in a fasted

state (nothing to eat or drink except water) and will receive a standard breakfast between 45 - 30 minutes prior to scheduled dosing time.

The following evaluations and procedures will be performed at Study Visit 1 (see Appendix A for summary):

1. Brief physical examination pre-dose (performed by a physician, nurse practitioner, physician's assistant or nurse). This includes weight and vital signs as well as HEENT, heart, lungs, abdomen and lower extremity.

2. Vital signs pre-dose and after the post-dose ECG (BP after being seated for 5 minutes, pulse, respiratory rate and temperature)

3. Concomitant medications will be recorded

4. Adverse events will be recorded

5. 12-Lead ECG

6. Randomization

   Subjects will be randomized to one of the following groups:

   Group 1: EBP-994 (up to 600 mg daily dose) monotherapy

   Group 2: EBP-994 (up to 200 mg daily dose) in combination with Norvir®

   Group 3: EBP-994 (up to 200 mg daily dose) in combination with Pegasys®

   Group 4: EBP-994 (up to 200 mg daily dose) in combination with Norvir® and Pegasys®

7. Laboratory studies (Pre-Dose) (non-fasting):
   a. Serum chemistry panel, including liver function tests and albumin
   b. Complete blood count (CBC with differential and platelet count)
   c. Quantitative PCR for HDV viral load
   d. Blood samples (plasma and serum) for viral mutation analysis, resistance phenotyping, and analysis of drug mechanism and treatment response. These analyses include molecular and genetic analysis of drug mechanism, viral/host factors influencing treatment response (e.g. genotype and subgenotype analysis, quasispecies analysis, determination of drug and potential metabolite levels in plasma).
   e. Urinalysis
   f. Urine pregnancy test (child-bearing females only)

g. Blood sample for monitoring immunologic changes in peripheral blood mononuclear cells (PBMC).

8. Pharmacokinetic blood samples (at the following time points: 0-pre-dose, post dose: 15 min, 30 min, 60 min, 90 min, 2h, 2.5 h, 3 h, 4 h, ,6 h, 8, 10, 12 h) (for those subjects participating in the PK portion of this trial)

9. Dosing Instructions:
   Dosing with EBP-994 alone or in combination with Norvir® and/or Pegasys® should occur after the pre-dose vital signs have been taken, the physical examination performed, the ECG performed and pre-dose lab samples drawn. EBP-994 capsules and/or Norvir® should be taken orally with 240 mL of water. After the morning dosing, the post-dose procedures should be conducted in the following order: ECG, vital signs, post-dose plasma and serum blood samples.

Subjects will be sent home 3 hours post-dose (except for those participating in the PK component of the study) with container(s) of study drug(s) and will be instructed to self-administer study drug(s) at appropriate intervals. Oral study drug should be swallowed with 240 mL of water. Subjects will also be given a diary to record the date, time and number of capsules they take.

Subjects should be instructed to bring all container(s) and any unused study medication to the study site at the next study visit. Subjects should be instructed NOT to take their morning dose of study drug on the morning of the next study visit, Day 2, as pre-dose assessments will be conducted.

6.3 Study Visit 3 (Day 2) – Treatment Period

Subjects are not to take their morning dose of study drug at home as pre-dose assessments are performed at this Study Visit.

1. Vital signs pre-dose (BP after being seated for 5 minutes, pulse, respiratory rate and temperature)

2. Concomitant medications will be recorded

3. Adverse events will be recorded

4. 12-Lead ECG (x3) 2-3 minutes apart pre-dose and 1 hour post-dose

5. Laboratory studies (pre-dose) (non-fasting):
   a. Quantitative PCR for HDV viral load

b. Pre-dose and 1 hour post-dose blood samples (plasma and serum) for viral mutation analysis, resistance phenotyping, and analysis of drug mechanism and treatment response. These analyses include molecular and genetic analysis of drug mechanism, viral/host factors influencing treatment response (e.g. genotype and subgenotype analysis, quasispecies analysis, determination of drug and potential metabolite levels in plasma).

c. Blood sample for monitoring immunologic changes in peripheral blood mononuclear cells (PBMC).

6. Dosing Instructions:

   Dosing with EBP-994 alone or in combination with Norvir® and/or Pegasys® should occur after the ECG has been performed and pre-dose lab samples drawn. The subject should receive morning dose of study drug(s). The post-dose ECG should be conducted one hour post-dose followed by the post-dose vitals and blood sampling.

The subject should bring the container(s) of study drug(s) dispensed at Study Visit 2 to this visit. Study personnel will assess dosing compliance and return container(s) to patient. No additional study drug will be dispensed at this visit. Subjects should be instructed to bring all container(s) and any unused study medication to the next study visit. Subjects should be instructed NOT to take their morning dose of study drug on the morning of the next Study Visit, Day 3, as pre-dose assessments will be conducted. Subjects should be sent home three hours post-dose.

6.4 Study Visit 4 (Day 3) - Treatment Period

Subjects are not to take their morning dose of study drug at home as pre-dose assessments are performed at this Study Visit.

