STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Open-Label Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic Activity of Titrating-Dose Lonafarnib in Combination with Ritonavir in Patients Chronically Infected with Hepatitis Delta Virus (LOWR-4)
Name of Test Drug:	Lonafarnib (also Sarasar, EBP994, SCH 66336) Ritonavir (Norvir)
Study Number:	EIG-LNF-002
Protocol Version:	Amendment 3
Protocol Date:	22 December 2015
Analysis Type:	Week 24 (End of Treatment); Week 48 (End of Study)
Analysis Plan Version:	Final 1.0
Analysis Plan Date:	21 Sep 2016
Analysis Plan Author:	Triangle Biostatistics, LLC

CONFIDENTIAL AND PROPRIETARY INFORMATION

SIGNATURE PAGE 4

LIST OF ABBREVIATIONS 5

1. INTRODUCTION 7

1.1. Study Objectives 7
1.2. Study Design 8
1.3. Sample Size and Power 15

2. TYPE OF PLANNED ANALYSIS 17

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES 18

3.1. Analysis Sets 18
3.1.1. Safety 18
3.1.2. Efficacy 18
3.1.3. Pharmacokinetic 18
3.2. Missing Data 18

4. PATIENT DISPOSITION 19

4.1. Disposition of Patients 19
4.2. Extent of Exposure 19
4.2.1. Duration of Exposure to Study Drug 19
4.3. Protocol Deviations 20

5. BASELINE DATA 21

5.1. Demographics and Baseline Characteristics 21
5.2. Medical History 21

6. EFFICACY ANALYSES 22

6.1. Primary Efficacy Endpoint 22
6.2. Analysis of the Primary Efficacy Endpoint 22
6.3. Secondary Efficacy Endpoints 23
6.4. Analysis of the Secondary Efficacy Endpoints 23

7. SAFETY ANALYSES 24

7.1. Adverse Events and Deaths 24
7.1.1. Adverse Event Dictionary 24
7.1.2. Adverse Event Severity 24
7.1.3. Relationship of Adverse Events to Study Drug 25
7.1.4. Serious Adverse Events 25
7.1.5. Treatment-Emergent Adverse Events 26
7.1.5.1. Definition of Treatment-Emergent 26
7.1.5.2. Incomplete Dates 26
7.1.6. Summaries of Adverse Events and Deaths 26
7.2. Laboratory Evaluations 27
7.2.1. Summaries of Numeric Laboratory Results 27
7.3. Body Weight and Vital Signs 28
7.4. Concomitant Medications 28
7.5. Electrocardiogram (ECG) Results 28
7.6. Other Safety Measures 29
7.7. Viral Resistance Analysis 29
7.8. Changes From Protocol-Specified Safety Analyses 29

8. PHARMACOKINETIC ANALYSES 30
9. REFERENCES 32
10. SOFTWARE 33
11. SAP REVISION 34
12. APPENDICES 35

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings 36
Appendix 2. Programming Specifications 39

LIST OF ABBREVIATIONS

Ab	Antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
bid	Twice each day
BMI	Body mass index
BPM	Beats per minute
CDER	Center for Drug Evaluation and Research
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
EAS	Efficacy analysis set
ECG	Electrocardiogram
FR	Federal Register
FSH	Follicle-stimulating hormone
FT	Farnesyltransferase
GI	Gastrointestinal
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDV	Hepatitis Delta Virus
HIV	Human Immunodeficiency Virus
HLT	High level term
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	International normalized ratio
IUD	Intrauterine device
LLT	Lower level term
MedDRA	Medical dictionary for regulatory activities
NCI	National Cancer Institute
PAH	Pulmonary arterial hypertension
PK	Pharmacokinetics
PT	Preferred term
qPCR	Quantitative polymerase chain reaction
QTc	Corrected QT interval
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan

SAS	Safety analysis set
SOC	System organ class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFLs	Tables, figures, and listings
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

SIGNATURE PAGE

SEP 29, 2016

Signature Date

Eduardo Martins, MD, DPhil

SVP, Liver and Infectious Diseases

Eiger BioPharmaceuticals

9/30/2016

Signature Date

Jeff Sorbel, MS

Managing Member, Statistics

Triangle Biostatistics, LLC

1. INTRODUCTION

Lonafarnib is an orally administered, potent and selective inhibitor of the enzyme farnesyltransferase (FT). Farnesylation is important in allowing association of the large hepatitis delta virus (HDV) protein and hepatitis B virus (HBV) surface antigens to form an infectious HDV particle. This association is critical in the development of HDV infection because HDV can propagate only in the presence of HBV. While HDV can replicate autonomously inside the hepatocyte, the virus requires co-infection with HBV to complete virion assembly and to facilitate transmission. Assembly of the HDV virion depends on prenylation with FT (Bordier, 2003). Compounds with FT inhibitory activity have been shown to prevent production of HDV virions after transfection of Huh7 cells with two different HDV genotypes (Bordier, 2002).

Worldwide more than 15 million people are co-infected with HDV and HBV. Co-infection results in more severe complications compared with infection with HBV alone, and hepatitis D is the most aggressive and virulent of the viral hepatitides. HDV is clinically important because, although it suppresses HBV replication, it causes severe liver disease with rapid progression to cirrhosis and hepatic decompensation when compared with the clinical course associated with HBV mono-infection. The prevalence of HDV is increasing in northern and central Europe through migration from areas endemic in HDV. Currently, there is no approved therapy for HDV infection.

Lonafarnib has been studied extensively in patients with cancer (more than 1500 patients in Phase 1, 2, and 3 studies) because FT also acts on Ras proteins, which play a central role on tumor cell growth. Eiger BioPharmaceuticals, Inc., is currently developing lonafarnib for the treatment of patients with chronic HDV infection. Based on the known properties of lonafarnib, variable absorption in patients, a metabolic pathway that occurs primarily via cytochrome P450 3A4 (CYP3A4), and the occurrence of dose-dependent gastrointestinal (GI) adverse events (AEs), Eiger plans to has combined lonafarnib with low-dose ritonavir, a potent CYP3A4 inhibitor, to increase systemic concentrations of lonafarnib and to reduce the total administered dose of lonafarnib necessary to achieve therapeutic effect.

