# CLINICAL STUDY PROTOCOL EIG-LNF-002

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| Protocol Title | A Phase 2, Open-Label Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic Activity of Titrating-Dose **Lo**nafarnib in Combination **w**ith **R**itonavir in Patients Chronically Infected with Hepatitis Delta Virus (LOWR-4) |
| EudraCT Number | 2015-003077-15 |
| IND Number | 110,877 |
| Test Products | Lonafarnib (also Sarasar, EBP994, SCH 66336)<br>Ritonavir (Norvir) |
| Sponsor Medical Monitor | Jon Ruckle, MD, CPI<br>Principal, Pacific Pharma Group, LLC<br>1402 S. Brookside Terrace<br>Tacoma, WA 98465-1210 |
| Clinical Program Manager | Eduardo Martins, MD, DPhil<br>SVP, Liver and Infectious Diseases<br>Eiger BioPharmaceuticals |
| Sponsor | Eiger BioPharmaceuticals<br>350 Cambridge Avenue, Suite 350<br>Palo Alto, CA 94306<br>USA |
| Version | Amendment 3 |
| Date Final | 22 December 2015 |

# SPONSOR SIGNATURE PAGE

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APPROVAL STATEMENT

The undersigned have reviewed the format and content of the above protocol and approved for issuance.

Signed:

Eduardo B. Martins, MD, DPhil
SVP, Liver and Infectious Diseases
Eiger BioPharmaceuticals

22-DECEMBER-2015

Date

# INVESTIGATOR SIGNATURE PAGE

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INVESTIGATOR AGREEMENT

By my signature below, I attest to the following:

1. I have received and reviewed the Investigator's Brochure for lonafarnib provided to me by Eiger BioPharmaceuticals or designee.
2. I have read the attached protocol and the product labeling information for ritonavir.
3. I agree to conduct the study as outlined in the protocol and in accordance with all applicable regulations and guidelines, including the Declaration of Helsinki (version as currently endorsed by the European Medicines Evaluation Agency and the United States Food and Drug Administration [FDA]); the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 21 CFR parts 50, 54, 56, and 312; EU Directive 2005/28/EC; and the ICH document "Guideline for Good Clinical Practice, E6 (R1)" dated 10 June 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements.
4. I will initiate this study only with written and dated approval from the appropriate Independent Ethics Committee (IEC). I understand that any changes in the protocol must be approved in writing by the Sponsor, the IEC, and, in certain cases the FDA or other applicable regulatory agencies, before they can be implemented, except where necessary to eliminate hazards to patients in compliance with Directive 2001/20/EC.
5. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signed:

| | |
|---|---|
| Signature | Date |
| Name | Institution |

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# PROTOCOL SYNOPSIS

## Study Title

A Phase 2, Open-Label Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic Activity of Titrating-Dose **Lo**nafarnib in Combination **w**ith **R**itonavir in Patients Chronically Infected with Hepatitis Delta Virus (LOWR-4)

## Sponsor

Eiger BioPharmaceuticals, Inc. (United States)

## Study Objectives

The primary objectives of the study are to

- 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

The secondary objectives of the study are to 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

Exploratory objectives of the study are to evaluate the effects of the dose-titration regimen of lonafarnib/ritonavir on immunologic parameters during treatment.

## Study Design

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.

The duration of the study for each patient is approximately 52 weeks (up to 4 weeks for screening, 24 weeks of treatment, 4 weeks for the primary follow-up visit, and every 4 weeks safety follow-up visits for 20 weeks thereafter). The 24-week 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.

## Study Population and Number of Patients

Approximately15 patients with chronic HDV infection with detectable HDV RNA by quantitative polymerase chain reaction (qPCR) will be enrolled. Patients who discontinue the study before Week 12 for reasons other than an adverse event (AE) may be replaced on approval of the Sponsor.

## 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/$m^2$ 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. ALT <10x ULN
7. 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).
8. 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 at least 90 days after last dose of study drug, of which at least one must be a barrier method:
        - Hormonal contraceptives for at least 3 months before the start of screening and for at least 90 days after last dose of study drug
        - Intrauterine device (IUD) in place for at least 3 months before the start of screening and until at least 90 days 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 at least 90 days after last dose of study drug.
- Surgical sterilization of the partner (vasectomy for 1 month before the start of screening and, throughout study and for at least 90 days after last dose of study drug).

9. 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 at least 90 days 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 active infection with 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. A CPT score of >6 based on screening laboratory results.
8. 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
9. History of bleeding esophageal varices, ascites, or hepatic encephalopathy.
10. 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
11. Significant renal dysfunction, defined as serum creatinine concentration ≥1.5 times the ULN or an estimated glomerular filtration rate (eGFR) < 80 mL/min at screening, based on the Cockcroft-Gault equation
12. Evidence of another form of viral hepatitis (not including HBV or HCV) or another form of liver disease (e.g., autoimmune liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, alcoholic liver disease, nonalcoholic steatohepatitis, hemochromatosis, alpha-1-anti-trypsin deficiency)
13. Evidence of hepatocellular carcinoma
14. 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)
15. In the opinion of the Investigator, an alcohol use pattern that will interfere with study conduct
16. Drug abuse within the previous 6 months before the screening visit with the exception of medically prescribed cannabinoids and their derivatives
17. 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 suicidal ideation, suicidal attempts, or psychosis requiring medication and/or hospitalization

18. Solid organ transplantation, including liver

***Criteria Related to Use of Selected Medications***

19. Use of alpha interferon, either interferon alfa-2a or interferon alfa-2b, pegylated interferon alfa-2a or pegylated interferon alfa-2b within 2 months before the start of screening
20. 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 otherwise described in protocol (i.e. Ondansetron).
    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:
        – Alpha$_1$-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***

21. 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.

## Investigational Plan

### Study Periods and Visits

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 every 4 weeks for 24 weeks. 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 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 20 weeks of the follow-up period (that is, starting 4 weeks after last dose of study treatment) if considered by the investigator to be required for patient safety.

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.

### Study Assessments

Safety assessments will be performed as shown in the Schedule of Assessment in Appendix A.

**Safety—**After consent is obtained, screening assessments will include comprehensive physical examination, medical history, height, weight, vital signs, BMI calculation, 12-lead electrocardiogram (ECG), ophthalmic examination, retinal photography, concomitant medications, assessment of the presence or absence of cirrhosis, liver biopsy (if not done previously) and Fibroscan, safety laboratory tests (including hematology, chemistry, and coagulation), HDV RNA and HBV DNA analysis, serology (HBV, HCV, HDV, and HIV),

serum pregnancy test (females of childbearing potential only), thyroid-stimulating hormone (TSH), urinalysis, and urine drug screen.

During the remainder of the study, safety will be monitored by conducting brief physical examinations; assessing vital signs, AEs, concomitant medications, and laboratory and ECG results; and reviewing urine pregnancy tests (for women of childbearing potential only). At the end of treatment, the ophthalmic examination and retinal photographs will be repeated.

Peripheral blood mononuclear cell (PBMC) samples will be collected predose and at the end of treatment for future analysis.

**Efficacy/Pharmacodynamics—**PD activity will be assessed by measurement of HDV viral load by quantitative PCR (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 500 IU/mL and can detect genotypes 1, 2, 5, 6, 7 and 8.

**Pharmacokinetics—**PK sampling will be conducted on all patients. Single blood samples will be obtained for trough drug measurements at each study visit starting at Week 2 and through Week 16

Blood samples will be obtained for full PK analysis when patients have maintained a stable dose of lonafarnib/ritonavir for at least 2 weeks between Study Weeks 8 and 16 as follows (see Section 3.6.2 for dose-titration details). A stable dose is defined as a dose of lonafarnib/ritonavir that has been taken for at least 2 weeks and that is likely to be the highest tolerable dose taken by the patient during the study, in the opinion of the investigator. Samples for full PK will be taken as follows predose (within 30 minutes before the first dose of the day) and 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h postdose. On the day that full PK is performed, the second dose of study drug may not be taken until after the 12 hour sample is obtained. On the days that PK sampling occurs, patients will remain in clinic at least 13 hours.

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.

### Investigational Product

Lonafarnib is formulated in No. 3 and No. 4, hard gelatin, white, opaque capsule shells for oral administration. Each No. 4 capsule contains 50 mg of lonafarnib. Each No. 3 capsule contains 75 mg of lonafarnib.

Ritonavir is formulated in white, film-coated, ovaloid tablets providing 100 mg of ritonavir per tablet.

### Study Drug Administration and Dosage

Patients will be dispensed lonafarnib capsules and ritonavir tablets in quantities sufficient for a 2-week study during dose titration and for a 4-week supply once a stable dose is reached. Lonafarnib and ritonavir will each be dispensed in separate, clearly marked bottles.

All study treatments (lonafarnib/ritonavir) are administered orally. All doses of lonafarnib/ritonavir should be administered with food. Patients should be instructed to take the study medication at 12-hour intervals ±2 hours. Dose regimens are outlined below; details regarding dose titration (both up-titration and down-titration) are provided in Section 3.6.

| Study Day | Dose | |
|---|---|---|
| | **Lonafarnib** | **Ritonavir** |
| Days 1–28 | 50 mg bid | 100 mg bid |
| On or after Day 29[a, b] | 75 mg bid | 100 mg bid |
| On or after Day 43[a, b] | 100 mg bid | 100 mg bid |

bid = twice daily

[a] Patients will be evaluated for tolerability at each dose level as described in Section 3.6.2.2.

[b] Only if the patient has been at the previous lonafarnib/ritonavir dosage level for at least 2 weeks.

## Concomitant Medications

### *Treatment of Gastrointestinal Symptoms*

Gastrointestinal (GI) symptoms (diarrhea, nausea, dyspepsia, vomiting, and decreased appetite) are the most common AEs reported with lonafarnib single-agent therapy. Ritonavir may be associated with diarrhea. Occurrence of diarrhea may reduce the absorption of lonafarnib, ritonavir, and other medications from the GI tract. Diarrhea may result in loss of fluids and dehydration, which can be severe, and require hospitalization for supportive care. *Patients should receive therapy (antacids, anti-emetics, or anti-diarrheals) for GI symptoms at the earliest signs in order to avoid possible severe complications.* Electrolytes should be monitored in cases of diarrhea and volume depletion. Use of symptomatic treatments for GI toxicity should be recorded in the case report form (CRF).

Ondansetron does not inhibit or induce enzymes in the CYP system. No interaction is expected with concomitant administration with lonafarnib.

Famotidine has not been associated with any clinically significant drug-drug interactions. No significant interference with CYP system has been identified; thus, no interaction is expected with concomitant administration with lonafarnib.

Omeprazole inhibits CYP2C19 and P-gp and is completely metabolized, specifically by CYP3A4 and CYP2C19. Dose adjustments are typically not required when administering omeprazole with other medications metabolized by CYP2C19; however, dose adjustments are required for omeprazole when administered to patients with hepatic impairment (refer to the Prilosec Product Label for additional information).

### *Prohibited Medications*

Use of the following medications is prohibited during the conduct of the study:

- Drugs known to prolong the PR or QT interval (unless otherwise described within protocol as allowed (i.e. Ondansetron)
- Systemic immunosuppressive therapies
- Statins, due to inhibition of mevalonate synthesis, which reduces protein prenylation.

Drugs highly dependent on CYP3A4 for clearance are contraindicated with ritonavir (see list under Exclusion Criterion 19e above). Appendix C lists all drugs contraindicated with the use of ritonavir and also lists drugs that have established or other potentially significant drug interactions when used in combination with ritonavir.

***Medications To Be Used with Caution***

**Due to Possible Interaction with Lonafarnib—**An *in vitro* CYP inhibition study conducted with lonafarnib suggests that lonafarnib may be a mechanism-based inhibitor of CYP3A4 and CYP2C19 enzymes. Any medications that are *primarily* metabolized by CYP3A4 should be avoided. Any medicines that are *primarily* metabolized by CYP2C19 should be used with caution. If at all possible, alternative therapeutic agents that are not CYP3A4 substrates, inducers, or inhibitors or are less potent CYP3A4 substrates, inducers, or inhibitors should be considered. Concomitant administration of medications that are primarily metabolized by CYP3A4 or CYP2C19 may result in large increases in serum levels of these medications that may precipitate unwanted toxicities.

Entecavir, tenofovir, lamivudine, adefovir, and telbivudine do not substantially inhibit or induce the enzymes in the CYP system. Therefore, an interaction with lonafarnib is not anticipated due to CYP enzymes; however, there is a potential for interaction of lonafarnib with tenofovir due to inhibition of P-gp inhibition, breast cancer resistance protein (BCRP), and organic anion-transporting polypeptide (OATP) 1B1 (see below).

*In vitro* tests suggest that lonafarnib may be an inhibitor of efflux pumps p-glycoprotein (P-gp) and BCRP and the liver uptake transporter OATP1B1. Therefore, concomitant medications that are substrates of P-gp, BCRP, and/or OATP1B1 should be used with caution. Taking medications that are substrates of P-gp, BCRP, and/or OATP1B1 may result in unwanted increases in serum levels of these medications, especially medications with a narrow therapeutic index (eg, digoxin, loperamide, quinidine, talinolol, and vinblastine).