1. Brief physical examination pre-dose (performed by a physician, nurse practitioner, physician's assistant or nurse). This includes weight as well as HEENT, heart, lungs, abdomen and lower extremity.

2. Vital signs

3. Concomitant medications will be recorded

4. Adverse events will be recorded

5. Laboratory studies (Pre-Dose) (non-fasting):
   c. Serum chemistry panel, including liver function tests and albumin
   d. Complete blood count (CBC with differential and platelet count)
   e. Quantitative PCR for HDV viral load
   f. Urinalysis

g. Blood sample for monitoring immunologic changes in peripheral blood mononuclear cells (PBMC).

6. Dosing Instructions:

   Dosing with EBP-994 alone or in combination with Norvir® and/or Pegasys® should occur after the pre-dose vital signs have been taken, the physical examination performed, and pre-dose lab samples drawn. The subject should receive morning dose of study drug.

The subject should bring the container(s) of study drug(s) dispensed at Study Visit 1 to this visit. Study personnel will assess dosing compliance and return container(s) to patient. No additional study drug will be dispensed at this visit. Subjects should be instructed to return all container(s) and any unused study medication at the next study visit. At each subsequent Study Visit, drug accountability will be performed for each subject to ensure that the subject is compliant with dosing. Subjects should be instructed NOT to take their morning dose of study drug on the morning of the next Study Visit, Day 7, as pre-dose assessments will be conducted. Subjects should be sent home three hours post-dose.

6.5 Study Visit 5 (Day 7±2 days) - Treatment Period

Subjects are not to take their morning dose of study drug at home as pre-dose assessments are performed at this visit.

1. Brief physical examination pre-dose (performed by a physician, nurse practitioner, physician's assistant or nurse). This includes weight as well as HEENT, heart, lungs, abdomen and lower extremity.

2. Vital signs pre-dose.

3. Concomitant medications will be recorded

4. Adverse events will be recorded

5. Laboratory studies (Pre-Dose) (non-fasting):
   a. Serum chemistry panel, including liver function tests and albumin
   b. Complete blood count (CBC with differential and platelet count)
   c. Quantitative PCR for HDV viral load
   d. Pre-dose and post-dose blood samples (plasma and serum) for viral mutation analysis, resistance phenotyping, and analysis of drug mechanism and treatment response
   e. Urinalysis
   f. Blood sample for monitoring immunologic changes in peripheral blood mononuclear cells (PBMC).

6. Dosing Instructions

   Dosing with EBP-994 alone or in combination with Norvir® and/or Pegasys® should occur after the pre-dose vital signs have been taken, the physical examination performed, and pre-dose lab samples drawn. The subject should receive morning dose of study drug(s).

The subject should bring the container(s) of study drug(s) dispensed at Study Visit 1 to this visit. Study personnel will to assess dosing compliance and return container(s) to patient. A new container of study drug will be dispensed at this visit. Subjects should be instructed to return all container(s) and any unused study medication at the next Study Visit. At each subsequent Study Visit, drug accountability will be performed for each subject to ensure that the subject is compliant with dosing. Subjects should be instructed NOT to take their morning dose of study drug on the morning of the next Study Visit, Day 14, as pre-dose assessments will be conducted. Subjects should be sent home three hours post-dose.

6.6 Study Visit 6 (Day 14±2days) - Treatment Period

Subjects are not to take their morning dose of study drug at home as pre-dose assessments are conducted at this visit.

1. Brief physical examination pre-dose (performed by a physician, nurse practitioner, physician's assistant or nurse). This includes weight and vital signs as well as HEENT, heart, lungs, abdomen and lower extremity.

2. Vital signs pre-dose

3. Concomitant medications will be recorded

4. Adverse events will be recorded

5. Laboratory studies (Pre-Dose) (non-fasting):
   a. Serum chemistry panel, including liver function tests and albumin
   b. Complete blood count (CBC with differential and platelet count)
   c. Quantitative PCR for HDV viral load
   d. Pre-dose blood samples (plasma and serum) for viral mutation analysis, resistance phenotyping, and analysis of drug mechanism and treatment response
   e. Urinalysis
   f. Blood sample for monitoring immunologic changes in peripheral blood mononuclear cells (PBMC).

6. Dosing Instructions:

Dosing with EBP-994 alone or in combination with Norvir® and/or Pegasys® should occur after the pre-dose vital signs have been taken, the physical examination performed, and pre-dose lab samples drawn. The subject should receive morning dose of study drug(s). If there is not sufficient drug remaining the subject may take the capsules from the container dispensed at this study visit. EBP-994 and/or Norvir® should be taken orally with 240 mL of water.