1.1. Study Objectives

Primary Study Objectives	• Evaluate the safety and tolerability of the following dose-titration regimen of lonafarnib in combination with ritonavir over the 24-week Treatment Period: lonafarnib/ritonavir starting at 50 mg bid/100 mg twice daily (bid) and escalated to lonafarnib/ritonavir 75 mg bid/100 mg bid and then to 100 mg bid/100 mg bid as tolerated • Evaluate the pharmacodynamic activity (change in

	hepatitis D viral [HDV] load) of the dose-titration regimen of lonafarnib in combination with ritonavir over the 24-week Treatment Period
Secondary Study Objectives	• Evaluate the effect of the dose-titration regimen of lonafarnib/ritonavir on the following: • Pharmacokinetics (PK) • Change in alanine aminotransferase (ALT) levels • Change in hepatitis B virus (HBV) DNA levels

1.2. Study Design

Design Configuration and Patient Population	This is a Phase 2 study of 24 weeks of treatment with a dose-titration regimen of lonafarnib/ritonavir in patients chronically infected with HDV: lonafarnib starting at 50 mg bid and escalating to 75 mg bid and then 100 mg bid as tolerated in combination with ritonavir (100 mg bid). The initial dose of lonafarnib and ritonavir 50 mg bid/100 mg bid will be maintained for at least 4 weeks; subsequent dose escalation may occur at an interval of no less than 2 weeks after patients have received a particular dose. Up to 15 patients with chronic HDV infection with detectable HDV RNA by quantitative polymerase chain reaction (qPCR) will be enrolled.
Treatment Groups	Open-Label Lonafarnib in Combination with Ritonavir
Key Eligibility Criteria	**Inclusion Criteria** A patient may be included in this study if he or she meets all of the following criteria: 1. Willing and able to comply with study procedures and provide written informed consent. 2. Male or female, 18 to 65 years of age, inclusive. 3. Has a body mass index (BMI) of ≥18 kg/m2, inclusive, and has a body weight of ≥45 kg. 4. Chronic HDV infection documented by a positive HDV antibody (Ab) test of at least 6 months duration and detectable HDV RNA by qPCR at study entry. 5. Liver biopsy demonstrating evidence of chronic

	hepatitis. If no liver biopsy is available, the patient must be willing to consent to and have no contraindication to liver biopsy. Liver biopsy will be performed during screening. 6. Electrocardiogram (ECG) demonstrating no acute ischemia or clinically significant abnormality and a QT interval corrected for heart rate (QTc) of >450 ms using Fridericia correction (ICH Guidance for Industry E14: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs). 7. Females who meet the following criteria may be eligible to enter the study: a. *Of nonchildbearing potential*—defined as women who are surgically sterile (have had bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), have medically documented ovarian failure, or are postmenopausal (amenorrheic for more than 2 years, age appropriate, and confirmed by follicle-stimulating hormone [FSH] level indicating a postmenopausal state). b. *Of childbearing potential*—defined as women who have an intact uterus and ovaries and are within 1 year since the last menstrual period who – are not pregnant and have negative serum pregnancy test at screening and a negative urine pregnancy test on the Baseline/Day 1 Visit before randomization. – Are not lactating or breastfeeding. – Agree to use two of the following contraceptive methods until 1 month after last dose of study drug, of which at least one must be a barrier method: ▪ Hormonal contraceptives Intrauterine device (IUD) in place for at least 3 months before the start of screening and until 1 month after last dose of study drug. ▪ Double-barrier methods (use of condom [male partner] with either diaphragm with spermicide or cervical

	cap with spermicide) from the start of screening until 6 months after last dose of study drug. ▪ Surgical sterilization of the partner (vasectomy for 1 month before the start of screening and maintenance throughout study). 8. Males with female partners who are of childbearing potential (see above) who meet the following criteria may be eligible to enter the study: a. Are surgically sterile or b. Agree to practice two effective forms of birth control from those listed below from the start of screening until 1 month after their last dose of study drug, at least one of which must be a barrier method: – Consistently and correctly use a condom and – Their partner must agree to use a hormonal contraceptive or a nonhormonal barrier method (IUD or diaphragm with spermicide or cervical cap with spermicide). **Exclusion Criteria** A patient will be excluded from this study if he or she meets any of the following criteria: ***General Criteria*** 1. Participation in a clinical trial with or use of any investigational agent within 30 days of start of screening. 2. Pregnant or lactating/breastfeeding. 3. Previous use of lonafarnib. Patients who previously participated in a clinical trial of lonafarnib but are confirmed to have received placebo are allowed. ***Disease-related Criteria*** 4. Co-infected with human immunodeficiency virus (HIV) or hepatitis C virus (HCV).

	5. Positive results for HIV or HCV Ab at screening. Patients with a positive HCV Ab at screening are allowed if they have completed a curative antiviral regimen and are documented to be HCV RNA negative (undetectable) at least 3 months before screening and at screening. 6. Active jaundice defined by total bilirubin level >2.0 mg/dL and known not to have Gilbert's disease. 7. Decompensated liver disease or cirrhosis as defined by the presence of any of the following on screening laboratory tests: a. Bilirubin level >2.0 mg/dL b. Albumin level <3.0 g/dL c. Platelet count <90,000 cells/mm^3 d. International normalized ratio (INR) ≥1.5 8. History of bleeding esophageal varices, ascites, or hepatic encephalopathy. 9. Patients with any of the following abnormal laboratory test results at screening: a. White blood cell (WBC) count <3,000 cells/mm^3 b. Absolute neutrophil count (ANC) <1500 cells/mm^3 c. Hemoglobin <11 g/dL for women and <12 g/dL for men d. Abnormal thyroid-stimulating hormone (TSH), T_4, or T_3 levels; unless the patient is stable on thyroid hormone replacement therapy 10. Serum creatinine concentration ≥1.5 times upper limit of normal (ULN). 11. Evidence of another form of viral hepatitis or another form of liver disease (eg, autoimmune liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, alcoholic liver disease, nonalcoholic steatohepatitis, hemochromatosis, alpha-1-anti-trypsin deficiency) 12. Evidence of hepatocellular carcinoma 13. Patients with any one of the following: a. An eating disorder or alcohol abuse within the past 2 years b. Excessive alcohol intake defined as follows:

	>20 g/day for females (1.5 standard alcohol drinks) or >30 g/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) 14. In the opinion of the Investigator, an alcohol use pattern that will interfere with study conduct 15. Drug abuse within the previous 6 months before the screening visit with the exception of medically prescribed cannabinoids and their derivatives 16. History or clinical evidence of any of the following: a. Immunologically mediated disease (eg, rheumatoid arthritis, inflammatory bowel disease, severe psoriasis, systemic lupus erythematosus) that requires more than intermittent nonsteroidal anti-inflammatory medications for management or that requires use of systemic corticosteroids in prior 6 months (eg, inhaled asthma medications are allowed) b. History of or evidence of retinal disorder or clinically relevant ophthalmic disorder. c. Any malignancy within 5 years of the start of screening. Exceptions are superficial dermatologic malignancies (eg, squamous cell or basal cell skin cancer treated with curative intent). d. Significant or unstable cardiac disease (eg, angina, congestive heart failure, uncontrolled hypertension, history of arrhythmia) e. Chronic pulmonary disease (eg, chronic obstructive pulmonary disease) associated with functional impairment f. Pancreatitis g. Severe or uncontrolled psychiatric disease, including severe depression, history of h. suicidal ideation, suicidal attempts, or psychosis requiring medication and/or hospitalization 17. Solid organ transplantation, including liver

	Criteria Related to Use of Selected Medications 18. Use of alpha interferon, either interferon alfa-2a or interferon alfa-2b, or pegylated interferon alfa-2a within 2 months before the start of screening 19. Concomitant use of any of the following: a. Medications or foods that are known moderate or strong inducers or inhibitors of CYP3A4 or CYP2C19 b. Drugs known to prolong the PR or QT interval. c. Receipt of systemic immunosuppressive therapy within the 3 months before start of screening. d. Statins, due to inhibition of mevalonate synthesis, which reduces protein prenylation e. Medications contraindicated in the prescribing information for ritonavir: – Alpha1-adrenoreceptor antagonist: alfuzosin HCL – Analgesics*: pethidine*, piroxicam*, propoxyphene* – Antiarrhythmics: amiodarone, flecainide, propafenone, quinidine, bepridil*, encainide* – Antibiotic*: fusidic acid* – Antifungal: voriconazole – Antihistamines*: astemizole*, terfenadine* – Antimycobacterial*: rifabutin* – Ergot derivatives: dihydroergotamine, ergonovine*, ergotamine, methylergonovine – Gastrointestinal motility agent: cisapride – Herbal products: St. John's wort (hypericum perforatum) – HMG-CoA reductase inhibitors: lovastatin, simvastatin – Antipsychotics*/Neuroleptic: clozapine*, pimozide, quetiapine* – Phosphodiesterase type 5 (PDE5) enzyme inhibitor: sildenafil [Revatio®] only when used for the treatment of pulmonary arterial hypertension (PAH), avanafil*, vardenafil*

	– Sedative/hypnotics: clorazepate*, diazepam*, estazolam*, flurazepam*, oral midazolam, triazolam (Sources: Prescribing Information for Norvir® [ritonavir] Tablets, 2015. *Additional terms from the Summary of Product Characteristics for Norvir® [ritonavir] tablets, 2014) f. History or evidence for any intolerance or hypersensitivity to lonafarnib, ritonavir, or other substances that are part of the study medication. ***Other Medical Conditions*** 20. Other significant medical condition that may require intervention during the duration of the study. 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 patient of participation in the trial.
Study Periods/Phases	The study will consist of three periods: **Screening**—At the Screening Visit, patients providing written informed consent will have required evaluations to determine their eligibility to participate in the study. **Treatment**—Each eligible patient will undergo a minimum of 10 Treatment Study Visits. **Follow-up**—Follow-up visits will occur monthly for 6 months.

Schedule of Assessments

The study will consist of three periods:

Screening—At the Screening Visit, patients providing written informed consent will have required evaluations to determine their eligibility to participate in the study.

Screening evaluations may occur over more than one visit, depending on the facilities and personnel available at the clinical center. All screening procedures must occur within 4 weeks before the start of dosing (Day −28 through Day −1).

Treatment—Each eligible patient will undergo a minimum of 10 Treatment Study Visits: Week 0 (Day 1), Week 1 (Day 8 ± 2 d), Week 2 (Day 15 ± 2 d), Week 4 (Day 29 ± 2 d), Week 6 (Day 43 ± 2 d), Week 8 (Day 57 ± 5 d), Week 12 (Day 85 ± 5 d), Week 16 (Day 113 ± 5 d), Week 20 (Day 141 ± 5 d), and Week 24 (Day 169 ± 5 d).

Follow-up—Follow-up visits will occur monthly for 6 months. The first Follow-up Visit will be on Week 28 (4 weeks after last dose or if the patient discontinues treatment early) and will also include evaluation of lonafarnib level. All monthly Follow-up Visits will include evaluations of safety (AEs, concomitant medications, and laboratory values) and viral loads (HDV and HBV). Alpha-interferon treatments will be allowed during the last 5 months of the follow-up period (that is, starting 4 weeks after last dose of study treatment).

In addition to the planned visits, unscheduled visits may be required if, in the opinion of the Investigator, the clinical status of the patient warrants interim evaluation.

Study Visits should be scheduled according to the study protocol; however, the window for Study Visits for Weeks 1 through 6 will be ±2 days of the nominal Study Visit day, and for study visits thereafter the window will be ±5 days.

See Appendix 3 for a complete tabular depiction of study procedures.

Randomization	Patients will not be randomized in this open-label, single-arm study.
Site and/or Stratum Enrollment Limits	N/A
Study Duration	The duration of the study for each patient is approximately 13 months (up to 4 weeks for screening, 24 weeks of treatment, 4 weeks for the primary follow-up visit, and monthly safety follow-up visits for 5 months thereafter). The 6-month follow-up after the last dose of study drug is designed to allow evaluation of the clinical and virologic course after completion of the 24-week Treatment Period.

1.3. Sample Size and Power

Planned Sample Size	Up to 15 patients

Power Statement	The sample size was chosen to allow assessment of the safety and tolerability of the combination of lonafarnib/ritonavir, recognizing that drug exposures may be highly variable and will likely result in an observable range of patient tolerabilities to the same administered dose

2. TYPE OF PLANNED ANALYSIS

This Statistical Analysis Plan (SAP) has been prepared based on the amendment 3 version of the protocol (dated December 22, 2015). This SAP documents the two planned statistical analysis of the study for the Week 24 (End of Treatment) and Week 48 (End of Study) analysis.

The interim analysis for Week 24 (End of Treatment) will include all data collected from Screening up until the end of the Treatment Period at Week 24 for each subject. The final analysis will include all data collected from Screening through the Follow-Up Period/End of Study at Week 48 for each subject. As the primary and secondary efficacy endpoints will be summarized descriptively and no inferential analysis is planned, there will be no adjustments for alpha spending.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

3.1. Analysis Sets

Analysis sets define which patients are included in an analysis.