Because tenofovir is a substrate of P-gp, BCRP, and OATP1B1, concomitant administration of lonafarnib and tenofovir may result in increased levels of tenofovir. Therefore, tenofovir should be used with caution when co-administered with lonafarnib.

A source that should be used to check for potential drug-drug interactions is at the following website: http://www.Drug-Interactions.com. The website provides a list of drugs known to be metabolized by cytochrome P450 enzymes including CYP3A4. Although this list is periodically updated, it is not an exhaustive list; therefore, using more than one source is recommended when checking for potential interactions. Another source that can be used is by searching the drug name and reviewing the product label (Sections 7 and Section 12) at this site: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

**Due to Possible Interaction with Ritonavir—**Ritonavir inhibits CYP3A4, P-gp, MRP1, OATP-C, and BCRP. Ritonavir induces CYP1A2, CYP2C8, CYP2C9, CYP2C19, and MRP1. Ritonavir is a substrate of CYP3A4 and CYP2D6. For contraindicated drugs with ritonavir, refer to the list under Exclusion Criterion 19e above and Appendix C).

While patients are receiving ritonavir, the Investigator should review all other medications taken by patients and monitor patients for adverse effects due to metabolism interactions of ritonavir with concomitant medications. Initiating treatment with ritonavir in patients receiving medications primarily metabolized by CYP3A or initiating medications metabolized by CYP3A in patients already maintained on ritonavir may result in increased plasma concentrations of these medications. Higher plasma concentrations of concomitant medications can precipitate adverse effects that can potentially lead to severe, life-threatening, or fatal events. The potential

for drug-drug interactions must be considered before initiating therapy or during therapy with ritonavir.

### Randomization

Patients will not be randomized in this open-label, single-arm study.

## Statistical Methods

The study is designed to evaluate the safety and tolerability of the dose-titration regimen of lonafarnib/ritonavir. As such, the sample size is 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.

The primary PD/efficacy analysis will compare the change from Baseline (Day 1) to Week 24 (End of Treatment Visit) in HDV viral load.

Analysis populations will consist of the following:

- Safety population—all patients who receive at least one dose of study drug.
- Primary PD/efficacy population—patients who receive study drug throughout the entire 24-week Treatment Period and for whom viral load data are available from baseline (Week 0) and end-of-treatment (Week 24) study visits.
- PK population—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.

### Analysis Plan

**Baseline Values—**Demographics and baseline characteristics of patients will be summarized.

**Safety—**All reported AEs will be mapped to standard coding terms (Medical Dictionary for Regulatory Activities [MedDRA]) and grouped by system organ class and preferred terms. 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. TEAEs will be summarized by seriousness, severity, and relationship to study drug. If an AE is reported more than once during the study period, the greatest severity and worst-case attribution will be presented in tables. AEs will also be listed for individual patients, along with information regarding onset, duration, severity, and relationship to study drug. AEs that lead to withdrawal from the study will be listed and summarized. Summary tables and listings of serious AEs will also be generated.

Descriptive statistics will be used to summarize clinical laboratory data at each time point and the change from baseline in postbaseline measurements. The number of patients above, below, and within normal range will be assessed. In addition, ALT, AST, total bilirubin, and AP will be summarized by CTCAE grade. Values for vital signs, weight, and ECGs will be summarized and listed for each patient.

**Pharmacodynamics/Efficacy—**PD data will be presented by dose level in summary tabulations and listings that will display viral load data at each time point collected by patient. These data will also be presented graphically. Mean and median levels and change from baseline of the viral load will be calculated at each time point. The number of patients with 1 and 1 log reductions from baseline will be summarized at each time point. The number of patients with reduction in viral load below the limit of quantitation and the limit of detection will be summarized. Missing data will not be imputed.

**Pharmacokinetics—**The following PK parameters will be derived from plasma concentrations for lonafarnib and ritonavir:

| | |
|---|---|
| $C_{max}$ | 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/ $AUC_{0-\infty}$<br>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 $0.693/K_{el}$. |

A noncompartmental method will be used to derive the PK parameters for lonafarnib and ritonavir. Additional PK parameters using noncompartmental methods may also be used if data permit. Plasma concentrations of lonafarnib and ritonavir and the generated PK parameters will be summarized descriptively by dose level and by patient. 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 may be performed include linearity and dose proportionality across the different lonafarnib dose levels. These analyses will be conducted for patients who receive titrated doses. 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 formal statistical analyses are planned for PK parameters.

### Viral Resistance Analysis

Screening visit and baseline serum samples will be collected from all patients for HDV genotypic analysis to determine HDV subtypes (1–8) and to understand natural genetic polymorphisms of HDV.

For resistance surveillance, genotypic analysis of large HDV antigen 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. In vitro phenotypic analysis may be explored as necessary.

# ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1 provides the definitions of the abbreviations and acronyms used in this protocol.

**Table 1 List of Abbreviations and Acronyms**

| Abbreviation/Acronym | Definition |
|---|---|
| 17-OHP | 17-hydroxyprogesterone |
| Ab | antibody |
| AE | adverse event |
| Ag | antigen |
| ALT | alanine aminotransferase |
| AMH | anti-Müllerian hormone |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| AUC | area under the time-concentration curve |
| $AUC_{0-t}$ | Area under the plasma concentration versus time curve during the dosing interval calculated by the linear trapezoidal rule |
| BCRP | breast cancer resistance protein |
| bid | twice each day |
| BMI | body mass index |
| BUN | blood urea nitrogen |
| $C_{avg}$ | average plasma drug concentration during multiple-dose administration |
| CFR | Code of Federal Regulations |
| CK | creatine kinase |
| CL/F | apparent total body clearance |
| $C_{max}$ | peak plasma concentration as observed |
| $C_{min}$ | minimum concentration |
| CRF | case report form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTP | Child-Turcotte-Pugh |
| CYP | cytochrome P450 |
| DHEA | dehydroepiandrosterone |
| DHEAS | dehydroepiandrosterone sulfate |
| ECG | electrocardiogram |
| Eiger | Eiger BioPharmaceuticals |
| FDA | Food and Drug Administration |
| FSH | follicle-stimulating hormone |
| FT | farnesyltransferase |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GI | gastrointestinal |
| HBV | hepatitis B virus |
| HBeAb | hepatitis B e antibody |
| HBsAg | hepatitis B surface antigen |
| HBeAg | hepatitis B e antigen |
| HCV | hepatitis C virus |
| HDV | hepatitis D virus |
| HIV | human immunodeficiency virus |
| ICF | informed consent form |

| Abbreviation/Acronym | Definition |
|---|---|
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethic Committee |
| INR | international normalized ratio |
| IU | international unit |
| IUD | intrauterine device |
| $K_{el}$ | apparent first-order terminal elimination constant |
| kPa | kilopascal |
| LDH | lactate dehydrogenase |
| LOWR | **Lo**nafarnib **W**ith and Without **R**itonavir |
| LT | luteinizing hormone |
| MHH | Medizinische Hochschule Hannover (Hannover Medical School) |
| ms | millisecond |
| NIDDK | United States National Institute of Diabetes and Digestive and Kidney Diseases |
| OATP | organic anion-transporting polypeptide |
| PBMC | peripheral blood mononuclear cell |
| PCR | polymerase chain reaction |
| PD | pharmacodynamics |
| PEG-IFN-α2a | pegylated interferon alfa 2a |
| P-gp | P-glycoprotein |
| PK | pharmacokinetics |
| qd | once each day |
| qPCR | quantitative polymerase chain reaction |
| QTc | corrected QT interval |
| QTcF | QT interval corrected using Fridericia formula |
| qw | once each week |
| SAE | serious adverse event |
| $T_{max}$ | time of the peak plasma concentration |
| $T_{1/2}$ | apparent first-order terminal elimination half-life |
| SHBG | sex hormone binding globulin |
| SHIM | sexual health interest questionnaire |
| tid | three times each day |
| TSH | thyroid-stimulating hormone |
| ULN | upper limit of normal |
| $V_{area/F}$ | apparent total volume of distribution |
| WBC | white blood cell |

# 1 INTRODUCTION AND BACKGROUND

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 et al, 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 et al, 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 combine 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 Nonclinical Data

An extensive nonclinical program has been conducted using lonafarnib; key results are summarized below and additional details are provided in the Investigator's Brochure.

**Pharmacology—**Lonafarnib is a potent and selective inhibitor of human FT. Farnesylation of large HDV antigen by the human FT is required for the association of the large HDV antigens with hepatitis B surface antigen to form an infectious HDV virion (Glenn 1992, Otto 1996). Lonafarnib exerts anti-HDV activity by blocking the formation and release of HDV virions.

Blocking the release of HDV virions by lonafarnib will trap large HDV antigens within HDV infected hepatocytes. Since large HDV antigen is a potent trans-dominant inhibitor of HDV genome replication, accumulation of large HDV antigens within hepatocytes may further suppress HDV genome replication.

Using a standard *in vitro* model of HDV virus-like particle release, Eiger demonstrated that lonafarnib is highly potent in inhibiting cellular prenyl transferase. Lonafarnib has half-maximal effective concentration ($EC_{50}$) of approximately 35 pM (2.4 ng/mL), which is 400- to 1000-fold lower than the expected $C_{max}$ (maximum observed plasma concentration) and trough levels for 100 and 200 mg of lonafarnib given by mouth twice a day (bid) with food.

Lonafarnib was tested in a standard model of HBV activity to assess its effect on the anti-HBV effects of tenofovir, adefovir, entecavir, lamivudine, and telbivudine. Lonafarnib has no direct anti-HBV activity. Lonafarnib has no positive or negative effects on the activity of the approved anti-HBV therapies. Lonafarnib appears to be metabolized primarily by CYP450 enzymes. None of the standard anti-HBV therapies are metabolized by CYP450 enzymes and all are excreted through the urine making it unlikely that there will be metabolic interference due to CYP450 enzymes between lonafarnib and any of these drugs when given in vivo.

However, because tenofovir is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion-transporter polypeptide (OATP) 1B1, concomitant administration of lonafarnib and tenofovir may result in increased levels of tenofovir. Therefore, tenofovir should be used with caution.

**Toxicity—**The *in vivo* toxicology of lonafarnib has been evaluated in acute studies in mice and rats, and in repeat-dose studies for up to 6 months in rats and for 1 year in monkeys. Lonafarnib caused mixed induction/inhibition of hepatic drug-metabolizing enzymes in rats and monkeys when administered once daily for 3 months in toxicology studies.

Lonafarnib was well tolerated and had no major end-organ toxicities at repeated doses of 15 mg/kg up to 6 months in rats and 10 mg/kg up to 1 year in monkeys; these doses resulted in systemic exposures that are less than those attained at a clinical dose of 200 mg twice per day (bid). At higher doses, representing animal to human exposure multiples less than or similar to that seen in humans at 200 mg bid, the key toxicological findings were bone marrow suppression and testicular toxicity in rats and monkeys, lymphoid and kidney changes in rats, and diarrhea and electroretinographic changes in monkeys.

Reproductive toxicity has been evaluated in fertility studies in rats, in embryo-fetal development studies in rats and rabbits, and in a peri- and postnatal development study in rats. Studies in pregnant and lactating rats administered a single oral dose of 30 mg/kg showed that lonafarnib crosses the placenta and is secreted into milk.

The no-effect doses for reproductive effects on fertility (10 mg/kg in rats) and embryo-fetal development (15 mg/kg in rats and <10 mg/kg in rabbits) result in systemic exposures less than those attained at a clinical dose of 200 mg BID. The no-effect dose for peri- and postnatal development in rats was ≥20 mg/kg, the highest dose evaluated. Lonafarnib was not mutagenic or clastogenic.

## 1.2 Clinical Data

Lonafarnib has been investigated, alone and in combination with pegylated interferon or ritonavir, as a treatment for patients with chronic HDV infections in the following clinical studies:

- Protocol 12-DK-0046, conducted under IND 113,137 in the United States National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) was a first-in-human, proof-of-principle, two-cohort, randomized, double-blind, placebo-controlled trial testing lonafarnib 100 or 200 mg bid administered orally for 28 days to patients with chronic HDV infections (Koh et al, 2015). Eight patients were enrolled in each arm with 6 patients receiving lonafarnib and 2 patients receiving placebo. This study is completed. All patients underwent 72-hour viral kinetic evaluations at the start of therapy and blood HDV RNA was measured at each study visit. A total of 14 patients were treated for 4 weeks.
- Protocol EIG-300, a Phase 2 study performed at a single site in Ankara, Turkey, under the auspices of Turkish Medicines and Medical Devices Agency, consists of two parts, LOWR -1 and LOWR-2.
  - LOWR-1: This study is investigating the safety and clinical activity of lonafarnib alone and in early combinations with ritonavir and pegylated interferon. Monotherapy lonafarnib treatments include 100 mg 3 times daily [tid] for 4 weeks, 200 mg bid for 12 weeks, and 300 mg bid for 12 week). Combination treatments include lonafarnib/ritonavir combinations of 100 mg bid/100 mg once daily (qd) for 8 weeks and lonafarnib/pegylated interferon (PEG-IFN) combinations of 100 mg bid/180 mcg once a week (qw) for 8 weeks, 200 mg bid/180 mcg qw for 8 weeks, and 300 mg bid/180 mcg qw for 8 weeks. A total of 21 patients have been treated.
  - LOWR-2: This study is investigating the safety and clinical activity of lonafarnib in combination with ritonavir. This study is currently ongoing. As of 30 June 2015, a total of 22 patients have been treated.