The container(s) of study drug(s) along with any unused drug dispensed at Study Visit 4 should be returned at this visit. Study personnel will perform drug accountability on the returned container(s) of study drug(s). A new container(s) of drug will be dispensed at this visit. Subjects should be instructed to return all container(s) and any unused study medication at the next study visit. At each subsequent Study Visit, drug accountability will be performed for each subject and reviewed to ensure that subject is compliant with dosing. Subjects should be instructed NOT to take their morning dose of study drug on the morning of the next Study Visit, Day 28, as pre-dose assessments will be conducted. Subjects should be sent home 3 hours post-dose.

6.7 Study Visit 7 (Day 28±2days) - Treatment Period

Subjects are not to take their morning dose of study drug at home as pre-dose assessments are conducted at this visit.

7 Brief physical examination pre-dose (performed by a physician, nurse practitioner, physician's assistant or nurse). This includes weight and vital signs as well as HEENT, heart, lungs, abdomen and lower extremity.

8 Vital signs pre-dose and after the post-dose ECG (BP after being seated for 5 minutes, pulse, respiratory rate and temperature)

9 Concomitant medications will be recorded

10 Adverse events will be recorded

11 12-Lead ECG (x3) 2-3 minutes apart pre-dose and 1 hour post-dose

12 Laboratory studies (Pre-Dose) (non-fasting):

- f. Serum chemistry panel, including liver function tests and albumin
- g. Complete blood count (CBC with differential and platelet count)
- h. Quantitative PCR for HDV viral load
- i. Pre-dose and post-dose blood samples (plasma and serum) for viral mutation analysis, resistance phenotyping, and analysis of drug mechanism and treatment response
- j. Urinalysis

k. Blood sample for monitoring immunologic changes in peripheral blood mononuclear cells (PBMC).

13 Pharmacokinetic blood samples (at the following time points: 0-pre-dose, post dose: 15 min, 30 min, 60 min, 90 min, 2 h, 2.5 h, 3 h, 4 h, ,6 h, 8, 10, 12 h) (for those subjects participating in the PK portion of this trial)

8 Dosing Instructions:

Dosing with EBP-994 EBP-994 alone or in combination with Norvir® and/or Pegasys® should occur after the pre-dose vital signs have been taken, the physical examination performed, the pre-dose ECG performed and pre-dose lab samples drawn. The subject should receive morning dose of study drug(s). If there is not sufficient drug remaining the subject may take the capsules from the container dispensed at this study visit. EBP994 alone or in combination with Norvir® should be taken orally with 240 mL of water. After dosing the post-dose procedures should be conducted in the following order: ECG (one hour post-dose), vital signs (post ECG), post-dose plasma and serum blood samples.

The container(s) of study drug(s) along with any unused drug dispensed at Study Visit 5 should be returned at this visit. Study personnel will perform drug accountability on the returned container(s) of study drug(s) to assess dosing compliance. A new container of drug will be dispensed at this visit to the subject. Subjects should be instructed to return all container(s) and any unused study medication at the next study visit. At each subsequent Study Visit, drug accountability will be performed for each subject to ensure that subject is compliant with dosing. Subjects should be instructed NOT to take their morning dose of study drug on the morning of the next Study Visit, Day 56, as pre-dose assessments will be conducted. Subjects should be sent home 3 hours post-dose, except for those participating in the PK component of the study.

If this is the last treatment visit, no new containers of drug(s) will be dispensed and all unused study medication will be collected.

6.8 Study Visit 8 (Week 8 = Day 56±2days) - Treatment Period

Subjects are not to take their morning dose of study drug at home as pre-dose assessments are conducted at this visit.

1 Brief physical examination pre-dose (performed by a physician, nurse practitioner, physician's assistant or nurse). This includes weight and vital signs as well as HEENT, heart, lungs, abdomen and lower extremity.

2 Vital signs pre-dose

3 Concomitant medications will be recorded

4 Adverse events will be recorded

5 Laboratory studies (Pre-Dose) (non-fasting):
   k. Serum chemistry panel, including liver function tests and albumin
   l. Complete blood count (CBC with differential and platelet count)
   m. Quantitative PCR for HDV viral load
   n. Pre-dose blood samples (plasma and serum) for viral mutation analysis, resistance phenotyping, and analysis of drug mechanism and treatment response
   o. Urinalysis
   p. Blood sample for monitoring immunologic changes in peripheral blood mononuclear cells (PBMC).

6 Dosing Instructions:
   Dosing with EBP-994 EBP-994 alone or in combination with Norvir® and/or Pegasys® should occur after the pre-dose vital signs have been taken, the physical examination performed, and pre-dose lab samples drawn. The subject should receive morning dose of study drug(s). If there is not sufficient drug remaining the subject may take the capsules from the container dispensed at this study visit. EBP-994 alone or in combination with Norvir® should be taken orally with 240 mL of water.

The container(s) of study drug(s) along with any unused drug dispensed at Study Visit 6 should be returned at this visit. Study personnel will perform drug accountability on the returned container(s) of study drug(s) to assess dosing compliance. A new container of drug will be dispensed at this visit as well as the diary at the next study visit. At each subsequent Study Visit, drug accountability will be performed for each subject to ensure that subject is compliant with dosing. Subjects should be instructed NOT to take their morning dose of study drug on the morning of the next Study Visit, Day 84, as pre-dose assessments will be conducted. Subjects should be sent home 3 hours post-dose.