The assignment of patients to analysis sets will be done before database lock. A summary of the number and percent of patients in each analysis set will be provided.

3.1.1. Safety

The **Safety** analysis set (SAS) will consist of all patients who receive at least one dose of study drug.

3.1.2. Efficacy

The **Efficacy** analysis set (EAS) will consist of patients who receive study drug throughout the entire 24 week treatment period and for whom viral load data are available from baseline and end-of-treatment (Week 24) study visits.

3.1.3. Pharmacokinetic

The **Pharmarcokinetic (PK)** analysis set include patients who received at least 2 weeks of study drug at a stable dose level, and in whom a sufficient number of blood samples were collected, plasma samples were analyzed, concentration data were analyzed, and PK parameter values were derived.

3.2. Missing Data

A missing datum for a given study visit window may be due to:

1. a visit occurring in the window but data were not collected or were unusable, or
2. a visit not occurring in the window, or
3. a patient permanently discontinuing from study before reaching the window.

Values for missing data will not be imputed.

4. PATIENT DISPOSITION

4.1. Disposition of Patients

A summary of patient disposition will be provided for all subjects. This summary will present the number of patients screened, randomized, included in the safety analysis set, and the number and percent of patients:

- within each dose level of lonafarnib/ritonavir (50 mg /100 mg, 75 mg /100 mg, 100 mg /100 mg),
- completing the study treatment period,
- not completing the study treatment period (with summary of reasons for not completing the study treatment period),
- completing the study (includes the study treatment period and post-treatment follow-up period), and
- not completing the study, (with summary of reasons for not completing the study).

The denominator for the percentages of patients in each category will be the number of patients in the safety analysis set.

No inferential statistics will be generated. A data listing of reasons for premature study treatment/study discontinuation will be provided.

4.2. Extent of Exposure

4.2.1. Duration of Exposure to Study Drug

Duration of exposure to study drug will be defined as (last dose date – first dose date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks (recorded to one decimal place, e.g., 4.5 weeks). Duration of exposure to study drug will be summarized by dose level using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum).

Summaries will be provided for the safety analysis set.

No inferential statistics will be provided.

4.3. Protocol Deviations

A summary table of major protocol deviations and a listing of all patients with protocol deviations will be presented.

5. BASELINE DATA

5.1. Demographics and Baseline Characteristics

Patient demographic data (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., body weight, height, BMI, hepatitis history, Fibroscan, liver biopsy) will be summarized using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) for continuous data and by the number and percent of patients for categorical data. The summaries of demographic data and baseline characteristics will be provided for the safety analysis set.

5.2. Medical History

Baseline medical histories and pre-existing conditions will be summarized based on mapping to system organ classes and preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA).

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

The primary PD/efficacy analysis will compare the change from Baseline (Day 1) to Week 24 (End of Treatment) in HDV RNA (log10 IU/mL).

HDV RNA will be measured by qPCR. The assay will be performed at Lademannbogen Laboratory, a subsidiary of Sonic Healthcare, using the RoboGene HDV RNA Quantification Kit. This assay has a limit of quantitation of 14 IU/mL and can detect genotypes 1, 2, 5, 6, 7 and 8.

6.2. Analysis of the Primary Efficacy Endpoint

Pharmacodynamic data will be presented in by dose level summary tabulations and listings that will display HDV RNA (log10 IU/mL) at each period/time point collected by patient. Mean and median levels and change from baseline of the HDV RNA (log10 IU/mL) will be calculated at each time point. For analysis of change from baseline, baseline will be defined as the geometric mean of the HDV RNA titer obtained at the Screening and Day 1 (pretreatment) visits. The number of patients with 1 log10 reduction from baseline will be summarized at each time point. The number of patients with reduction in HDV RNA below the limit of quantitation and the limit of detection will be summarized.

HDV RNA (log10 IU/mL) mean levels and mean change from baseline levels at each timepoint will be presented graphically. Individual subject plots at each timepoint will also be presented graphically.

Results below the level of detection will be imputed as half the lower limit of detection (14 IU/mL). Missing data will not be imputed. All summaries and figures will show the number of non-missing data at each visit.

6.3. Secondary Efficacy Endpoints

The secondary endpoints of the study are:

- PK parameters
- Change in ALT levels
- Change in HBV DNA levels

6.4. Analysis of the Secondary Efficacy Endpoints

Plasma concentrations of lonafarnib and ritonavir will be summarized descriptively by dose level at each scheduled timepoint. PK parameters for multiple-dose lonafarnib and ritonavir defined in Section 8 - Table 4 will be summarized descriptively by dose level. Arithmetic means, coefficients of variation (%CV), standard deviations (SD), median, minimum, and maximum values; and number of observations PK parameter values will be generated for multiple-dose lonafarnib and ritonavir. More detail on the analysis of the PK parameters is outlined in Section 8.

ALT levels and change from baseline will be summarized by descriptive statistics (mean, standard deviation, median, and range) for each measurement time point. Baseline is defined as the last non-missing value prior to first dose of study drug.

HBV DNA (log10 IU/mL) levels and change from baseline will be summarized by descriptive statistics (mean, standard deviation, median, and range) for each measurement time point. Baseline is defined as the last non-missing value prior to first dose of study drug. HBV DNA (log10 IU/mL) mean levels and mean change from baseline levels at each timepoint will be presented graphically. Individual subject plots at each timepoint will also be presented graphically.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of the drug (eg, off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. For events not listed in the CTCAE, the definitions from the CTCAE provided in Table 1 should be used to evaluate the grade of severity for the AE.

Table 1. Adverse Event Grades Based on the Common Terminology Criteria for Adverse Events

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, and managing money)
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

Source: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03

The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings, and will be considered the least severe for the purposes of sorting for data presentation.

7.1.3. Relationship of Adverse Events to Study Drug

The Investigator's assessment of causality must be provided for all AEs (serious and nonserious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. To describe the relationship of the AE to study drug on the AE CRF, the Investigator will use the terms and definitions provided in Table 2. For a particular AE, the Investigator will assess both the relationship to lonafarnib and the relationship to ritonavir.