As of 30 June 2015, a total of 57 patients with chronic HDV infection have been treated with lonafarnib, with or without ritonavir, for periods of up to 12 weeks.

### 1.2.1 Clinical Pharmacokinetics

The pharmacokinetics of lonafarnib are dose-dependent, and plasma concentrations in patients and healthy volunteers increase in a greater-than-dose-proportional manner (refer to the Investigator's Brochure for additional information). Lonafarnib was absorbed slowly after twice daily oral administration with food, with the mean $C_{max}$ (maximum observed plasma concentration) occurring between 2.5 and 8 hours postdose. In a single-dose setting, lonafarnib absorption was decreased when administered under fed conditions. The relative oral bioavailability of lonafarnib under the fed as compared to the fasted condition was 48% and 77% based on $C_{max}$ and $AUC_{(tf)}$ (area under the concentration-time curve from 0 to time of the final quantifiable sample), respectively. However, this food-effect was not observed following multiple-dose lonafarnib administration. Based on these findings, lonafarnib should be administered with food for both safety/tolerability and exposure reasons.

Multiple co-administered doses of the P450 inhibitor ketoconazole resulted in a 5-fold increase in lonafarnib exposures. Conversely, lonafarnib had no apparent effects on the PK of other co-administered agents (paclitaxel, carboplatin, docetaxel, gemcitabine), and these agents had no apparent effect on the PK of lonafarnib. Lonafarnib is primarily metabolized by CYP3A4, with negligible renal elimination (<1%).

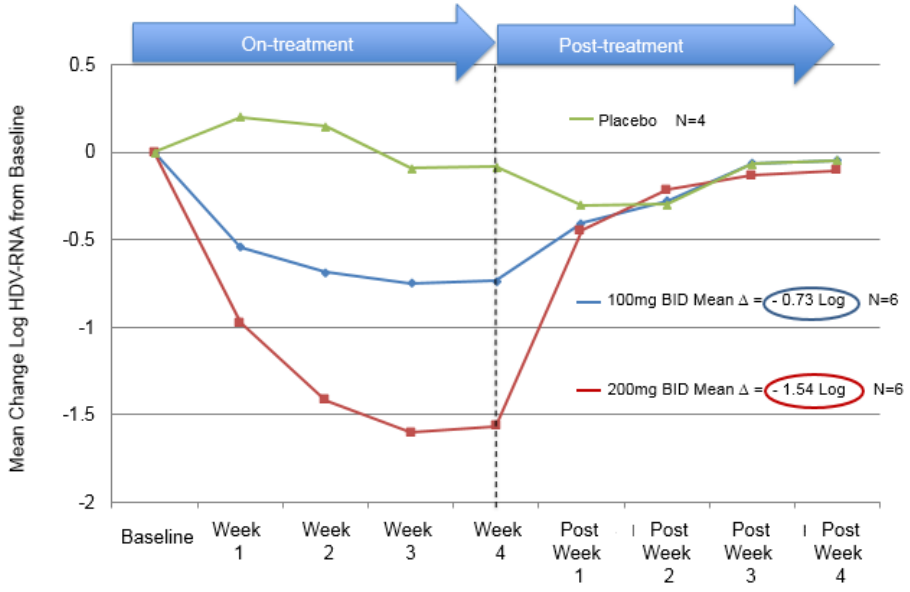
### 1.2.2 Clinical Efficacy/Pharmacodynamics

#### 1.2.2.1 Study 12-DK-0016

Study 12-DK-0046 was a Phase 2a study performed by NIDDK (Koh et al, 2015). The study enrolled a total of 14 patients, 6 treated with lonafarnib at 100 mg BID and 2 treated with placebo (Group 1) and 6 treated at 200 mg BID and 2 on placebo (Group 2) for 28 days. The 2 placebo patients from Group 1 received lonafarnib 200 mg BID in Group 2. All patients were infected with HDV genotype 1.

From Baseline to Day 28, the mean changes in serum HDV RNA were −0.73,−1.54, and −0.13 $\log_{10}$ for patients who received lonafarnib 100 mg BID, lonafarnib 200 mg BID, and placebo, respectively (Figure 1).

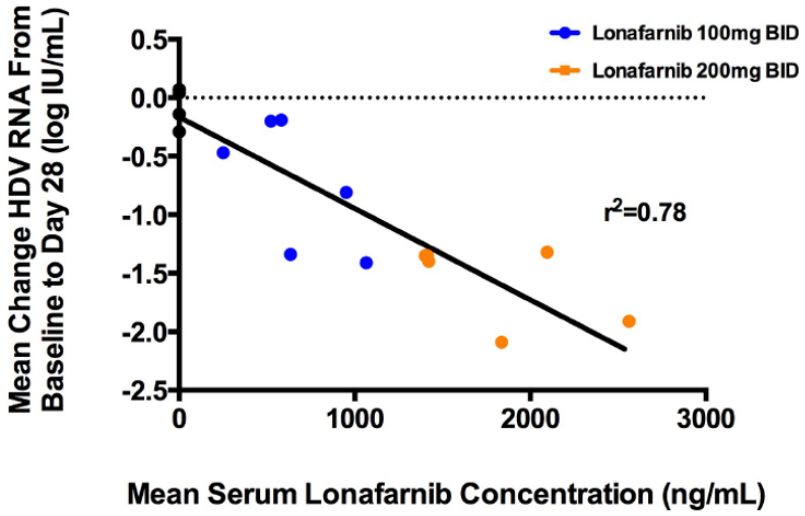
**Figure 1 Study 12-DK-0046: Mean Change in HDV RNA Levels from Baseline During and After 4 Weeks of Treatment with Lonafarnib**




Half of patients in the 200 mg bid group achieved a decrease from baseline-to-nadir of greater than −2 log IU/mL. As shown in Figure 2, lonafarnib serum concentrations correlated with HDV RNA change ($R^2 = 0.78$, $p < 0.0001$).

After lonafarnib treatment was stopped, viral loads increased back to baseline by 4 weeks posttreatment, suggesting that longer treatment with lonafarnib may be required. Treatment with lonafarnib for 28 days significantly reduced viral loads in patients chronically infected with HDV, and these effects appear dose-dependent.

**Figure 2 Study 12-DK-0016: Relationship Between Lonafarnib Serum Concentration and Change in Log HDV RNA Levels**




The development of potential HDV resistance to lonafarnib was monitored during treatment by sequencing the large HDV antigen coding region at baseline, viral nadir, and at the 24-week follow-up. All patients were found to be infected with HDV genotype 1. The most likely place to find resistance-conferring mutations would be in the CXXX-box amino acid motif, that is, codons 211–214, which is the substrate for prenyltransferases. No evidence of mutations was found in that region or anywhere in the large delta antigen coding region. Thus, resistance was not observed during 4 weeks treatment with lonafarnib alone and after 24 weeks of follow-up. This observation is consistent with the mechanism of action of lonafarnib as inhibiting a host enzyme.

HBV DNA was measured at the same time as HDV RNA. Evidence of virus-virus interactions was observed: a decrease in HDV RNA while on lonafarnib treatment was associated with an increase in HBV DNA, and an increase in HDV RNA after treatment cessation was associated with a decrease in HBV DNA levels. However, the changes in HBV for a single patient were generally 1 log or less. HBV levels were generally unchanged in the patients who were on anti-HBV treatment during the study.

#### 1.2.2.2 Study EIG-300/LOWR-1

In the Phase 2 EIG-300/LOWR-1/EIG-300 study, HDV viral load was evaluated by measuring HDV RNA by real-time qPCR in all patients at baseline and periodically thereafter. Interim results from 15 patients in Study LOWR-1/EIG-300 who received lonafarnib alone or with ritonavir boosting or in combination with PEG IFN indicated that all treatments led to decreased viral loads.

Combination therapy of lonafarnib 100 mg bid with ritonavir or pegylated interferon alfa 2a (PEG-IFN-α2a) demonstrated numerically improved anti-HDV activity compared with lonafarnib 100 mg tid monotherapy at Week 4 (Figure 3, Yurdaydin 2015). Serum HDV RNA declined further from Week 4 to Week 8 in patients on lonafarnib in combination with ritonavir

or PEG-IFN-α2a. The mean change in HDV RNA in either combination group was approximately −3 log copies/mL from baseline to Week 8 (Figure 4).

**Figure 3 Study EIG-300/LOWR-1: Change in HDV RNA in Patients at Week 4**

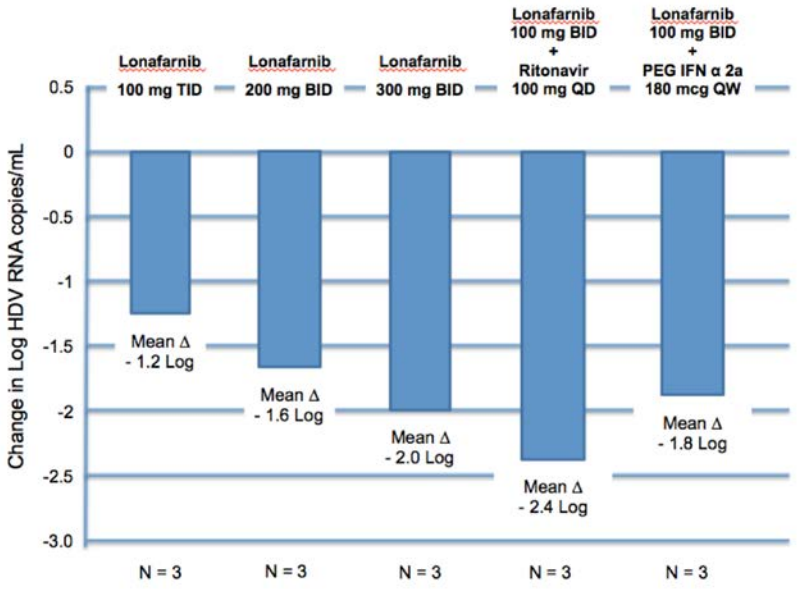
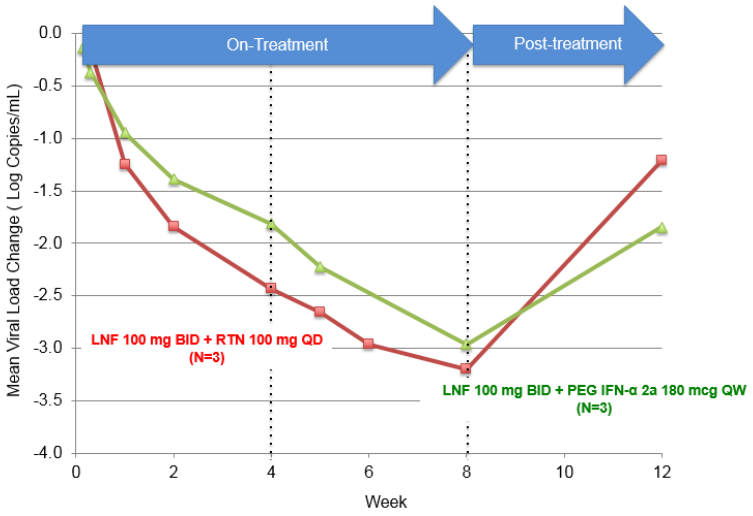



**Figure 4 Study EIG-300/LOWR-1: Change in HDV RNA in Patients Treated with Lonafarnib and Ritonavir or with Lonafarnib and PEG-IFN-α2a for 8 Weeks**




Alanine aminotransferase (ALT) levels also decreased in patients who received lonafarnib 100 mg bid with ritonavir or PEG-IFN-α2a.

Similar to the observations in Study 12-NK-0046, the mean serum HBV DNA level of all patients remained stable and no mutation(s) in the large HDV antigen was detected in patients in the 200 mg and 300 mg bid groups during lonafarnib treatment in EIG-300/LOWR-1.

### 1.2.3 Clinical Safety

The dose-limiting, significant AEs due to lonafarnib treatment in all patients were primarily GI (diarrhea, nausea, vomiting, dyspepsia, and anorexia), as has been reported with many other FT inhibitors, with less common and reversible neurological, renal, hematologic, and liver effects. Loss of fluids and dehydration due to severe diarrhea can lead to hospitalization; early intervention has been effective for the diarrhea.

#### 1.2.3.1 Study 12-DK-0016

The most common systemic AEs seen in patients receiving lonafarnib monotherapy in Study 12-DK-0016 are summarized in Table 2, and included: diarrhea, nausea, dyspepsia, weight loss, decreased appetite, and vomiting (Koh et al, 2015). The frequencies of gastrointestinal AEs (nausea, diarrhea, decreased appetite, abdominal bloating, vomiting and weight loss) were dose-dependent.