If this is the last treatment visit, no new containers of drug(s) will be dispensed and all unused study medication will be collected.

6.9 Study Visit 9-18 (Week 12-48) - Treatment Period

Subjects are not to take their morning dose of study drug at home as pre-dose assessments are conducted at this visit.

7 Brief physical examination pre-dose (performed by a physician, nurse practitioner, physician's assistant or nurse). This includes weight and vital signs as well as HEENT, heart, lungs, abdomen and lower extremity.

8 Vital signs pre-dose

9 Concomitant medications will be recorded

10 Adverse events will be recorded

11 Laboratory studies (Pre-Dose) (non-fasting):

p. Serum chemistry panel, including liver function tests and albumin
q. Complete blood count (CBC with differential and platelet count)
r. Quantitative PCR for HDV viral load
s. Pre-dose blood samples (plasma and serum) for viral mutation analysis, resistance phenotyping, and analysis of drug mechanism and treatment response
t. Urinalysis
u. Blood sample for monitoring immunologic changes in peripheral blood mononuclear cells (PBMC).

12 Dosing Instructions:

Dosing with EBP-994 EBP-994 alone or in combination with Norvir® and/or Pegasys® should occur after the pre-dose vital signs have been taken, the physical examination performed, and pre-dose lab samples drawn. The subject should receive morning dose of study drug. If there is not sufficient drug remaining the subject may take the capsules from the container dispensed at this study visit. EBP-994 and/or Norvir® should be taken orally with 240 mL of water.

The container(s) of study drug(s) along with any unused drug dispensed at Study Visit 7 should be returned at this visit. Study personnel will perform drug accountability on the returned container(s) of study drug(s) to assess dosing compliance. A new container of drug will be dispensed at this visit to the subject. Subjects should be instructed to return all container(s) and any unused study medication at the next study visit. At each subsequent Study Visit, drug accountability will be performed for each subject to ensure that subject is compliant with dosing. Subjects should be instructed NOT to take their morning dose of study drug on the morning of the next Study Visit, Day 112, as pre-dose assessments will be conducted. Subjects should be sent home 3 hours post-dose.

If this is the last treatment visit, no new containers of drug(s) will be dispensed and all unused study medication will be collected.

6.10 Study Visit 19 – Four Week Post-Treatment Follow-Up

Same assessments are taken as in 6.9. No new containers of drug(s) will be dispensed. All unused study medication will be collected. No dosing at this visit.

6.11 Supplemental Safety Evaluation Visit(s)

During the course of the study, if the Investigator has a specific safety concern that may merit additional safety evaluation(s), the Medical Monitor should be notified of the intent to perform additional Study Visit(s) and/or additional laboratory assessments(s). These visits will be considered Unscheduled Visits.

7 ASSESSMENT OF SAFETY

7.1 Procedures For Recording Adverse Events

All adverse events encountered during the clinical study will be recorded on the case report form (CRF). An adverse event is defined by the International Conference on Harmonization (ICH) as follows:

- Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship to this treatment
- An adverse event (AE) can therefore be any unfavorable and unintended sign (including any abnormal laboratory finding for example), symptom, or disease temporarily associated with the use of a experimental drug, whether or not considered related to the experimental drug

An adverse event is any adverse change from the subject's baseline condition, including any clinical or clinically significant laboratory test value abnormality that occurs during the course of the clinical study after the experimental drug has been utilized, whether the adverse event is considered related to the treatment or not.

All adverse events will be followed until resolution. This may require obtaining clinical blood samples for appropriate laboratory tests until their values return to baseline levels or performing follow-up physical examinations until resolution of identified abnormalities.

7.1.1 Routine Reporting of Adverse Events

Adverse events, whether or not associated with study drug administration, will be recorded on the Adverse Event Reporting form of the CRF and will be submitted to the sponsor at regularly scheduled intervals.

The information to be entered in the CRF will include:

1. The time of onset of any new adverse event or the worsening of a previously observed adverse event

2. The specific type of reaction in standard medical terminology

3. The duration of the adverse event (start and stop dates)

4. The severity/grade of the adverse event

5. As assessment should be made of the relationship of the adverse event to the study drug, i.e., according to the definitions in Section 7.1.4.

6. Description of action taken in treating the adverse event and/or change in study drug administration or dose

Follow-up assessments should be repeated to document return of any abnormalities to normal, or to document other outcome of the adverse event.

7.1.2 Reporting of Serious Adverse Drug Experiences, including Deaths

A serious adverse drug experience (SAE), as defined by the International Conference on Harmonization and in 21 CFR 312.32 is:

> Any adverse drug experience occurring at any dose that results in any of the following outcomes:
>
> 1. Death
>
> 2. A life threatening adverse drug experience
>
> 3. Inpatient hospitalization or prolongation of existing hospitalization
>
> 4. A persistent or significant disability/incapacity
>
> 5. Congenital anomaly/birth defect
>
> Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or

convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Serious adverse experiences, including death due to any cause, which occur during this study or within 30 days following the last dose of study medication, whether or not related to the administration of study drug, must be reported immediately (within 24 hours of learning of the event) to the Medical Monitor.