Table 2. Categories for Assessing Relationship of Adverse Events to Investigational Products

Assessment of Causality	Definition
Not related	No relationship between the event and the administration of study drug or another cause of the event is most plausible, the experience does not follow a clear temporal association with study drug administration, or the event is related to other etiologies such as concomitant medications or patient's clinical state
Possibly related	An event that follows a plausible temporal sequence from administration of the study drug and follows a known or expected response pattern to the suspected study drug but that might have been produced by a number of other factors
Definitely related	An event that follows a plausible temporal sequence from administration of the study drug and without significant alternative etiology. In addition, the relationship may be supported by improvement on study drug discontinuation and/or a positive rechallenge

7.1.4. Serious Adverse Events

An AE or suspected adverse reaction is considered ''serious'' if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient 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 department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent

Events occurring after administration of the first dose of study drug will be recorded on the AE CRF. Treatment-emergent AEs (TEAEs) are defined as those that start or worsen after the start of study treatment and up to 28 days after the last dose of study treatment; any AEs that occur after that time will be considered posttreatment AEs.

7.1.5.2. Incomplete Dates

If the date of onset is incomplete, then the month and year (or year alone if month is not recorded) of onset determine treatment emergent as follows. The event is treatment emergent if the month and year of onset (or year of onset) of the event is

a) the same as or after the month and year (or year) of the first dose of study drug, and

b) the same as or before the month and year (or year) of the 28th day after the date of the last dose of study drug

7.1.6. Summaries of Adverse Events and Deaths

A brief summary of adverse events will show, by dose level, the number and percentage of patients who (1) had any TEAE, (2) had any treatment-emergent serious adverse event (TESAE), (3) had any treatment-emergent treatment-related AE, (4) had any treatment-emergent treatment-related SAE, (5) had any AEs leading to early discontinuation of study treatment, (6) had any AEs leading to dose reduction, and (7) died during study.

Summaries (number and percent of patients) of adverse events (by SOC and PT) will be provided by dose level using the safety analysis set as follows:

- All TEAE,
- All TESAE
- All treatment-emergent treatment-related AE,

- All treatment-emergent treatment-related SAE,
- All AEs leading to early discontinuation of study treatment,
- All AEs leading to dose reduction, and
- Deaths

TEAEs and TESAEs will also be summarized by dose level, system organ class, preferred term, and severity as well as by dose level, system organ class, preferred term, and the event's relationship to study treatment.

At each level of summation, patients will be counted only once, under the greatest severity and strongest study-drug relationship (as reported by the Investigator). If an AE is reported more than once during the study period, the greatest severity and worst-case attribution will be presented in tables. For data presentation, SOC will be ordered alphabetically, with PT sorted by decreasing total frequency.

In addition to the by-treatment summaries, data listings will be provided for the following:

- All adverse events (with a variable indicating whether the event is treatment-emergent)
- Serious adverse events
- Deaths
- Adverse events leading to discontinuation of study drug

7.2. Laboratory Evaluations

A list of the routine clinical laboratory test done for this study can be found in Table 5 of the study protocol (pp. 55-56).

Summaries of laboratory data will be provided for the safety analysis set. No inferential statistics will be generated.

7.2.1. Summaries of Numeric Laboratory Results

Clinical laboratory data will be summarized at each measurement time point and for each patient's final post-baseline measurement in the following ways: (1) with descriptive statistics(mean, standard deviation, median, and range) for each measurement time point and (2) with descriptive statistics for the change from baseline in the measurements at each post-baseline time point. All clinical laboratory values collected during the study will be listed, with values outside the normal ranges flagged for clinical evaluation. Grade 3 and 4

laboratory results will be listed and summarized. In addition, ALT, AST, total bilirubin and AP will be summarized by CTCAE grade.

7.3. Body Weight and Vital Signs

Actual values for vital signs and changes from baseline will be summarized and listed for each patient.

Summaries of vital signs will be provided for the safety analysis set. No inferential statistics will be generated.

7.4. Concomitant Medications

Concomitant medications will be summarized based on mapping to drug classes and generic terms in the World Health Organization Drug Dictionary Enhanced (WHO-DD Enhanced).

Summaries of concomitant medications will be provided for the safety analysis set. No inferential statistics will be generated.

7.5. Electrocardiogram (ECG) Results

Actual values for ECG intervals and changes from baseline will be summarized by study visit using descriptive statistics. Clinical interpretation of ECG results will be listed.

Summaries of ECG results will be provided for the safety analysis set. No inferential statistics will be generated.

7.6. Other Safety Measures

A data listing will be provided for patients experiencing pregnancy during the study.

7.7. Viral Resistance Analysis

For resistance surveillance, genotypic analysis of HDV genome from patients with virologic failure will be conducted. Virologic failure is defined as an increase in serum HDV RNA of at least 1.0 log from the nadir value on 2 consecutive visits in patients who stay on lonafarnib treatment. The number and percentage of patients who experience virologic failure will be summarized by dose level.

In addition, the number and percentage of patients who shift from HDV RNA baseline value (positive, negative) to post-baseline value (positive, negative) at each post-baseline visit will be summarized by dose level.

In vitro phenotypic analysis may be explored as necessary.

7.8. Changes From Protocol-Specified Safety Analyses

There are no changes from the protocol-specified safety analyses.

8. PHARMACOKINETIC ANALYSES

All the available data from subjects who have a sufficient number of samples will be used in the pharmacokinetic analyses. Any sample concentration reported as less than the assay limit of quantitation will be set to zero for use in the analyses. Analyses will be conducted on reported values. No concentration estimates will be made for missing values.
Time-sensitive pharmacokinetic parameters (area, time to peak and elimination rate) will be calculated using the scheduled times of sample collection unless actual collection times deviate significantly. Deviations will be considered significant if the time between scheduled and actual times is more than the reporting standards listed in Table 3.

Table 3. Time Windows for Collection of Pharmacokinetic Samples

Nominal Time	Reporting Standards
Predose	Within 30 minutes before first dose
0.0–2.0 hours	$\leq \pm 1$ minute
>2.0–8.0 hours	$\leq \pm 2$ minutes
>8.0-12 hours	$\leq \pm 5$ minutes

A non-compartmental method will be used to derive the PK parameters listed in Table 4 from plasma concentrations for lonafarnib and ritonavir. Additional PK parameters using non-compartmental methods may also be used if data permit.

Table 4. Pharmacokinetic Parameters Derived from Plasma Concentrations for Lonafarnib and Ritonavir

PK Parameter	Definition
C_{max}	Peak plasma concentration as observed.
T_{max}	Time of the peak plasma concentration.
$AUC_{0-\tau}$	Area under the plasma concentration versus time curve during the dosing interval calculated by the linear trapezoidal rule.
C_{avg}	Average plasma drug concentration during multiple-dose administration.
C_{min}	Minimum plasma concentration.
K_{el}	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 (eg, three or more non-zero plasma concentrations).