**Table 2 Most Frequent Adverse Events in Study 12-DK-0016**

| Adverse Event | Placebo (N = 4) | Group 1 LFN 100 mg bid N = 6 | Group 2 LFN 200 mg bid N = 6 |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| Discontinuation of therapy due to Adverse Event | 0 | 0 | 0 |
| Serious Adverse Event | 0 | 0 | 0 |
| Common Adverse Events | | | |
| Nausea | 1 (25%) | 2 (33%) | 6 (100%) |
| Diarrhea | 0 | 3 (50%) | 6 (100%) |
| Decreased appetite | 0 | 1 (17%) | 5 (83%) |
| Abdominal bloating/dyspepsia | 1 (25%) | 1 (17%) | 6 (100%) |
| Vomiting | 0 | 0 | 3 (50%) |
| Weight loss >2 kg | 0 | 1 (17%) | 6 (100%) |
| Headache | 1 (25%) | 1 (17%) | 1 (17%) |
| Testicular pain | 0 | 1 (17%) | 0 |
| Lightheadedness | 1 (25%) | 0 | 0 |
| Fatigue | 0 | 1 (17%) | 1 (17%) |

From (Koh et al, 2015).

The side effects of dyspepsia, nausea, and diarrhea were successfully treated with antacids, anti-emetics, and anti-diarrheals on an as-needed basis. All AEs resolved rapidly after stopping therapy. Lonafarnib 100 mg or 200 mg bid was reasonably well tolerated, and no symptoms impaired daily functioning in the study.

Liver function tests were performed weekly during the 28 days of treatment and for 2 weeks after cessation of treatment, and every 4 weeks during the remainder of the follow-up period. The 28-day treatment with either 100 mg or 200 mg lonafarnib bid appeared to have no adverse effect on liver enzymes and lowered the ALT and aspartate aminotransferase (AST) levels from baseline.

Full ophthalmologic and comprehensive reproductive physiology examinations were performed for patients in Study 12-DK-0046. No significant changes were observed in these patients.

There were no serious AEs (SAEs) in this study. No patients discontinued study drug due to AEs.

#### 1.2.3.2 Study EIG-300/LOWR-1

Study EIG-300/LOWR-1 tested 100 mg TID, 200 mg BID, and 300 mg BID of lonafarnib alone. The study also evaluated lonafarnib 100 mg BID in combination with either 180 mcg Peg-IFN-α2a QW or ritonavir 100 mg QD. The most common AEs were diarrhea, nausea, vomiting, and weight loss. There were no SAEs.

## 1.3 Potential Risks and Benefits to Human Patients in This Study

Collectively, the data from studies in chronic HDV patients treated with lonafarnib as a monotherapy or in combination with ritonavir have demonstrated significant reductions in HDV viral loads. While these proof-of-principle and early-stage studies are limited in size and scope, they provide promising evidence that lonafarnib, especially in combination with ritonavir, may offer clinically meaningful benefit to patients with chronic HDV infections.

The most common, significant AEs due to lonafarnib treatment in all patients were primarily vomiting, diarrhea, and anorexia, which were treated as-needed with anti-emetics, antacids, and anti-diarrhea medications. Loss of fluids and dehydration due to severe diarrhea can lead to hospitalization; early intervention has been effective for treatment of diarrhea.

Preliminary data indicate that to date two patients (one from the lonafarnib 200 bid group and one from the 300 bid group) had posttreatment ALT flares. It is possible that a host-induced flare due to “awakening” of hose immune function and/or viral flare may occur during or after antiviral treatment. For this reason, patients with decompensated cirrhosis are excluded, and all patients will be closely monitored in order to assess the risks of these outcomes during the 6-month Follow-up Period.

A risk associated with the use of direct-acting antiviral agents is the development of resistance by the virus. However, because prenylation is a host function not coded for by the HDV genome, preliminary data suggest that the risk of resistance development may be low for lonafarnib. As proof of absence of viral resistance with prenylation inhibitors in HDV, population-based sequencing of the large delta antigen coding region at baseline, end of therapy, and 24 weeks after end of therapy was performed in Study 12-DK-0046. Analysis at these time points revealed no changes in viral sequences, thus confirming the absence of viral resistance.

Ritonavir is an orally bio-available protease inhibitor that has been used in low doses as a PK booster (coadministration of 100 mg ritonavir) of second protease inhibitors or other retroviral agents. In this study, ritonavir will be used as a pharmacokinetic booster of lonafarnib. The most frequently reported adverse drug reactions among patients receiving ritonavir alone or in combination with other antiretroviral drugs were GI (including diarrhea, nausea, vomiting, abdominal pain), neurological disturbances (including paresthesia and oral paresthesia), rash, and fatigue/asthenia nausea, anorexia, diarrhea, vomiting, weight loss, and fatigue (Prescribing Information for Norvir® [ritonavir] Tablets, 2015; Summary of Product Characteristics for Norvir® [ritonavir] tablets, 2014).

While dose-limiting toxicities of lonafarnib are GI AEs, available data suggest that lower doses of lonafarnib as planned in this study administered in combination with low-dose ritonavir (100 mg bid) will be tolerable. Given that the toxicities appear to be dose-related and respond to dose reduction and/or discontinuation, we anticipate that AEs can be readily managed in this study with frequent study visits and monitoring. Treatment with the initial dose level for a minimum of 4 weeks, escalation in a step-wise fashion, dosing with food, prompt symptomatic management of intolerance (eg, GI effects), and monitoring of liver function tests during treatment will be implemented to ensure tolerability and minimize risk to the patient.

## 1.4 Rationale for the Study

Chronic HDV infections represent a serious unmet medical need. No therapies are currently approved for the treatment of chronic HDV infection. Interferon alpha has been shown to be effective in decreasing viral load in approximately 25% of patients after 48–96 weeks of treatment, but requires prolonged therapy and is associated with significant rate of relapse after treatment discontinuation.

Lonafarnib monotherapy has been shown to decrease viral load in patients with chronic HDV infection in a dose-dependent manner. Given the wide intersubject variability in exposure when administered orally as well as the GI toxicities that may be dose-limiting, co-administration of lonafarnib with ritonavir, as a PK enhancer, may allow lower lonafarnib doses to be administered to the gut and minimize GI adverse effects while resulting in higher systemic levels.

Currently, it is not known whether initiation of lonafarnib at a lower dose may allow greater tolerability over time, and whether the dose of lonafarnib may be titrated upward to allow a higher dose to be administered. The previous observation that lonafarnib treatment was not associated with viral resistance suggests that dose titration is not likely to be associated with development of viral resistance.

This study will evaluate the effects of dose titration on the tolerability of lonafarnib administered in combination with ritonavir and will provide corresponding data of the effects on viral load. Taken together, these evaluations will provide insights regarding the most effective and tolerable dose combination for use in future, confirmatory studies.

The results of this study will help determine the optimal regimen(s) of lonafarnib and ritonavir that may be further studied as treatment for eradication of chronic HDV infection.

# 2 STUDY OBJECTIVES

The primary objectives of the study are to

- 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 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 HDV viral load) of the dose-titration regimen of lonafarnib in combination with ritonavir over the 24-week Treatment Period

The secondary objectives of the study are to evaluate the effect the dose-titration regimen of lonafarnib/ritonavir on the following:

- Pharmacokinetics
- Change in ALT levels
- Change in HBV DNA levels

Exploratory objectives of the study are to evaluate the effects of the dose-titration regimen of lonafarnib/ritonavir on immunologic parameters during treatment.

# 3 INVESTIGATIONAL PLAN

## 3.1 Overall Study Design

This is a Phase 2, open-label, single-arm study that will evaluate the dose-titration regimen of lonafarnib/ritonavir starting at 50 mg bid/100 mg bid and escalated to 75 mg bid/100 mg bid and then to 100 mg bid/100 mg bid as tolerated in patients chronically infected with HDV. 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 the patients have received a particular dose. The pharmacokinetic (PD) activity (change in HDV viral load) of the lonafarnib/ritonavir dose-titration regimen over the 24-week Treatment Period will be evaluated. PK assessments will be performed as will evaluations of ALT and the change in HBV DNA levels.

Approximately 15 evaluable patients with chronic HDV infection with detectable HDV RNA by quantitative polymerase chain reaction (qPCR) will be enrolled. The duration of the study for each patient is approximately 52 weeks and divided into three periods: Screening (up to 4 weeks), Treatment (24 weeks), and Follow-up (4 weeks after last dose of study drugs for the primary follow-up visit, and every 4 weeks safety follow-up visits for 20 weeks thereafter). The 24-week Follow-up Period 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.

All study treatments (lonafarnib/ritonavir) will be administered orally. All doses of lonafarnib/ritonavir should be taken with food. Patients will be instructed to take the study medication at 12-hour intervals ±2 hours.

PK sampling will be conducted on all patients. Single blood samples will be obtained for trough drug measurements at each study visit starting at Week 2 and through Week 16.

Blood samples will be obtained for full PK analysis when patients have maintained a stable dose of lonafarnib/ritonavir for at least 2 weeks between Study Weeks 8 and 16 as follows (see Section 3.6.2 for dose-titration details). A stable dose is defined as a dose of lonafarnib/ritonavir that has been taken for at least 2 weeks and that is likely to be the highest tolerable dose taken by the patient during the study. Samples for full PK will be taken as follows predose (within 30 minutes before the first dose of the day) and 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h postdose. The second daily dose of study drug may not be taken until after the 12 hour sample is obtained. On the days that PK sampling occurs, patients will remain in clinic at least 13 hours.

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.

## 3.2 Rationale for Study Design

This will be conducted as an open-label study. It is not known whether lonafarnib/ritonavir titration will increase tolerability and allow greater systemic exposure that can result in a decrease in viral load. The open-label design was chosen to allow flexibility in dosing to determine parameters for dose titration for further investigation in a randomized, blinded, parallel-group study of lonafarnib/ritonavir. It is anticipated that individual tolerability to

lonafarnib may vary and that some, but not all, patients may tolerate escalation to higher doses. Safety and tolerability will be assessed by the Investigator before each escalation of the lonafarnib dose. The dose of lonafarnib may be decreased or increased as outlined in Section 3.6.2. The protocol allows for decrease in the dose of lonafarnib at any time for reasons of safety and tolerability. Strict guidelines are provided for dose escalation, including minimum timeframes at the previous dose, assessment of AEs, and monitoring.

The primary efficacy evaluation is an objective endpoint, HDV viral load, which will be evaluated during the study treatment. It is well accepted that HDV viral load does not change appreciably in the absence of effective therapy.

The duration of treatment (24 weeks) is based on results of previous clinical studies, which have tested various doses of lonafarnib with and without ritonavir for up to 3 months. In these studies, treatment with lonafarnib with and without ritonavir was associated with decreases in viral load. Longer treatment may allow further decreases in viral load and eradication of HDV RNA in some patients. The 24-week follow-up period is chosen in order to assess the virologic course after 24 weeks of treatment. Based on other studies of antiviral agents, including interferon alpha for chronic HDV infection, it is possible that eradication of HDV RNA during or shortly after treatment may be associated with relapse. It is also possible that a host-induced flare due to "awakening" of host immune function and/or viral flare may occur during or after antiviral treatment; patients will be closely monitored and the risks of these outcomes will be assessed during the 24-week Follow-up Period.

Blood sample collection will be performed to assess lonafarnib exposures at steady state, that is, once the patient is on a stable dose for at least 2 weeks. This approach will allow an exposure-response assessment (eg, the relationship of lonafarnib exposure vs. decrease in viral load).

This clinical trial will be conducted as a single-site study at a facility (Medizinische Hochschule Hannover [MHH, Hannover Medical School]) with expert personnel and full capabilities for identification, assessment, monitoring, and follow-up of patients with chronic HDV infection.

## 3.3 Rationale for Use of Lonafarnib in Combination with Ritonavir in HDV

Experience from Study EIG-300 (LOWR-1 and 2) suggests that administration of lonafarnib with ritonavir may allow higher lonafarnib systemic exposures while limiting the GI exposure to the drug, and thereby minimize adverse effects.

Lonafarnib monotherapy has been shown to decrease viral load in patients with chronic HDV infection in a dose-dependent manner. Given the wide intersubject variability in exposure when administered orally as well as the GI toxicities that may be dose-limiting, co-administration of lonafarnib with ritonavir, as a PK enhancer, may allow lower lonafarnib doses to be administered to the gut and minimize GI adverse effects while resulting in higher systemic levels. Currently, it is not known whether initiation of lonafarnib at a lower dose may allow greater tolerability over time, and whether the dose of lonafarnib may be titrated upward to allow a higher dose to be administered. The previous observation that lonafarnib treatment was not associated with viral resistance suggests that dose titration is not likely to be associated with development of viral resistance.

## 3.4 Selection of Study Population

The study participants will consist of male or female patients 18 to 65 years old who have chronic HDV infection documented by detectable HDV RNA by qPCR who meet the inclusion and exclusion criteria specified below.

### 3.4.1 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/$m^2$ 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. ALT <10x ULN
7. 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).
8. 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 FS] 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 at least 90 days after last dose of study drug, of which at least one must be a barrier method:
        - Hormonal contraceptives for at least 3 months before the start of screening and for at least 90 days after last dose of study drug
        - IUD in place for at least 3 months before the start of screening and until at least 90 days 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 at least 90 days after last dose of study drug.
9. Surgical sterilization of the partner (vasectomy for 1 month before the start of screening and maintenance throughout study and at least 90 days after the last dose of study drug).