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International calls to the United States: dial 00 + 1 before the telephone number

7.1.3 Severity of Adverse Drug Experiences

Clinical adverse events will be categorized using the following definitions:

Mild: discomfort noted, but no disruption of normal daily activity

Moderate: discomfort noted of sufficient severity to reduce or adversely affect normal activity

Severe: incapacitating, with inability to work or perform normal daily activity

7.1.4 Relationship of Adverse Events to the Study Drug

The investigator and/or Medical Monitor should record on the CRF whether the event is best described as unrelated, possibly, probably, or definitely related association to the study medications, according to the following definitions.

Unrelated: There is evidence that the adverse event definitely has an etiology other than the assigned study drug.

Possibly Related: The adverse event has a temporal relationship to study drug administration. However, an alternative etiology may be responsible for the adverse event. Information on drug/product withdrawal may be lacking or unclear.

Probably Related: The adverse event has a temporal relationship to study drug administration. The event is unlikely to be related to an alternative etiology. There is a reasonable response on withdrawal (dechallenge). Rechallenge information is not required.

Related: The adverse event has a temporal relationship to study drug administration and resolves when the drug is discontinued. An alternative etiology is not apparent. If the subject is rechallenged with the assigned study drug, the adverse event recurs. Rechallenge is not necessarily required.

7.2 Withdrawal From Study Treatment Due To Adverse Experience

Subjects withdrawn from receiving additional study drug due to an adverse experience will be followed by the Investigator until the outcome is determined; additional reports will be provided to the Sponsor or regulatory authorities when requested. Every effort will be made to follow the subject for the full study period as per the schedule of Study Visits.

7.3 Management Of Toxicity Related To Study Drug

Safety will be monitored by assessing vital signs, adverse events, concomitant medications and laboratory and ECG results. ECGs will be conducted in triplicate and vital signs assessed at each Study Visit. During the treatment period, ECGs will be conducted pre and one hour post-dose. Vital signs will be taken pre-dose and following the post-dose ECG.

The most common side effects seen with lonafarnib (the active ingredient of EBP-994) are gastrointestinal (diarrhea, nausea, and vomiting).
There were no serious adverse events (SAEs) observed in the studies conducted in healthy volunteers. The SAEs reported in at least 2% of subjects in the Phase 1 and Phase 2 studies conducted in subjects with solid tumors or hematologic malignancies included fever (6%), diarrhea (6%), dehydration (6%), febrile neutropenia (4%) and sepsis (4%).

As with any anti-viral medication, a possible effect of EBP-994 is viral resistance. Hepatitis D viral load levels will be measured through quantitative PCR at all Study Visits. Viral mutation analysis and resistance phenotyping will be conducted to assess viral resistance to the study medication. The investigator may terminate the subject from the trial if, in his/her opinion, there is an unacceptable increase in HDV viral load. Moreover, the investigator is free to initiate licensed medications at any time point and decrease the dose of EBP-994 if deemed warranted for GI side effects.

During the conduct of the study, safety laboratory values will be assayed within 48 hours of the study visit and the Medical Monitor and Investigator will be informed within 24 hours of assay performance of laboratory abnormalities.

8 STATISTICS

8.1 Blinding

This is an open-label study; subjects will not be blinded.

8.2 Analysis Populations

The Safety Population comprises all subjects who are enrolled and receive at least one dose of study drug, and who have at least one post-dosing safety evaluation. All safety endpoints will be analyzed using the Safety Population.

The Per-Protocol Population comprises all subjects who complete at least Study Visit 4, as specified in the protocol. All pharmacodynamic analysis will be conducted using the Per-Protocol Population.

8.3 Demographics And Baseline Characteristics

Demographic and baseline characteristics will be presented descriptively.

8.4 Safety

8.4.1 Adverse Events

All reported adverse events will be mapped to standard coding terms (MedDRA) and grouped by system organ class and preferred terms. The incidence of adverse events will be tabulated by seriousness, severity, and relationship to study drug. If an adverse event is reported more than once during the study period, the greatest severity and worst-case attribution will be presented in tables. Adverse events will also be listed for individual subjects, along with information regarding onset, duration, severity, and relationship to study drug. Adverse events that lead to withdrawal from the study will be listed and summarized by treatment group separately. Summary tables and listings of serious adverse events will also be generated.

8.4.2 Clinical Laboratory and Vital Signs

Clinical laboratory data (hematology, blood chemistry, and urinalysis) and vital signs will be summarized using descriptive statistics at baseline and each timepoint. Listings will display laboratory data at each period/timepoint collected by subject.

8.5 Pharmacokinetics

Blood samples will be obtained for pharmacokinetics of EBP-994 at Study Visit 1 (Day 1) and Study Visit 6 (Day 28).