V_{area}/F	Apparent total volume of distribution calculated as follows: total dose/(total $AUC_{0-\infty} \times K_{el}$).
CL/F	Apparent total body clearance, calculated as follows: dose/ $AUC_{0-\infty}$ Weight-adjusted CL/F (CL/F/kg) will also be calculated.
$T_{1/2}$	Apparent first-order terminal elimination half-life will be calculated as $0.693/K_{el}$.

Plasma concentrations of lonafarnib and ritonavir will be summarized descriptively by dose level at each scheduled timepoint. PK parameters will be summarized descriptively by dose level. The following will be calculated for multiple-dose lonafarnib and ritonavir: arithmetic means; coefficients of variation (%CV); standard deviations (SD); median, minimum, and maximum values; and number of observations PK parameter values will be generated for multiple-dose lonafarnib and ritonavir.

Other PK analyses for lonafarnib that will be performed include linearity and dose proportionality across the different lonafarnib dose levels. These analyses will be conducted for patients who receive titrated doses. Dose proportionality for lonafarnib will be evaluated using the relationship between each lonafarnib PK parameter ($AUC_{0-\tau}$ and C_{max}) and dose using the following power model:

$$\text{PK parameter} = \text{Exp}(\alpha)(\text{Dose})^{\beta}\,\text{Exp}(\varepsilon)$$

Where, β is a measure of the dose proportionality. Each lonafarnib PK parameter and dose will be ln-transformed before analysis therefore the power model can be expressed as:

$$\ln(\text{PK parameter}) = \alpha + \beta \ln(\text{Dose}) + \varepsilon$$

where β, the slope, measures the proportionality between dose and each lonafarnib PK parameter. If $\beta=0$, then this implies that the response is independent from the dose and when $\beta=1$, dose proportionality can be determined.

The relationship between lonafarnib dose and achieved AUC, C_{max}, and measured viral load (PD) may also be explored by plotting the PK parameters versus the dose of lonafarnib and viral log decay. The relationship between lonafarnib dose, lonafarnib exposure, and specific AEs may also be explored.

No other formal statistical analyses are planned for PK parameters.

9. REFERENCES

Bordier BB, Marion PL, Ohashi K, Kay MA, Greenberg HB, Casey JL, et al. 2002. A prenylation inhibitor prevents production of infectious hepatitis delta virus particles. J Virol 76(20):10465-72.

Bordier BB, Ohkanda J, Liu P, Lee SY, Salazar FH, Marion PL, et al. 2003. In vivo antiviral efficacy of prenylation inhibitors against hepatitis delta virus. J Clin Invest 112(3):407-14.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guideline for Industry: E3 Structure and Content of Clinical Study Reports *Federal Register.* July 17, 1996 (61 FR 37320).

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: E9 Statistical Principles for Clinical Trials. *Federal Register*. September 16, 1998 (63 FR 49583).

U.S Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Pro-arrhythmic Potential for Non-Antiarrhythmic Drugs. *Federal Register*, October 19, 2005

Karjalainen J, Viitasalo M, Manttari M, Manninen V. 1994. Relation between QT intervals and heart rates from 40 to 120 beats/min in rest electrocardiograms of men and a simple method to adjust QT interval values. *J Am Coll Cardiol* **23**:1547-1553.

10. SOFTWARE

SAS Software Version 9.2. SAS Institute Inc., Cary, NC, USA.

11. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings

Appendix 2. Programming Specifications

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings

Tables

#	Table	Analysis Set
14.1.1	Patient Disposition	SAS
14.1.2	Extent of Exposure to Study Drug	SAS
14.1.3	Adherence with Study Vaccine Regimen	SAS
14.1.4	Protocol Deviations	SAS
14.1.5	Demographics and Baseline Characteristics	SAS
14.1.6	Medical History	SAS
14.1.7	Concomitant Medications	SAS
14.2.1.1	Viral Load by Dose Level and Time post First Dose of Study Treatment	EAS
14.2.1.2	Number and Percentage of Patients with 1 and 1 Log Reductions from Baseline by Dose Level and Time post First Dose of Study Treatment	EAS
14.2.1.3	Number and Percentage of Patients with Reduction in Viral Load Below the Limit of Quantitation and the Limit of Detection by Dose Level	EAS
14.2.2.1	Lonafarnib Plasma Concentrations by Dose Level and Timepoint	PK
14.2.2.2	Ritonavir Plasma Concentrations by Dose Level and Timepoint	PK
14.2.2.3	Lonafarnib Pharmacokinetic Parameters by Dose Level	PK
14.2.2.4	Ritonavir Pharmacokinetic Parameters by Dose Level	PK
14.2.2.5	Assessment of Dose Proportionality for Lonafarnib	PK
14.2.2.6	Assessment of Dose Proportionality for Ritonavir	PK
14.3.1	Overall Summary of Adverse Events	SAS
14.3.2.1	Treatment-Emergent Adverse Events by Dose Level, SOC, and PT	SAS
14.3.2.2	Treatment-Emergent Serious Adverse Events by Dose Level, SOC, and PT	SAS
14.3.2.3	Treatment-Emergent Treatment-Related Adverse Events by Dose Level, SOC, and PT	SAS
14.3.2.4	Treatment-Emergent Treatment-Related Serious Adverse Events by Dose Level, SOC, and PT	SAS
14.3.2.5	Adverse Events Leading to Early Discontinuation of Study Treatment by Dose Level, SOC, and PT	SAS
14.3.2.6	Adverse Events Leading to Dose Reduction by Dose Level, SOC, and PT	SAS
14.3.2.7	Deaths	SAS
14.3.2.8	Treatment-Emergent Adverse Events by Dose Level, SOC, Preferred Term, and Maximum Severity	SAS
14.3.2.9	Treatment-Emergent Adverse Events by Dose Level, SOC, Preferred Term, and Maximum Relationship	SAS
14.3.2.10	Treatment-Emergent Serious Adverse Events by Dose Level, SOC, Preferred Term, and Maximum Severity	SAS
14.3.2.11	Treatment-Emergent Serious Adverse Events by Dose Level, SOC, Preferred Term, and Maximum Relationship	SAS
14.4.1	Laboratory Summary - Hematology	SAS
14.4.2	Laboratory Summary - Clinical Chemistry	SAS
14.4.3	Laboratory Summary - Coagulation	SAS
14.4.4	Laboratory Summary - Urinalysis	SAS
14.4.5	Laboratory Summary - Viral Serology	SAS
14.4.6	Laboratory Summary - Reproductive Serology (Females)	SAS
14.4.7	Laboratory Summary - Reproductive Serology (Males)	SAS
14.4.8	Laboratory Summary - Quantitative Polymerase Chain Reaction	SAS