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 at least 90 days 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).37

### 3.4.2 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 active infection with 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 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. A CPT score of >6 based on screening laboratory results
8. 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
9. History of bleeding esophageal varices, ascites, or hepatic encephalopathy.
10. 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
11. Significant renal dysfunction, defined as serum creatinine concentration ≥1.5 times the ULN or an estimated glomerular filtration rate (eGFR) < 80 mL/min at screening, based on the Cockcroft-Gault equation
12. Evidence of another form of viral hepatitis (not including HBV or HCV) 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)
13. Evidence of hepatocellular carcinoma
14. 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)
15. In the opinion of the Investigator, an alcohol use pattern that will interfere with study conduct
16. Drug abuse within the previous 6 months before the screening visit with the exception of medically prescribed cannabinoids and their derivatives
17. 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 suicidal ideation, suicidal attempts, or psychosis requiring medication and/or hospitalization
18. Solid organ transplantation, including liver

***Criteria Related to Use of Selected Medications***

19. Use of alpha interferon, either interferon alfa-2a or interferon alfa-2b, pegylated interferon alfa-2a, or pegylated interferon alfa-2b within 2 months before the start of screening

20. 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 unless otherwise described in protocol (i.e. Ondansetron).
    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:
        – Alpha$_1$-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***

21. 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.

### 3.4.3 Replacement of Patients in Study

Patients who discontinue the study before Week 12 for reasons other than an AE may be replaced on approval of the Sponsor.

### 3.4.4 Early Discontinuation of Study Treatment

Study treatment may be discontinued for any of the following reasons:

- Unacceptable toxicity
- Patient request or withdrawal of consent
- Pregnancy
- Protocol deviation (at the Sponsor's discretion)
- Investigator discretion
- Termination of study by the Sponsor

If early discontinuation of study treatment is being considered, it must be immediately reported to the Medical Monitor or designee to discuss the circumstances of the case.

### 3.4.5 Early Withdrawal from Study

If a patient discontinues study treatment early, every effort should be made to encourage the patient to return to the clinic as soon as possible for early termination (ET) assessments (refer to the Schedule of Assessments in Appendix A). If a patient discontinues study treatment after Week 12 but before Week 24 the ET visit should include the ophthalmic examination. Patients who discontinue study drug treatment are encouraged to remain in the study through the 24-week follow up period. For patients terminating study participation during the off-treatment follow-up phase additional early termination visits are not required. The reason for early withdrawal will be noted in the appropriate case report form (CRF).

### 3.4.6 Study Termination by the Sponsor

Eiger BioPharmaceuticals reserves the right to terminate the study at any time. Reasons for terminating the study may include but are not limited to the following:

- Potential health hazard to patients, as indicated by the incidence or severity of AEs in this or other studies
- Unsatisfactory patient enrollment
- Inaccurate or incomplete data recording
- Stopping rules and criteria specific to this protocol
- Administrative reasons

In addition, the regulatory agency or the site's Independent Ethics Committee (IEC) has the authority to stop the study.

## 3.5 Investigational Products

### 3.5.1 Product Identity and Storage

**Lonafarnib—**Lonafarnib is a crystalline solid with a melting point of approximately 200°C and is nonhygroscopic. Lonafarnib is formulated in No. 3 and No. 4, hard gelatin, white, opaque capsule shells for oral administration. Each No. 4 capsule contains 50 mg of lonafarnib. Each No. 3 capsule contains 75 mg of lonafarnib. Excipients include povidone, poloxamer 188, croscarmellose sodium, silicon dioxide, and magnesium stearate and are considered safe because they are well tested and commonly used in marketed products. Lonafarnib capsules are formulated in a 1:1 drug:povidine co-precipitate ratio to achieve optimal bioavailability.

Lonafarnib capsules are provided in white, opaque, high-density polyethylene (HDPE) bottles with polypropylene twist-off caps,. Lonafarnib is stable if stored at 15°C–25°C (59°F–77°F). A "use by" date is included on the product label. Lonafarnib should be stored at room temperature 15°C–25°C (59°F–77°F) in a locked, limited-access storage area before dispensing.

**Ritonavir**—The formulation of ritonavir (Novir®) marketed in Germany (AbbVie Deutschland GmbH &Co, Ludwigshafen, Germany) will be provided by Eiger BioPharmaceuticals during the study. Ritonavir will be supplied as 100-mg, white, film-coated, ovaloid tablets debossed with the "a" logo and the code NK (Prescribing Information for Norvir® [ritonavir] Tablets, 2015; Summary of Product Characteristics for Norvir® [ritonavir] tablets, 2014) in white, opaque, HDPE bottles with polypropylene twist-off caps.

Ritonavir should be stored at or below 30°C (86°F). Exposure to temperatures up to 50°C (122°F) for 7 days is permitted. Exposure of this product to high humidity outside the original or USP-equivalent tight container (60 mL or less) for longer than 2 weeks is not recommended.

### 3.5.2 Study Treatment Distribution

Patients will be provided appropriate quantities of study drug based on dosage, for a period of 2 or 4 weeks. Lonafarnib and ritonavir will be supplied in separate, clearly marked bottles. Patients will be provided quantities sufficient for a 2-week or 4-week period based on the individual patient's titration schedule.

## 3.6 Dosage and Titration

### 3.6.1 Dosage

All study treatments (lonafarnib/ritonavir) are administered orally. All doses of lonafarnib/ritonavir should be taken with food. Patients will be instructed to take the study medication at 12-hour intervals ±2 hours.

Dosages are outlined in Table 3. Ritonavir doses are to remain at 100 mg bid during the Treatment Period. The planned combinations of lonafarnib and ritonavir are 50 mg bid/100 mg bid, 75 mg bid/100 mg bid, and 100 mg bid/100 mg bid. All dose escalations will be based on patient tolerability (see Section 3.6.2.2) and approval of the Investigator. Doses of lonafarnib may be reduced and/or discontinued for patient tolerability; the dose of ritonavir will remain at 100 mg bid, unless lonafarnib is discontinued, in which case ritonavir will be discontinued as well Section 3.6.2.1).

**Table 3 Planned Dose Combinations During Study**

| Study Day | Dose | |
|---|---|---|
| | Lonafarnib | Ritonavir |
| Days 1–28 | 50 mg bid | 100 mg bid |
| On or after Day 29[a, b] | 75 mg bid | 100 mg bid |
| On or after Day 43[a, b] | 100 mg bid | 100 mg bid |

bid = twice daily

[a] Patients will be evaluated for tolerability at each dose level as described in Section 3.6.2.2.

[b] Only if the patient has been at the previous lonafarnib/ritonavir dosage level for at least 2 weeks.

### 3.6.2 Dose Titration

#### 3.6.2.1 Dose Levels

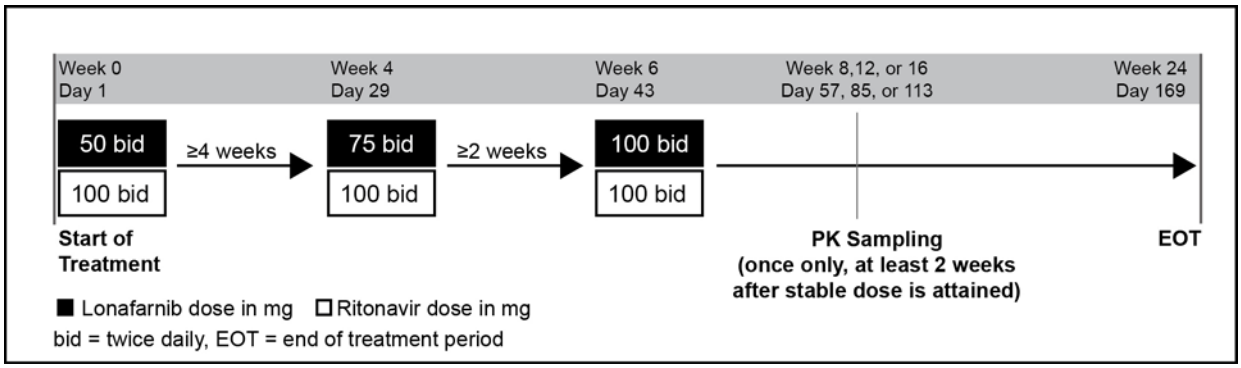
At each study visit, patients will be evaluated for tolerability by objective criteria (AEs and body weight) as outlined in Section 3.6.2.2.

Patients will be instructed to record doses of drugs taken in a patient diary. The patient diary should be brought to the clinic at each study visit during the Treatment Period.

**Planned Titration—**Lonafarnib/ritonavir dosages start on Day 1 (baseline, Week 0) at 50 mg bid/100 mg bid (Figure 5). On or after Day 29, if the lonafarnib/ritonavir dosage of 50 mg bid/100 mg bid is tolerated and with approval of the Investigator, the dosage of lonafarnib/ritonavir may be escalated to 75 mg bid/100 mg bid. On or after Day 43, if the lonafarnib/ritonavir dosage of 75 mg bid/100 mg bid is tolerated for at least 2 weeks and with approval of the Investigator, the dosage of lonafarnib/ritonavir may be escalated to 100 mg bid/100 mg bid.

The goal of dose titration is to determine dosages that are well tolerated for chronic (24 weeks) dosing. The treatment duration at the initial tolerated dose of lonafarnib/ should be maintained for at least 4 weeks before upward titration; the treatment duration at a particular dosage level for any subsequent dose escalation is at least 2 weeks. Therefore, the above treatment intervals should be considered as minimum intervals, and longer treatment durations may be used to optimize patient tolerability.

**Figure 5 Planned Dose-Titration Scheme**

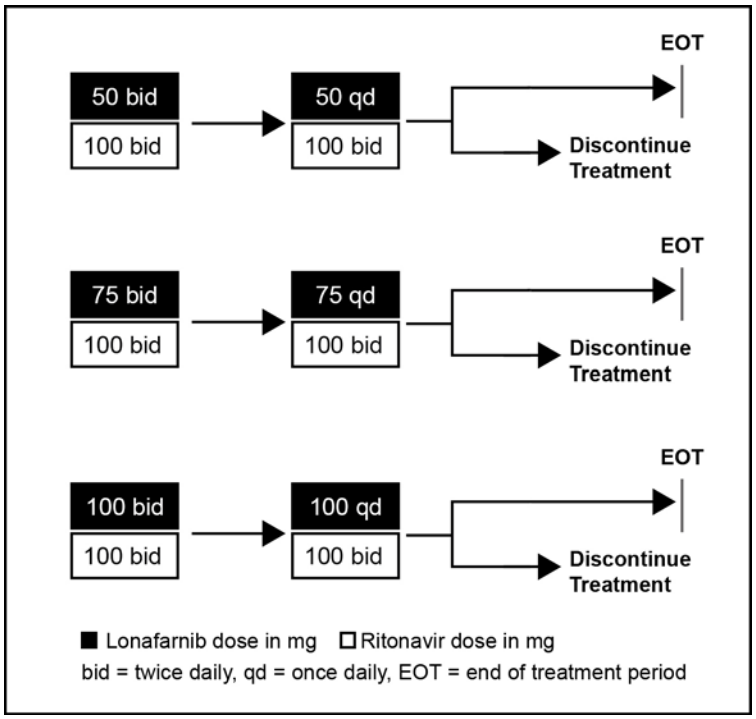



Note: A stable dose is defined as a dose of lonafarnib/ritonavir that has been taken for at least 2 weeks and that is likely to be the highest tolerable dose taken by the patient during the study.

**Down Titration—**If at any time the current twice daily (bid) lonafarnib dosage is not tolerable, the lonafarnib dosage will be reduced to once daily (qd); if the once-daily lonafarnib dosage is not tolerable, the lonafarnib/ritonavir will be stopped (Figure 6). Thus, the dosage for a patient taking lonafarnib/ritonavir 50 mg bid/100 mg bid will be reduced to lonafarnib/ritonavir 50 mg qd/100 mg bid; if the patient does not tolerate this regimen, then all study drug treatment should be discontinued. For a patient taking lonafarnib/ritonavir 75 mg bid/100 mg bid, the dose will be reduced to lonafarnib/ritonavir 75 mg qd/100 mg bid; if the patient does not tolerate this regimen, then all study dug treatment should be discontinued. Similarly, for a patient taking lonafarnib/ritonavir 100 mg bid/100 mg bid, the dose will be reduced to lonafarnib/ritonavir 100 mg qd/100 mg bid; if the patient does not tolerate this regimen, then all study drug treatment should be discontinued.

If lonafarnib/ritonavir has been discontinued in a patient for tolerability reasons, it may not be restarted; the patient should complete the early termination procedures and should enter the Follow-up Period. All follow-up procedures should be conducted according to the Schedule of Events (Appendix A).