The following pharmacokinetic parameters will be calculated for EBP-994 on Day 1 using non-compartmental analysis, when applicable.

AUC_{0-t}:	The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.
AUC_{inf}:	The area under the plasma concentration versus time curve from time 0 to infinity. AUC_{inf} is calculated as the sum of AUC_{0-t} plus the ratio of the last measurable plasma concentration to the elimination rate constant.
AUC/AUC_{inf}:	The ratio of AUC_{0-t} to $AUC_{inf.}$
C_{max}:	Maximum measured plasma concentration over the time span specified.

t_{max}	Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value.
kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g. three or more non-zero plasma concentrations).
$t_{½}$:	Apparent first-order elimination half-life will be calculated as 0.693/kel.
CL/F:	The apparent total body clearance after extravascular administration, calculated as Dose/AUC_{inf}
$V_{area/F}$:	The apparent total volume of distribution after extravascular administration, calculated as Dose/(AUC_{inf} x kel)

No value for kel, AUC_{inf} or $t_{½}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

Other PK parameters may be calculated if deemed appropriate.

The following pharmacokinetic parameters will be calculated for EBP-994 on Day 28 using non-compartmental analysis, when applicable.

$AUC_{0-\tau}$	The area under the plasma concentration versus time curve over the dosing interval at steady-state, as calculated by the linear trapezoidal method.
$C_{max,ss}$	Maximum measure plasma concentration over the time span specified.
$C_{min,ss}$	Measured plasma concentration at the end of the dosing interval.
$t_{max,ss}$	Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value
Flux	Percent fluctuation will be calculated as follows: $\frac{(C_{max} - C_{min}) \times 100}{C_{ssav}}$ where C_{ssav} is calculated as the ratio of AUC_{0-t} to the dosing interval, t.
Swing	Percent fluctuation will be calculated as follows: $\frac{(C_{max} - C_{min}) \times 100}{C_{min}}$

where C_{ssav} is calculated as the ratio of AUC_{0-t} to the dosing interval, t.

Other PK parameters may be calculated if deemed appropriate.

Compartmental analysis may be performed , if deemed necessary.

8.5.1 PK Linearity and Accumulation Assessment

The pharmacokinetic parameter AUC_{0-t} values will be compared against AUC_{inf} values using an analysis of variance (ANOVA) on the ln-transformed values for EBP-994. The ANOVA model will include Day (Day 1 (AUC_{inf}) and Day 28 ($AUC_{0-\tau}$)) as fixed effects. The ANOVA will include calculation of least-squares means (LSM), the difference between day LSM and the standard error associated with this difference. The above statistical analysis will be done using the appropriate SAS® procedure.

Ratio of LSM will be calculated using the exponentiation of the LSM from the analysis on the ln-transformed response. The ratio will be expressed as a percentage relative to AUC_{inf} (Day 1).

Ninety percent confidence interval for the ratio will be derived by exponentiation of the confidence interval obtained for the difference between day LSM resulting from the analysis on the ln-transformed response. The confidence interval will be expressed as a percentage relative to AUC_{inf} (Day 1).

Accumulation will be evaluated by comparing the plasma exposure of EBP-994 on Day 28 ($AUC_{0-\tau}$) to the exposure on Day 1 (AUC_{0-t}).

8.6 Pharmacodynamics

Listings will display viral load data at each period/timepoint collected by subject and these data will be presented graphically. Mean and median levels of the viral load will be calculated at each period/timepoint.

8.7 Sample Size And Power

The sample size has not been determined by strict statistical considerations. From a safety, pharmacokinetic and pharmacodynamic perspective, no a-priori assumptions are made as to the expected treatment effect and associated variability.

8.8 Interim Analyses

No interim analyses are planned.

8.9 Missing Data And Data Imputation

No missing safety or pharmacodynamic data will be estimated.

9 ACCESS TO SOURCE DOCUMENTS

The investigator will make the source documents for this trial available to the sponsor or its representatives, or to the regulatory authority or health authority inspectors.

Subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by government regulatory agency auditors, the Sponsor Clinical Monitor (or designee), and the Institutional Review Board/Ethics Committee (IRB, EC).

The information developed in this clinical study will be used by the Sponsor in the clinical development of the study medication and therefore may be disclosed by the Sponsor as required for disclosure as a public company to other clinical investigators, to other pharmaceutical companies, and/or to other government agencies.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate to obtain patents in the Sponsor's name covering any of the foregoing.

The investigator will retain all study documents for at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan), and until there are no pending or contemplated marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the investigator will retain all study documents for at least 2 years after the investigation is discontinued and regulatory authorities have been notified.

The investigator will notify the sponsor prior to destroying any study records. Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in writing in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements will be made between the investigator and the sponsor for storage. If source documents are required for continued care of the subject, then appropriate copies for storage off site will be made.