14.4.9	Laboratory Summary - Other Tests	SAS
14.4.10	Categorical Summary of Abnormal Laboratory Results - Hematology	SAS
14.4.11	Categorical Summary of Abnormal Laboratory Results - Clinical Chemistry	SAS
14.4.12	Categorical Summary of Abnormal Laboratory Results - Coagulation	SAS
14.4.13	Categorical Summary of Abnormal Laboratory Results - Urinalysis	SAS
14.5.1	ALT Summary by CTCAE Severity Grade	SAS
14.5.2	AST Summary by CTCAE Severity Grade	SAS
14.5.3	Total Bilirubin Summary by CTCAE Severity Grade	SAS
14.5.4	Alkaline Phosphatase Summary by CTCAE Severity Grade	SAS
14.6.1	Vital Signs Summary	SAS
14.7.1	Electrocardiogram Summary	SAS
14.8.1	Viral Resistance Summary	SAS

Listings

#	**Listing**	**Analysis Set**
16.2.1.1	Study Disposition	All Patients
16.2.1.2	Reason for Screening Failure	All Patients
16.2.2	Protocol Deviations	All Patients with Protocol Deviations
16.2.3	Analysis Sets	All Patients
16.2.4.1	Demographics	All Patients
16.2.4.2	Medical History	All Patients
16.2.4.3	Concomitant Medications	All Patients
16.2.5.1	Study Drug Administration	All Patients
16.2.5.2	Plasma Concentrations	All Patients
16.2.5.3	Pharmacokinetic Parameters	All Patients
16.2.7.1	Adverse Events	All Patients
16.2.7.2	Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug	All Patients
16.2.7.3	Serious Adverse Events	All Patients
16.2.7.4	Deaths (if required)	All Patients
16.2.8.1	Laboratory Results - Hematology	All Patients
16.2.8.2	Laboratory Results - Clinical Chemistry	All Patients
16.2.8.3	Laboratory Results - Coagulation	All Patients
16.2.8.4	Laboratory Results - Urinalysis	All Patients
16.2.8.5	Laboratory Results - Viral Serology	All Patients
16.2.8.6	Laboratory Results - Reproductive Serology (Females)	All Female Patients
16.2.8.7	Laboratory Results - Reproductive Serology (Males)	All Male Patients
16.2.8.8	Laboratory Results - Quantitative Polymerase Chain Reaction	All Patients
16.2.8.9	Laboratory Results - Other Tests	All Patients
16.2.9	Vital Sign Results	All Patients
16.2.10	Electrocardiogram Results	All Patients
16.2.11	Viral Resistance Results	All Patients

Figure

#	Figure	Analysis Set
1.1	Mean Change from Baseline in Log10 HDV RNA by Dose Level and Time post First Dose of Study Treatment	EAS
1.2	Mean Log10 HDV RNA by Dose Level and Time post First Dose of Study Treatment	EAS
1.3	Mean Log10 HBV RNA by Dose Level and Time post First Dose of Study Treatment	EAS
2.1	Change from Baseline in Log10 HDV RNA by Dose Level and Time post First Dose of Study Treatment	EAS
2.2	Log10 HDV RNA by Dose Level and Time post First Dose of Study Treatment	EAS
2.3	Log10 HBV RNA by Dose Level and Time post First Dose of Study Treatment	EAS
3.1	Lonafarnib Plasma Concentrations vs Time by Dose Level	PK
3.2	Ritonavir Plasma Concentrations vs Time by Dose Level	PK

Appendix 2. Programming Specifications

Appendix 3. Schedule of Study Assessments

		Study Period										
		Screening	Treatment [a]							Follow-up		ET [b]
	Study Week	−4 to −1	0	1	2	4, 6	8, 12, 16	20	24 (EOT)	28	32, 36, 40, 44, 48, or Unscheduled Visit	—
	Study Day	−28 to −1	1 (±2)	8 (±2)	15 (±2)	29, 43 (±2)	57, 85, 113 (±5)	141 (±5)	169 (±5)	197 (±5)	225, 253, 281, 309, 337 (±5)	—
Activity	Visit Number	1	2	3	4	5, 6	7, 8, 9	10	11	12	13, 14, 15, 16, 17	—
Informed consent		X										
Inclusion/exclusion criteria		X	X [c]									
Medical history		X	X									
Comprehensive physical examination [d]		X										
Brief physical examination			X	X	X	X	X	X	X	X	X	X
Genital examination		X							X			X
Concomitant medications [e]		X	X	X	X	X	X	X	X	X	X	X
Weight [f]		X	X	X	X	X	X	X	X	X	X	X
Height		X										
BMI calculation [g]		X	X									
Ophthalmic examination [h]		X							X			
Retinal photography		X							X			
Vital signs [i]		X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [j]		X	X	X	X	X	X	X	X	X	X	X
Liver biopsy (if needed) [k]		X										
Fibroscan [l]			X						X			
Hematology [m]		X	X	X	X	X	X	X	X	X	X	X
Chemistry panel [n]		X	X	X	X	X	X	X	X	X	X	X
Prothrombin time and INR		X							X	X	X	X
Pregnancy test (serum) [o]		X										
Pregnancy test (urine) [p]			X [p]			X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]
Reproductive serology (includes FSH) [q]			X			X	X	X	X	X	X	X
HBV DNA analysis for genotype and quantitation		X	X	X	X	X	X	X	X	X	X	X