**Figure 6 Dose Down-Titration Scheme**

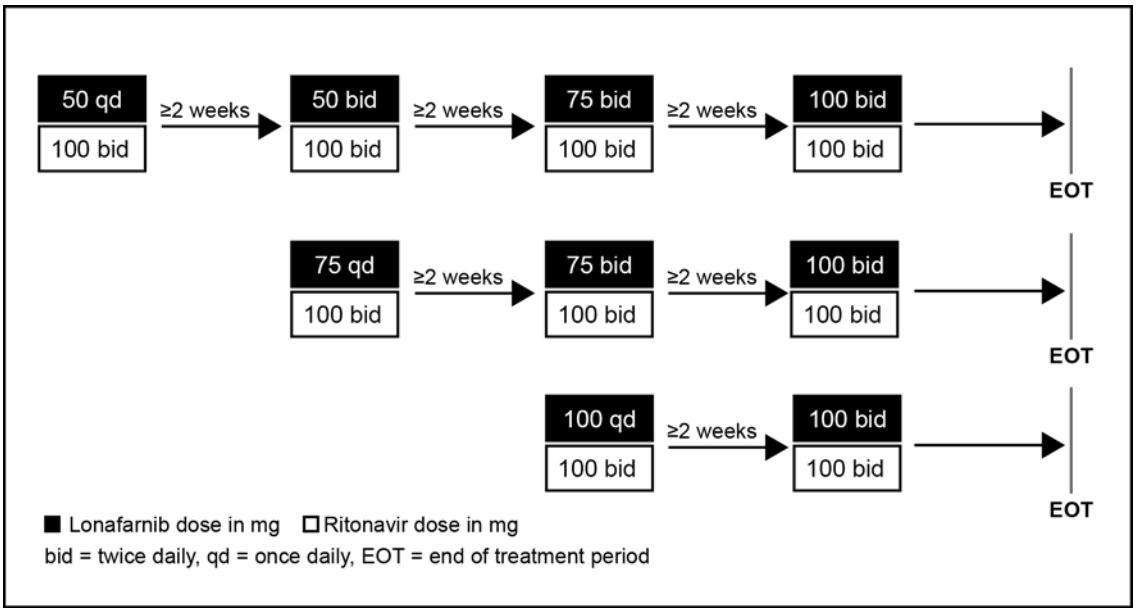



**Re-Escalation—**At the direction of the Investigator, each patient whose dose has been decreased but not discontinued will have the option to re-escalate his or her dose according to the schedule shown in Figure 7. The dose level should not be increased until the previous dose has been maintained for at least 2 weeks and should be done with the approval of the Investigator. Thus, a patient who is taking lonafarnib/ritonavir 50 mg qd/100 mg bid may advance to lonafarnib/ritonavir 50 mg bid/100 mg bid; if this is well tolerated for at least 2 weeks, then the patient may advance to lonafarnib/ritonavir 75 mg bid/100 mg bid. A patient who has taken lonafarnib/ritonavir 75 mg qd/100 mg bid for at least 2 weeks may advance to lonafarnib/ritonavir 75 mg bid/100 mg bid; if this is well tolerated for at least 2 weeks, then the patient may advance to lonafarnib/ritonavir 100 mg bid/100 mg bid.

The goal of dose titration is to determine a dosage that is well tolerated for chronic (24 weeks) dosing. Therefore, the above treatment intervals should be considered as minimum intervals, and longer treatment durations at a particular dose level may be used to optimize patient tolerability.

Note that ritonavir doses should be maintained at 100 mg bid, unless lonafarnib is discontinued, in which case ritonavir should be discontinued as well.

**Figure 7 Dose Re-Escalation Scheme**




### 3.6.2.2 Evaluation of Tolerability

The Investigator will evaluate all AEs and laboratory abnormalities. The intensity (ie, "grade") of an AE will be based on the definitions in the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 (CTCAE 2010), and the guidelines provided in Section 6.4.1. Based on findings from previous studies, the following AEs are expected events with lonafarnib administration and occur with greater frequency and severity at higher exposures: diarrhea, nausea, dyspepsia, vomiting, decrease in appetite, anorexia, fatigue, and weight loss. The criteria for assessing the intensity of these AEs from the CTCAE are listed in Table 4.

The goal is to determine a dosage suitable for chronic dosing of lonafarnib/ritonavir. The following guidelines will apply to management of AEs, patient tolerability, and lonafarnib dose adjustments:

- If a patient experiences any study-drug-related AE that is Grade 3 or above (as defined in Section 6.4.1), the patient's lonafarnib dose must be decreased according to the dose down-titration scheme (Figure 6). If a patient experiences unintentional weight loss of at least 3 kg or 5% from baseline weight, whichever is greater, the Investigator should assess for factors contributing to weight loss and encourage optimum nutrition. The lonafarnib dose may be decreased according to the dose down-titration scheme at the Investigator's discretion. If a patient experiences unintentional study-drug related weight loss of at least 6 kg or 10% from baseline weight, whichever is greater, and this is considered to be study drug related, then the patient's lonafarnib dose must be decreased according to the dose down-titration scheme. In this instance, "weight loss" should be entered as an AE and outcome captured as "resulted in dose reduction."
- If a patient develops a study-drug-related Grade 1 or 2 AE (as defined in Section 6.4.1), the Investigator will exercise medical judgement regarding the need to adjust

the lonafarnib dose. If a patient experiences unintentional weight loss of at least 3 kg or 5% from baseline weight, whichever is greater, the Investigator should assess for factors contributing to weight loss and encourage optimum nutrition. The Lonafarnib dose may be decreased according to the dose down-titration scheme at the Investigator's discretion. If a patient experiences unintentional study-drug related weight loss of at least 6 kg or 10% from baseline weight, whichever is greater, and this is considered to be study drug related, then the patient's Lonafarnib dose must be decreased according to the dose down-titration scheme. In this instance, "weight loss" should be entered as an AE and outcome captured as "resulted in dose reduction."

Ritonavir doses should be maintained at 100 mg bid, unless lonafarnib is discontinued, in which case ritonavir should be discontinued as well.

**Table 4 Grades of Common Expected Adverse Events with Lonafarnib Treatment as Defined in the CTCAE (Version 4.03)**

| Adverse Event | Grade | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Diarrhea | Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline | Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline | Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL | Life-threatening consequences; urgent intervention indicated | Death |
| Nausea | Loss of appetite without alteration in eating habits | Oral intake decreased without significant weight loss, dehydration or malnutrition | Inadequate oral caloric or fluid intake; tube feeding; TPN or hospitalization indicated | — | — |
| Dyspepsia | Mild symptoms; intervention not indicated | Moderate symptoms; medical intervention indicated | Severe symptoms; surgical intervention indicated | — | — |
| Vomiting | 1–2 episodes (separated by 5 minutes) in 24 hours | 3–5 episodes (separated by 5 minutes) in 24 hours | ≥6 episodes (separated by 5 minutes) in 24 hours; tube feeding, TPN or hospitalization indicated | Life-threatening consequences; urgent intervention indicated | Death |
| Anorexia | Loss of appetite without alteration in eating habits | Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated | Associated with significant weight loss or malnutrition (eg, inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated | Life-threatening consequences; urgent intervention indicated | Death |
| Fatigue | Fatigue relieved by rest | Fatigue not relieved by rest; limiting instrumental ADL | Fatigue not relieved by rest; limiting self care ADL | — | — |
| Weight loss | 5% to <10% from baseline; intervention not indicated | 10% to <20% from baseline; nutritional support indicated | ≥20% from baseline; tube feeding or TPN indicated | — | — |

ADL = activities of daily living; TPN = total parenteral nutrition

### 3.6.2.3 Management of Flares

Patients should be followed closely for the possibility of hepatic flare, as defined by an increase in ALT of ≥10x the ULN. A flare may be associated with an increase in viral replication ("viral

flare") or with a decrease in viral replication ("hepatic flare"). An unscheduled visit may be used to evaluate the patient.

For patients who are not on concurrent nucleos(t)ide therapy, consideration should be given to initiation of nucleos(t)ide therapy to address HBV reactivation/flare.

### 3.6.3 Missed Doses

Patients will be instructed to self-administer lonafarnib and ritonavir at 12-hour intervals ±2 hours. If a dosing window is missed, the patient should skip the dose completely. Patients should not "double up" at the next scheduled dose period.

## 3.7 Treatment Adherence and Product Accountability

Patients will receive instructions regarding how to self-administer all study drugs. Patients will also be instructed to bring their patient diary and to return study drug bottles when they come to the clinic for each study visit during the Treatment Period. Adherence with the prescribed regimen for each study drug will be measured using bottle and capsule/tablet counts.

Patients will be instructed to record all study drug administrations in the patient diary. A sample patient diary is included in Appendix D.

## 3.8 Prior and Concomitant Therapies

All prior medications taken within 28 days before baseline (Day 1) and all concomitant medications taken during the study will be recorded in the CRF. All prior treatments administered for HDV and HBV infections will be recorded on the CRF.

### 3.8.1 Prior Therapies

Patients are prohibited from using systemic immunosuppressive therapy within the 3 months before start of screening and from using alpha interferon, either interferon alfa-2a or interferon alfa-2b, or pegylated interferon alfa-2a or alfa-2b within 2 months before the start of screening.

Patients are prohibited from participating in a clinical trial with or receiving an investigational product within 30 days before the start of screening.

### 3.8.2 Concomitant Therapies During the Treatment Period

#### 3.8.2.1 Treatment of Gastrointestinal Symptoms

Gastrointestinal (GI) symptoms (diarrhea, nausea, dyspepsia, vomiting, and decreased appetite) are the most common AEs reported with lonafarnib single-agent therapy. Ritonavir may be associated with diarrhea. Occurrence of diarrhea may reduce the absorption of lonafarnib, ritonavir, and other medications from the GI tract. Diarrhea may result in loss of fluids and dehydration, which can be severe, and require hospitalization for supportive care. *Patients should receive therapy (antacids, anti-emetics, or anti-diarrheals) for GI symptoms at the earliest signs in order to avoid possible severe complications.* Electrolytes should be monitored in cases of diarrhea and volume depletion. Use of symptomatic treatments for GI toxicity should be recorded in the CRF.

Ondansetron does not inhibit or induce enzymes in the CYP system. No interaction is expected with concomitant administration with lonafarnib.

Famotidine has not been associated with any clinically significant drug-drug interactions. No significant interference with CYP system has been identified; thus, no interaction is expected with concomitant administration with lonafarnib.

Omeprazole inhibits CYP2C19 and P-glycoprotein (P-gp) and is completely metabolized, specifically by CYP3A4 and CYP2C19. Dose adjustments are typically not required when administering omeprazole with other medications metabolized by CYP2C19; however, dose adjustments are required for omeprazole when administered to patients with hepatic impairment (refer to the Prilosec Product Label for additional information).

#### 3.8.2.2 Prohibited Medications

Use of the following medications is prohibited during the conduct of the study:

- Drugs known to prolong the PR or QT interval
- Use of ondansetron for symptomatic treatment of nausea is allowed; prudent medical judgment should be applied as to the dose and duration of its use.
- Systemic immunosuppressive therapies
- Statins, due to inhibition of mevalonate synthesis, which reduces protein prenylation.

Use of any prescription, nonprescription or natural medications (herbal medicines) is excluded unless use of such medication is medically necessary; as drug-drug interactions with lonafarnib and ritonavir and other drugs have not been fully explored; all concomitant medications should be appropriately monitored for possible interactions throughout the course of the study.

Drugs highly dependent on CYP3A4 for clearance are contraindicated with ritonavir (Table 5). Appendix C lists all drugs contraindicated with the use of ritonavir and also lists drugs that have established or other potentially significant drug interactions when used in combination with ritonavir.