10 QUALITY CONTROL AND QUALITY ASSURANCE

Study monitors will periodically audit, at mutually convenient times during and after the study, all CRFs and corresponding office and clinical laboratory records for each subject. The monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study, to verify the accuracy and completeness of CRFs, to resolve any inconsistencies in the study records, and to assure that all protocol requirements, applicable regulations, other requirements, and investigator's obligations are being fulfilled.

11 ETHICS

11.1 Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendment up to and including the Scotland revision (2000) as described in Appendix D.

11.2 Institutional Review Board/Ethics Committee

The protocol, informed consent form, and any materials (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) for this study will be reviewed and approved by a duly constituted institutional review board (IRB)/ethics committee (EC).

The investigator will ensure that all aspects of the IRB/EC review are conducted in accordance with current institutional, local, and national regulations. A letter documenting the IRB/EC approval will be provided to the sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol. The Investigator will submit all periodic reports and updates that the IRB/EC may require, including any final close out reports. The Investigator will inform the IRB/EC of any reportable adverse events.

11.3 Informed Consent

Each subject will be provided with oral and written information describing the nature and duration of the study, in a language they can understand, and must consent in writing to participate before undergoing screening. The date of the consent shall be entered by the subject. The original signed consent form will be retained with the study center's records. Each subject will also be given a copy of his/her signed consent form.

12 DATA HANDLING AND RECORDING

Data for each subject will be recorded on the CRF using indelible black ink. CRFs must be completed for every subject who signs an informed consent and has screening procedures performed.

The investigator is responsible for the completeness and accuracy of information collected on the CRFs for each individual enrolled. The CRFs will be signed and dated by the investigator.

If an entry on a CRF requires change, a single line will be drawn throughout the incorrect entry, the correction will be entered, initialed, and dated. White-out, erasures, or obliterations on CRFs or on source data are not permitted.

The sponsor or designee will conduct data processing. Completed CRFs will be reviewed carefully for accuracy and completeness. If necessary, the study site will be contacted for corrections and/or clarifications. All data will be entered into a study database for analysis and reporting. Any data captured electronically (such as laboratory data) will be transferred electronically to the database. Upon completion of data entry, the database will receive a quality assurance check to ensure acceptable accuracy and completeness.

13 PUBLICATION POLICY

The Institution and Investigator shall be permitted to communicate and or/publish data from the study in a manner consistent with customary academic standards. However, copies of any proposed publication or summaries of any prepared presentation should be submitted to Eiger BioPharmaceuticals at least 30 days in advance of the submission of such proposed publication or presentation. Eiger BioPharmaceuticals shall have a 30-day period to object to the proposed presentation or publication in order to permit Eiger BioPharmaceuticals to identify and remove Eiger BioPharmaceuticals confidential information.

14 PROTOCOL AMENDMENTS AND MODIFICATIONS

The investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. The sponsor is responsible for all protocol amendments and modifications, except those intended to reduce immediate risk to subjects. The sponsor is responsible for submitting protocol amendments to the appropriate government regulatory authorities. The investigator is responsible for submitting protocol amendments to the appropriate IRB or ethics committee. Approval by the IRB/EC will be obtained before changes are implemented.

15 REFERENCES

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APPENDIX A: SCHEDULE OF ASSESSMENTS

EVENT	Screening	Day 1	Day 2	Day 3	Day 7	Day 14	Day 28	Treat wk 8	Treat wk 12-48	Follow wk 4
visit number	1	2	3	4	5	6	7	8	9-18	19
Informed consent	X									
Comprehensive physical exam	X									
Inclusion/exclusion criteria	X									
Medical history	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X
Weight	X	X								
Height	X	X								
BMI calculation	X	X								
Brief physical exam		X		X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X
12 lead ECG pre/post-dose[1]	X	X	X				X			X
Liver biopsy (if needed)[2]	X									
Complete blood count	X	X		X	X	X	X	X	X	X
Chemistry panel	X	X		X	X	X	X	X	X	X
Thyroid function	X									
Pregnancy test (serum)	X									
Pregnancy test (urine)		X								X
HBV DNA, HDV RNA	X	HDV RNA	HDV RNA	HDV RNA	HDV RNA	HDV RNA	HDV RNA	HDV RNA	HDV RNA	HDV RNA
Viral mutation analysis[3]		X	X		X	X	X	X	X	X
HIV serology	X									
Urinalysis (pre-dose)	X			X	X		X	X	X	X
Urine drug screen[4]	X									
PBMC Collection	X	X	X	X	X	X	X	X	X	X
HCV viral load (quant PCR)	X									
PK sampling (pre-/post-dose)[5]		X	X	X	X	X	X	X	X	
INR	X									
Study drug administration		X			X					
Dispense study drug		X			X		X	X	X	
Study drug accountability			X		X		X	X	X	