		Study Period										
		Screening	Treatment [a]							Follow-up		ET [b]
	Study Week	−4 to −1	0	1	2	4, 6	8, 12, 16	20	24 (EOT)	28	32, 36, 40, 44, 48, or Unscheduled Visit	—
	Study Day	−28 to −1	1 (±2)	8 (±2)	15 (±2)	29, 43 (±2)	57, 85, 113 (±5)	141 (±5)	169 (±5)	197 (±5)	225, 253, 281, 309, 337 (±5)	—
Activity	Visit Number	1	2	3	4	5, 6	7, 8, 9	10	11	12	13, 14, 15, 16, 17	—
HBeAg, HBeAb			X						X			
HBsAg		X	X	X	X	X	X	X	X	X	X	X
HCV serology [r]		X										
HDV serology [s]		X	X		X	X	X	X	X	X	X	X
HDV viral load (qPCR) [t]		X	X	X	X	X	X [t]	X	X	X	X	X
Large HDV Ag genotype [u]			X	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]
HIV serology		X										
Urinalysis (predose) [v]		X	X		X	X	X	X	X	X	X	X
Urine drug screen [w]		X										
PBMC collection			X		X		X [x]					
PK sampling [x]							X [x] (Collect once at either Wk 8, 12, or 16)					
Evaluate for dose escalation						X						
Dispense study drug [y]			X		X	X	X	X				
Study drug administration			X	X	X	X	X	X	X			
Study drug accountability [y]				X	X	X	X	X	X			
Provide patient diary/patient information sheet			X									
Review patient diary				X	X	X	X	X	X			X [z]
Collect patient diary									X			
Adverse events			X	X	X	X	X	X	X	X	X	X

BMI = body mass index, ECG = electrocardiogram, EOT = end of treatment, ET = early termination, HBV = hepatitis B virus, HDV = hepatitis D virus, PBMC = peripheral blood mononuclear cell, qPCR = quantitative polymerase chain reaction,

[a] Complete all assessments before the first dose of the day is administered.
[b] Early termination visit: Patients who withdraw from treatment early during the Treatment Period should return 4 weeks after their last dose to undergo these assessments; patients who withdraw early during the Follow-Up Period should undergo the assessments planned at the next scheduled study visit.
[c] Inclusion criteria: Review and confirm inclusion eligibility.
[d] Conduct comprehensive physical examination, including measurement of height and weight, calculate BMI, and assess CTP score and encephalopathy (see Appendix B of the Protocol)
[e] See Section 3.8.2 and Appendix C of the Protocol for lists of prohibited concomitant medications.
[f] Body weight of ≥45 kg. Weight should be measured with inner clothing and without shoes.
[g] BMI of ≥18 kg/m2 or ≤30 kg/m2, inclusive.
[h] Ophthalmic examination includes visual acuity examination, dilatation, and slit lamp examination. On slit lamp examination, orbit, eyelids, lashes, lacrimal gland, conjunctiva, cornea, sclera, anterior chamber, and iris are examined. On the dilated fundus examination, lens, vitreous, optic disc, and retina are examined.
[i] Blood pressure, heart rate, respiratory rate, and body temperature; blood pressure and heart rate should be measured after 5 minutes in sitting position.
[j] Serial ECG (×3) 2 to 3 minutes apart. Patients should rest in a supine position for ≥5 minutes before the ECG recording is made. ECGs must be read by the Investigator or a qualified designee, and the results recorded in the CRF. On days that PK sampling is performed, obtain sample for viral load determination and conduct ECGs before first dose of lonafarnib/ritonavir.
[k] Each patient must have documentation of a liver biopsy demonstrating evidence of chronic hepatitis. If no liver biopsy was performed or no documentation of a biopsy is available, a liver biopsy must be performed within the screening period. To avoid unnecessary biopsies for ineligible patients, it is recommended that the liver biopsy be performed after the patient successfully completes all other screening assessments.
[l] Patients must fast for at least 3 hours before the Fibroscan is performed.
[m] Hematology assessments include the following: complete blood count (hemoglobin, hematocrit, red blood cell [RBC] count, mean corpuscular volume [MCV], mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), white blood cell [WBC] count with differential, absolute lymphocytes, absolute monocytes, absolute neutrophils, absolute eosinophils, absolute basophils, and platelets, and cell morphology).
[n] Serum chemistry profile (alanine aminotransferase [ALT], albumin, alkaline phosphatase, amylase, aspartate aminotransferase [AST], bicarbonate, bilirubin (direct, indirect, total), blood urea nitrogen [BUN], calcium, chloride, cholesterol, creatine kinase [CK], creatinine, gamma-glutamyl transferase [GGT], globulin, glucose (nonfasting), lactate dehydrogenase [LDH], magnesium, phosphorus, potassium, sodium, triglycerides, total protein, and uric acid).
[o] For women of childbearing potential only.
[p] Urine pregnancy test performed before first dose is administered. For women of childbearing potential only. A positive urine pregnancy test requires immediate confirmation by serum pregnancy test.
[q] Morning levels of the following: females—luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, progesterone, anit-Müullerian hormone (AMH), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), androstenedione, testosterone, free testosterone, sex hormone binding globulin (SHBG), 17-hydroxyprogesterone (17-OHP); males—inhibin B, LH, FSH, and free and total testosterone.
[r] Patients with a positive HCV Ab at screening must have completed a curative antiviral regimen and documented to be HCV RNA negative (undetectable) at least 3 months before screening and at screening.
[s] HDV serology: positive HDV Ab test of at least 6 months duration.

[t] Serum and plasma samples for viral mutation analysis, resistance phenotyping, and analysis of drug mechanism and treatment response. On the day that PK sampling is performed, obtain sample for viral load determination and conduct ECGs before first dose of lonafarnib/ritonavir is administered.
[u] Perform postbaseline genotypic analysis of large HDV antigen only in case of viral load rebound.
[v] Urinalysis assessments include the following: specific gravity, protein, ketones, bilirubin, urobilinogen, blood, nitrite, and microscopic examination of sediment.
[w] Urine drug screen for opiates, amphetamines, barbiturates, benzodiazepenes, and cocaine.
[x] Collect PK blood samples only once at either Week 8, 12, or 16 if the patient is on a stable dose. On the day that PK sampling is performed, obtain sample for viral load determination and PBMC analysis and conduct ECGs before first dose of lonafarnib/ritonavir. Patients providing PK samples will remain in clinic at least 13 hours on the day samples are drawn. The time points for PK sampling are as follows: predose (within 30 min before the first dose of the day) and 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h postdose. Fasting is not required on the day of PK sampling.
Note: For any lonafarnib dose adjustments that occur due to patient tolerability issues (refer to Section 3.6.2 of the Protocol), PK sampling will be performed after the patient has been at a stable dose for the 2 weeks before the study visit. If the patient has not been at a stable dose for the 2 weeks before the study visit, PK sampling will be performed at a future visit, after the patient has been on a stable dose for at least 2 weeks.
[y] Before dispensing study drugs, instruct patients to bring back empty bottles or any unused study drug(s) in the original bottle at every postbaseline study visit through the end of treatment.
[z] Collect and review the patient diary if the visit occurs during the Treatment Period.