**Table 5 Drugs Contraindicated with Use of Ritonavir**

| Class | Drug | Clinical Outcome/Rationale |
|---|---|---|
| Alpha$_1$- adrenoreceptor antagonist | Alfuzosin HCL | Potential for hypotension. Increased plasma concentrations of alfuzosin which may lead to severe hypotension |
| Analgesics* | Pethidine*, piroxicam*, propoxyphene* | Increased plasma concentrations of norpethidine, piroxicam and propoxyphene. Thereby, increasing the risk of serious respiratory depression or haematologic abnormalities, or other serious adverse effects from these agents. |
| Antiarrhythmics | Amiodarone, bepridil*, encainide*, flecainide, propafenone, quinidine | Potential for cardiac arrhythmias. Increased plasma concentrations of amiodarone, bepridil, encainide, flecainide, |

| Class | Drug | Clinical Outcome/Rationale |
|---|---|---|
| | | propafenone, quinidine. Thereby, increasing the risk of arrhythmias or other serious adverse effects from these agents. |
| Antibiotic* | Fusidic acid* | Increased plasma concentrations of fusidic acid and ritonavir. |
| Antifungal | Voriconazole | Co-administration of voriconazole with ritonavir 400 mg every 12 hours significantly decreases voriconazole plasma concentrations and may lead to loss of antifungal response. Voriconazole is contraindicated with ritonavir doses of 400 mg every 12 hours or greater |
| Antihistamines* | Astemizole*, terfenadine* | Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents. |
| Antimycobacterial* | Rifabutin* | Concomitant use of ritonavir dosed as an antiretroviral agent (600 mg twice daily) and rifabutin due to an increase of rifabutin serum concentrations and risk of adverse reactions including uveitis). Recommendations regarding use of ritonavir dosed as a pharmacokinetic enhancer with rifabutin are noted in section 4.5 of the Summary of Product Characteristics |
| Antipsychotics*/Neuroleptics | Clozapine*, pimozide | Potential for cardiac arrhythmias. Increased plasma concentrations of clozapine and pimozide. Thereby, increasing the risk of serious haematologic abnormalities, or other serious adverse effects from these agents. |
| | Quetiapine* | Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated |
| Ergot Derivatives | Dihydroergotamine, ergonovine, ergotamine, methylergonovine | Potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system. |

| Class | Drug | Clinical Outcome/Rationale |
|---|---|---|
| Gastrointestinal Motility Agent | Cisapride | Increased plasma concentrations of cisapride. Potential for cardiac arrhythmias. |
| Herbal Products | St. John's Wort (hypericum perforatum) | Co-administration of NORVIR with St. John's Wort may result in decreased ritonavir plasma concentrations and may lead to loss of virologic response and possible resistance to NORVIR or to the class of protease inhibitors. |
| HMG-CoA Reductase Inhibitors: | Lovastatin, simvastatin | Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis |
| PDE5 enzyme inhibitor | Avanafil* | Increased plasma concentrations of avanafil |
| | Sildenafil (Revatio®) only when used for the treatment of pulmonary arterial hypertension (PAH) | A safe and effective dose has not been established when used with ritonavir. There is an increased potential for sildenafil- associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope. |
| | Vardenafil* | Increased plasma concentrations of vardenafil |
| Sedative/hypnotics | Clorazepate*, diazepam*, estazolam*, flurazepam*, oral midazolam, triazolam | Prolonged or increased sedation or respiratory depression. Thereby, increasing the risk of extreme sedation and respiratory depression from these agents |

Sources: Prescribing Information for Norvir® [ritonavir] Tablets, 2015. *Additional terms from the Summary of Product Characteristics for Norvir® [ritonavir] tablets, 2014

### 3.8.2.3 Medications to be Used with Caution

#### 3.8.2.3.1 Due to Possible Interaction with Lonafarnib

An *in vitro* CYP inhibition study conducted with lonafarnib suggests that lonafarnib may be a mechanism-based inhibitor of CYP3A4 and CYP2C19 enzymes. Any medications that are *primarily* metabolized by CYP3A4 should be avoided. Any medications that are *primarily* metabolized by CYP2C19 should be used with caution. If at all possible, alternative therapeutic agents that are not CYP3A4 substrates, inducers, or inhibitors or are less potent CYP3A4 substrates, inducers, or inhibitors should be considered. Concomitant administration of medications that are primarily metabolized by CYP3A4 or CYP2C19 may result in large increases in serum levels of these medications that may precipitate unwanted toxicities.

Entecavir, tenofovir, lamivudine, adefovir, and telbivudine do not substantially inhibit or induce the enzymes in the CYP system. Therefore an interaction with lonafarnib is not anticipated due

to CYP enzymes; however, there is a potential for interaction of lonafarnib with tenofovir due to inhibition of P-gp, BCRP, and OATP1B1 inhibition (see below).

*In vitro* tests suggest that lonafarnib may be an inhibitor of efflux pumps P-gp and BCRP and the liver uptake transporter OATP1B1. Therefore, concomitant medications that are substrates of P-gp, BCRP, and/or OATP1B1should be used with caution. Taking medications that are substrates of P-gp, BCRP, and/or OATP1B1 may result in unwanted increases in serum levels of these medications, especially medications with a narrow therapeutic index (eg, digoxin, loperamide, quinidine, talinolol, vinblastine).

Because tenofovir is a substrate of P-gp, BCRP, and OATP1B1, concomitant administration of lonafarnib and tenofovir may result in increased levels of tenofovir. Therefore, tenofovir should be used with caution when co-administered with lonafarnib.

A source that should be used to check for potential drug-drug interactions is at the following website: http://www.Drug-Interactions.com. The website provides a list of drugs known to be metabolized by cytochrome P450 enzymes including CYP3A4. Although this list is periodically updated, it is not an exhaustive list; therefore, using more than one source is recommended when checking for potential interactions. Another source that can be used is by searching the drug name and reviewing the product label (Sections 7 and Section 12) at this site: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

#### 3.8.2.3.2 Due to Possible Interaction with Ritonavir

Ritonavir inhibits CYP3A4, P-gp, MRP1, OATP-C, and BCRP. Ritonavir induces CYP1A2, CYP2C8, CYP2C9, CYP2C19, and MRP1. Ritonavir is a substrate of CYP3A4 and CYP2D6. Drugs highly dependent on CYP3A4 for clearance are contraindicated with ritonavir (refer to Table 5 and Appendix C).

While patients are receiving ritonavir, the Investigator should review all other medications taken by patients and monitor patients for adverse effects due to metabolism interactions of ritonavir with concomitant medications. Initiating treatment with ritonavir in patients receiving medications primarily metabolized by CYP3A or initiating medications metabolized by CYP3A in patients already maintained on ritonavir may result in increased plasma concentrations of these medications. Higher plasma concentrations of concomitant medications can precipitate adverse effects that can, potentially lead to severe, life-threatening or fatal events. The potential for drug-drug interactions must be considered before initiating therapy or during therapy with ritonavir.

### 3.8.2.4 Contraception

Female patients of childbearing potential and male patients with partners of childbearing potential must agree to use adequate methods of contraception during the study and for 1 month after end of study treatment. Adequate methods of contraception for patients or partner include the following:

- For females, **two** of the following contraceptive methods, with at least one being a barrier method
  - Hormonal contraceptives for at least 3 months before the start of screening and for at least 90 days after last dose of study drug

  - Intrauterine device (IUD) in place for at least 3 months before the start of screening and until 90 days 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 90 days after last dose of study drug.
  - Surgical sterilization of the partner (vasectomy for 1 month before the start of screening and maintenance until at least 90 days after the last dose of study drug.
- For males
  - Surgical sterilization (vasectomy for 1 month before the start of screening and maintenance throughout and for at least 90 days after the last dose of study drug).
    **or**
  - Two effective forms of birth control from those listed below from the start of screening until 90 days after their last dose of study drug, with at least one being 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)

Male patients must also refrain from sperm donation for 90 days after receiving the last dose of study drug.

### 3.8.3 Permitted Therapies During the Follow-up Period

Alpha interferon and pegylated interferon alfa-2a treatments are allowed during the last 20 weeks of the Follow-up Period (that is, starting 4 weeks after last dose of study treatment), if, in the opinion of the investigator, they are required for patient safety. Note that for patients who experience an HBV reactivation/flare, treatment with nucleos(t)ide therapy should be considered in those who are not currently receiving this therapy (see Section 3.6.2.3).

### 3.8.4 Randomization and Blinding

This is a nonrandomized, open-label study.

# 4 STUDY ASSESSMENTS AND PROCEDURES

## 4.1 Description of Assessments

Written informed consent must be obtained before initiating any study-mandated procedures. See Section 8.4 for additional information regarding informed consent

Study procedures are defined as liver biopsy (if required) and Fibroscan; medical history; physical examinations; ophthalmic examinations and retinal photographs; vital sign, height, weight, and ECG assessments; and blood draws for molecular (DNA/RNA) analyses and serologic tests, PK evaluations, and clinical laboratory tests (blood chemistry and hematology).

During the study, procedures and observations will be monitored to confirm that study requirements are being followed as outlined in the Schedule of Assessments in Appendix A. After patients complete the treatment period (through Week 24), they will be followed for every 4 weeks Follow-Up Visits through Week 48.

### 4.1.1 History, Physical Examination, and Vital Signs

Medical history, including details regarding illnesses and allergies, date(s) of onset, and whether conditions are currently ongoing, and medication history will be collected on all patients during screening. The medical history will be updated at the Day 1 Visit and will then serve as the baseline for other clinical assessments.

A comprehensive physical examination will be performed at screening, including all body systems pertinent to the patient and CTP scoring and encephalopathy assessment (see Appendix B). If clinically significant abnormalities are observed before Day 1, they should be reported in the patient's medical history. If clinically significant abnormalities are observed after Day 1, the Investigator should decide if they are new adverse events.

Brief, directed physical examinations will be performed during the remainder of the study performed by a physician, nurse practitioner, physician's assistant, or nurse). This includes weight and vital signs as well as HEENT (head, eyes, ears, nose, and throat), heart, lungs, abdomen, and lower extremity.

Vital signs will be followed throughout the study and will include resting heart rate, blood pressure, respiratory rate, and body temperature. Blood pressure and heart rate should be measured after 5 minutes in a sitting position.

Weight will be followed throughout the study and should be measured with inner clothing (ie, without heavy outer wear such as jackets and coats) and without shoes.

### 4.1.2 Ophthalmic Examination and Retinal Photography

Ophthalmic examinations will be performed during the study and will include visual acuity examination, dilatation, and slit lamp examination. On slit lamp examination, orbit, eyelids, lashes, lacrimal glands, conjunctiva, cornea, sclera, anterior chamber, and iris will examined. On the dilated fundus examination, lens, vitreous, optic disc, and retina will examined.

Retinal photography will also be performed predose and at the end of treatment.

Any visual symptoms that occur during the study (such as impairment in night vision) should be assessed, and if indicated, a repeat ophthalmic examination should be performed.

### 4.1.3 Liver Biopsy and Fibroscan

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, the patient must be willing to have a liver biopsy 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.

A Fibroscan is to be performed at baseline (Day 1) and at the end of treatment (Week 24 Visit). Patients must fast for at least 3 hours before the Fibroscan is performed.

### 4.1.4 Electrocardiograms

All ECGs for this study will be 12-lead, serial ECGs performed in triplicate (×3) 2 to 3 minutes apart. Three interpretable ECGS recordings (ie, without artifacts) should be obtained at each time point. The average of the three readings will be used to determine ECG intervals. (Single ECG recordings may be obtained at unscheduled time points as indicated.)

Patients should rest in a supine position for ≥5 minutes before the ECG recording is made. When ECG recordings coincide with PK draws, the EGCs should be obtained before the PK draw is performed. ECGs must be read by the Investigator or a qualified designee, and the results recorded in the CRF. On-treatment ECGs should be compared to the patient's baseline as part of routine safety monitoring. All clinically relevant abnormalities will be reported as AEs.

ECG printouts will be maintained with the source documentation.

### 4.1.5 Molecular and Serologic Tests

Serologic testing for HBV, HCV, HDV, and HIV will be performed during screening evaluation of entry criteria.

Throughout the study, serum and plasma samples will be obtained for HDV/HBV molecular and serologic tests.

- HDV RNA viral load will be quantified using the RoboGene® HDV RNA Quantification Kit, which uses real-time qPCR of HDV RNA in human serum samples. The assay is designed to detect genotypes 1, 2, 5, 6, 7, and 8 of HDV, applying probes and primers specific for a subsequence of the hepatitis delta antigen. The assay has a lower limit of quantitation of 500 U/mL based on calibrated standards using a reference HDV genotype 1 positive serum.
- HBV DNA will be analyzed using COBAS® AmpliPrep/COBAS® TaqMan® HBV Test. This is a nucleic acid amplification test for the quantification of Hepatitis B Virus (HBV) DNA in human plasma and serum. The COBAS® AmpliPrep/COBAS® TaqMan® HBV Test is based on two major processes: (1) specimen preparation to isolate HBV DNA and (2) simultaneous PCR amplification of target DNA and detection of cleaved dual-labeled oligonucleotide detection probe specific to the

target. The assay can quantitate HBV DNA levels with an upper limit of quantification of $1.7 \times 10^8$ IU/mL and a lower limit of detection of 20 IU/mL.

- In addition to HBV DNA levels, hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and hepatitis B e antibody (HBeAb) levels will be followed during the study because these may be important to indicate seroconversion or disease course.

### 4.1.6 Pharmacokinetic Sampling

#### 4.1.6.1 Pharmacokinetic Sampling Time Points

PK sampling will be conducted on all patients. Sampling times and windows are presented in Table 9.

Single blood samples will be obtained for trough drug measurements at each study visit starting at Week 2 and through Week 16.

Blood samples will be obtained for full PK analysis when patients have maintained a stable dose of lonafarnib/ritonavir for at least 2 weeks between Study Weeks 8 and 16 as follows (see Section 3.6.2 for dose-titration details). A stable dose is defined as a dose of lonafarnib/ritonavir that has been taken for at least 2 weeks and that is likely to be the highest tolerable dose taken by the patient during the study. Samples for full PK will be taken as follows predose (within 30 minutes before the first dose of the day) and 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h postdose. The second daily dose of study drug may not be taken until after the 12 hour sample is obtained. On the days that PK sampling occurs, patients will remain in clinic at least 13 hours.

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.

#### 4.1.6.2 Pharmacokinetic Sample Labeling and Shipping

Plasma samples for PK analysis must be labeled with unique identification numbers. Additional labeling information is provided in the laboratory manual. Labels must remain intact and indelible throughout processing and frozen storage.

Pharmacokinetic samples are to be shipped in insulated containers filled with dry ice to the following address:

The Doctors Laboratory
60 Whitfield Street
London, UK
W1T 4EU

Details for shipment to the analytical laboratory are included in the laboratory manual.