Schedule of Assessments Footnotes

1 = Serial ECG (x3) 2 -3 minutes apart
2 = See Appendix 4 for CTP scoring and encephalopathy results
3 = Serum and plasma samples for viral mutation analysis, resistance phenotyping and analysis of drug mechanism and treatment response
4 = Urine drug screen for opiates, amphetamines, barbiturates, benzodiazapenes, cocaine
5= Timepoints for optional PK sampling pre-dose (0), 15 min, 30 min, 60 min, 90 min, 2h, 2.5h, 3h, 4h, ,6 h, 10h, 12h

APPENDIX B: BODY MASS INDEX TABLE (METRIC), FORMULA AND CALCULATOR

BMI TABLE

BMI	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Height cms (metres)	Body Weight (kilograms)																
147cm (1.47m)	41	44	45	48	50	52	54	56	59	61	63	65	67	69	72	73	76
150cm (1.50m)	43	45	47	49	52	54	56	58	60	63	65	67	69	72	74	76	78
152cm (1.52m)	44	46	49	51	54	56	58	60	63	65	67	69	72	74	76	79	81
155cm (1.55m)	45	48	50	53	55	57	60	62	65	67	69	72	74	77	79	82	84
157cm (1.57m)	47	49	52	54	57	59	62	64	67	69	72	74	77	79	82	84	87
160cm (1.60m)	49	51	54	56	59	61	64	66	69	72	74	77	79	82	84	87	89
163cm (1.63m)	50	53	55	58	61	64	66	68	71	74	77	79	82	84	87	89	93
165cm (1.65m)	52	54	57	60	63	65	68	71	73	76	79	82	84	87	90	93	95
168cm (1.68m)	54	56	59	62	64	67	70	73	76	78	81	84	87	90	93	95	98
170cm (1.70m)	55	57	61	64	66	69	72	75	78	81	84	87	90	93	96	98	101
172cm (1.72m)	57	59	63	65	68	72	74	78	80	83	86	89	92	95	98	101	104
175cm (1.75m)	58	61	64	68	70	73	77	80	83	86	89	92	95	98	101	104	107
178cm (1.78m)	60	63	66	69	73	76	79	82	85	88	92	95	98	101	104	107	110
180cm (1.80m)	62	65	68	71	75	78	81	84	88	91	94	98	101	104	107	110	113
183cm (1.83m)	64	67	70	73	77	80	83	87	90	93	97	100	103	107	110	113	117
185cm (1.85m)	65	68	72	75	79	83	86	89	93	96	99	103	107	110	113	117	120
188cm (1.88m)	67	70	74	78	81	84	88	92	95	99	102	106	109	113	116	120	123
191cm (1.91m)	69	73	76	80	83	87	91	94	98	102	105	109	112	116	120	123	127
193cm (1.93m)	71	74	78	82	86	89	93	97	100	104	108	112	115	119	123	127	130
BMI	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35

Use this BMI chart to calculate your Body Mass Index (BMI).

- First select your height then select your weight.
- Select the nearest value/s to your own if they are not displayed in the chart.
- Your BMI will be listed at the top and bottom of the BMI chart.

Source: http://www.whathealth.com/bmi/chart-metric2.html

BMI FORMULA

$$\text{BMI} = \frac{\text{Weight in Kilograms}}{(\text{Height in centimeters}) \times (\text{Height in centimeters})}$$

For example a person who weighs 110 kgs and is 190.5 cm tall has a BMI of 30.3.

$$\frac{110 \text{ kgs}}{(190.5 \text{ cm}) \times (190.5 \text{ cm})} = 30.3$$

BMI CALCULATOR

For additional information, including a BMI Calculator, please consult www.whathealth.com/bmi/chart-metric.html

APPENDIX C: DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964

And amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A: INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B: BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a

well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRICIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

APPENDIX D: HEPATIC ASSESSMENTS

The Child-Turcotte-Pugh (CTP) Score

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement. Subjects with a total CTP score of 6 or higher are NOT eligible to participate in this study.

Measure	**1 point**	**2 points**	**3 points**	**units**
Bilirubin (total)	<34 (<2)	34-50 (2-3)	>50 (>3)	μmol/l (mg/dL)
Serum albumin	>35	28-35	<28	mg/L
INR	<1.7	1.71-2.20	> 2.20	*no unit*
Ascites	None	Suppressed with medication	Refractory	*no unit*
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)	*no unit*

http://www.doctorslounge.com/gastroenterology/scores/child.htm

Assessment for Hepatic Encephalopathy

Subjects with assessments of stage 1-4 are NOT eligible to participate in this study.

West Haven Criteria of Altered Mental Status In Hepatic Encephalopathy

Stage	**Consciousness**	**Intellect and Behavior**	**Neurologic Findings**
0	Normal	Normal	Normal examination; impaired psychomotor testing
1	Mild lack of awareness	Shortened attention span; impaired addition or subtraction	Mild asterixis or tremor
2	Lethargic	Disoriented; inappropriate behavior	Obvious asterixis; slurred speech
3	Somnolent but arousable	Gross disorientation; bizarre behavior	Muscular rigidity and clonus; Hyperreflexia
4	Coma	Coma	Decerebrate posturing

http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/gastro/henceph/table2.htm