Unused PK samples will be stored until directed by the Sponsor that they may be destroyed.

#### 4.1.6.3 Pharmacokinetic Analytical Methods

Plasma concentrations for lonafarnib and ritonavir will be determined using validated analytical methods for each of the analytes.

The validated range can be truncated when less than 5 calibrants appear to be below the expected maximum plasma concentration observed ($C_{max}$), provided that this new calibration curve range is validated before use.

Where possible, all samples from each patient will be analyzed on the same standard curve. Quality control samples will be distributed through each batch of study samples assayed. Samples with drug concentrations greater than the upper limit of quantitation (ULQ) of the assay range will be diluted with the appropriate drug-free biological fluid and re-assayed; those that are below the lower limit of this range will be reported as below the limit of quantitation (BLQ).

Unacceptable values attributable to bioanalytical reasons will be determined according to the standard operating procedures (SOPs) of the bioanalytical facility. Such re-assayed samples will be termed "repeats". The method of re-assay and the acceptance criteria for selecting which value to report for the re-assayed samples will also follow the SOPs of the bioanalytical facility. All cases of re-assay will be detailed in the final bioanalytical report. With the written consent of the patient, remaining plasma samples may be stored for possible future analyses by the Sponsor if deemed necessary (eg, for determination of active metabolite concentrations, HDV and HBV analyses, and host DNA analyses of polymorphisms that may impact drug response).

### 4.1.7 Routine Clinical Laboratory Tests

Serum and blood chemistry laboratory tests are listed in Table 6.

**Table 6 Serum and Blood Chemistry Laboratory Tests**

| Test Category | |
|---|---|
| **Hematology** | **Clinical Chemistry** |
| Hemoglobin | Alanine aminotransferase (ALT) |
| Hematocrit | Albumin |
| Erythrocyte count (red blood cell) | Alkaline phosphatase |
| Mean corpuscular volume | Amylase |
| Mean corpuscular hemoglobin | Aspartate aminotransferase (AST) |
| Mean corpuscular hemoglobin concentration | Bicarbonate |
| Leukocytes (white blood cell) | Bilirubin (direct, indirect, and total) |
| Neutrophils, segmented | Blood urea nitrogen (BUN) |
| Neutrophils, juvenile (bands) | Calcium |
| Lymphocytes | Chloride |
| Monocytes | Cholesterol |
| Eosinophils | Creatine kinase (CK) |
| Basophils | Creatinine |
| Platelets | Gamma-glutamyl transferase (GGT) |
| Cell morphology | Globulin |
| | Glucose, nonfasting |
| | Lactate dehydrogenase (LDH) |
| **Coagulation** | Magnesium |
| Prothrombin time | Phosphorus |
| INR | Potassium |

| Test Category | |
|---|---|
| | Sodium |
| **Urinalysis** | Triglycerides |
| Specific gravity | Total protein |
| Protein | Uric acid |
| Ketones | |
| Bilirubin | |
| Urobilinogen | **Quantitative Polymerase Chain Reaction** |
| Blood | Hepatitis B virus |
| Nitrite | Hepatitis C virus [a] |
| Microscopic examination of sediment | Hepatitis D virus |
| **Other Tests** | **Viral Serology** |
| Blood ethanol test [b] | Hepatitis B e serology |
| Urine drug screen [b] | Hepatitis B surface antigen (HBsAg) |
| Pregnancy test [c] | Hepatitis C virus serology [a] |
| Peripheral blood mononuclear cell (PBMC) | Hepatitis D virus serology |
| Triiodothyronine ($T_3$) | Human immunodeficiency virus serology |
| Thyroxine ($T_4$) | |
| Thyroid stimulating hormone (TSH) | |
| **Reproductive Serology - Males** | **Reproductive Serology - Females** |
| Inhibin B | Luteinizing hormone |
| Luteinizing hormone (LH) | Follicle-stimulating hormone (FSH) |
| Follicle-stimulating hormone (FSH) | Estradiol |
| Free and total testosterone | Progesterone |
| | Anti-Müllerian hormone (AMH) |
| | Dehydroepiandrosterone (DHEA) |
| | Dehydroepiandrosterone sulfate (DHEAS) |
| | Androstenedione |
| | Testosterone |
| | Free testosterone |
| | Sex hormone binding globulin (SHBG) |
| | 17-Hydroxyprogesterone (17-OHP) |

[a] Patients with a positive HCV Ab result 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.

[b] Blood alcohol test and urine drug screen for cannabinoids, opiates, amphetamines, barbiturates, benzodiazepenes, cocaine at screening.

[c] Serum pregnancy test at screening, and urine pregnancy test during remainder of the study; if urine pregnancy test result is positive, confirm immediately with serum pregnancy test.

### 4.1.8 Total Blood Sampling Volume

During the study, blood samples for hematology, chemistry, serology, and viral load analyses will be collected via venipuncture. Some plasma samples will be stored for possible future analytical analyses by the Sponsor (eg, for generation of active metabolite concentrations) for patients who have provided written informed consent for this procedure.

Blood sampling volumes to be collected during the study are listed in Table 7.

**Table 7 Blood Sampling Volumes**

| Test Group | Volume per Draw (mL) | Total Volume for Study (mL) |
|---|---|---|
| Biochemistry, HepB serology, HIV1&2 antibodies, Hepatitis B surface antigen, Hepatitis C Virus antibody, T3, T4, TSH, Serum pregnancy test | 5 | 90 |
| Hepatitis C Virus PCR | 4 | 4 |
| Blood alcohol | 2 | 2 |
| Hematology | 2 | 36 |
| Coagulation | 2.7 | 24.3 |
| Hepatitis B Virus PCR | 4 | 72 |
| Hepatitis D Virus PCR, Hepatitis D antibodies | 5 | 90 |
| HBV genotyping, HDV genotyping | 5 | 95 |
| Reproductive Serology | 7.5 | 105 |
| PK samples | 7.5 | 112.5 |
| PBMC | 45 | 360 |
| Total for study | | 990.8 |

[a] Volume for PK draw = 10 mL.

### 4.1.9 Appropriateness of Assessments

The assessments planned are standard, well-established procedures for a study of this type and duration and are designed to provide the data required to address the objectives of the study.

## 4.2 Description of Study Procedures by Study Visit

The results of all procedures listed below will be documented in the patient's medical record and recorded on the patient's case report forms (CRFs). See Appendix A for a schedule of study evaluations and procedures.

Study visits will occur during 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 every 4 weeks for 24 weeks. 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 Follow-up Visits will include evaluations of safety (adverse events, concomitant medications, and laboratory values) and viral loads (HDV and HBV). Alpha-interferon treatments will be allowed

during the last 20 weeks 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.

### 4.2.1 Screening Visit(s) (Weeks –4 to –1)

Written informed consent must be given before any study-related diagnostic or screening procedures are performed. At the Screening Visit, patients will have all required evaluations to determine their eligibility to participate in the study.

The Screening Period is defined as the time between the date of the first Screening procedure and Day −1 and may last up to 28 days. Screening procedures may be conducted over multiple days within the Screening period if convenient.

The following procedures will be performed during Screening:

- Obtain signed informed consent.
- Determine eligibility based on inclusion/exclusion criteria.
- Obtain medical history, review systems.
- Query use of concomitant medications.
- Conduct comprehensive physical examination, including measurements of height and weight (≥45 kg), calculate BMI (≥18 kg/$m^2$), and assess CTP score and encephalopathy (see Appendix B).
- Conduct genital examination.
- Conduct ophthalmic examination and obtain retinal photographs.
- Record ECGs (12-lead, serial ECGs in triplicate 2 to 3 minutes apart). Patients should rest in a supine position for ≥5 minutes before the ECG recording is made.
- Measure vital signs (heart rate, blood pressure, respiratory rate, and body temperature). Blood pressure and heart rate should be measured after 5 minutes in a sitting position
- Conduct liver biopsy (if patient lacks documentation of a liver biopsy demonstrating evidence of chronic hepatitis).
- Obtain blood samples for
  - Clinical laboratory assessments, including hematology, serum chemistries, serologic tests (HBsAg, HBeAg and HBeAb, HCV Ab, HDV Ab, and HIV Ab), prothrombin time and INR, Triiodothyronine ($T_3$) and thyroxine ($T_4$), and serum pregnancy test for women of childbearing capacity.
  - Quantitative PCR (HBV DNA, HDV RNA, HCV RNA [if positive HCV Ab])
- Obtain urine sample for urinalysis and drug screen.

Patients meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic for the first treatment visit (Week 0, Day 1) assessments and randomization.

### 4.2.2 Treatment Visit – Week 0, Day 1 (±2 Days)

Day 1 procedures that must be performed before administration of first study treatment are listed below.

**Before First Study Treatment:**

- Review and confirm inclusion eligibility.
- Update medical history as necessary.
- Review concomitant medications.
- Conduct brief physical examination and calculate BMI.
- Record ECGs (12-lead, serial ECGs in triplicate 2 to 3 minutes apart). Patients should rest in a supine position for ≥5 minutes before the ECG recording is made.
- Measure vital signs (heart rate, blood pressure, respiratory rate, and body temperature) and weight. Blood pressure and heart rate should be measured after 5 minutes in a sitting position.
- Conduct Fibroscan (patients must fast for at least 3 hours before the Fibroscan is performed).
- Obtain blood samples for
  - Clinical laboratory assessments, including hematology, serum chemistries, serologic tests (HDV, HBsAg, HBeAg, HBeAb, and reproductive).
  - PBMC analysis.
  - Quantitative PCR (HBV DNA, HDV RNA).
  - Genotypic analysis of sequences of large HDV antigen.
- Obtain urine sample for pregnancy test for women of childbearing capacity.
- Obtain urine sample for urinalysis.
- Inquire about AEs.

**Start of Study Treatment:**

- Instruct patients how to administer study drug; provide patient information sheet and patient diary.
- Dispense 2-week supply of study drugs. Start dosing on Day 1.

### 4.2.3 Treatment Visit – Week 1, Day 8 (±2 Days)

All Day 8 procedures must be performed before administration of study treatment.

- Review concomitant medications.
- Conduct brief physical examination.

- Record ECGs (12-lead, serial ECGs in triplicate 2 to 3 minutes apart). Patients should rest in a supine position for ≥5 minutes before the ECG recording is made.
- Measure vital signs (heart rate, blood pressure, respiratory rate, and body temperature) and weight. Blood pressure and heart rate should be measured after 5 minutes in a sitting position.
- Obtain blood samples for
  - Clinical laboratory assessments, including hematology, serum chemistries, serologic tests (HBsAg).
  - Quantitative PCR (HBV DNA, HDV RNA).
  - Genotypic analysis of sequences of large HDV antigen (analyzed only in case of viral load rebound).
- Inquire about AEs.
- Review patient diary and review instructions on administration of study drugs.
- Review bottles of study drugs for drug accountability; return bottles to patient.

### 4.2.4 Treatment Visit – Week 2, Day 15 (±2 Days)

All Day 15 procedures must be performed before administration of study treatment.

- Review concomitant medications.
- Conduct brief physical examination.
- Record ECGs (12-lead, serial ECGs in triplicate 2 to 3 minutes apart). Patients should rest in a supine position for ≥5 minutes before the ECG recording is made.
- Measure vital signs (heart rate, blood pressure, respiratory rate, and body temperature) and weight. Blood pressure and heart rate should be measured after 5 minutes in a sitting position.
- Obtain blood samples for
  - Clinical laboratory assessments, including hematology, serum chemistries, serologic tests (HDV, HBsAg).
  - PBMC analysis.
  - Quantitative PCR (HBV DNA, HDV RNA).
  - Genotypic analysis of sequences of large HDV antigen (analyzed only in case of viral load rebound).
  - Trough PK measurement
- Obtain urine sample for urinalysis.
- Inquire about AEs.
- Review patient diary and remind patients how to administer study drugs.
- Review returned bottles of study drugs for drug accountability.
- Dispense 2-week supply of study drugs.

### 4.2.5 Treatment Visits – Weeks 4 and 6, Days 29 and 43 (±2 Days)

All Day 29 and 43 procedures must be performed before administration of study treatment.

- Review concomitant medications.
- Conduct brief physical examination.
- Record ECGs (12-lead, serial ECGs in triplicate 2 to 3 minutes apart). Patients should rest in a supine position for ≥5 minutes before the ECG recording is made.
- Measure vital signs (heart rate, blood pressure, respiratory rate, and body temperature) and weight. Blood pressure and heart rate should be measured after 5 minutes in a sitting position.
- Obtain blood samples for
  - Clinical laboratory assessments, including hematology, serum chemistries, serologic tests (HDV, HBsAg and reproductive).
  - PBMC analysis (Week 4 only).
  - Quantitative PCR (HBV DNA, HDV RNA).
  - Genotypic analysis of sequences of large HDV antigen.
  - Trough PK measurement

- Obtain urine sample for pregnancy test for women of childbearing capacity.
- Obtain urine sample for urinalysis.
- Inquire about AEs.
- Evaluate patients for dose escalation.
- Review patient diary and remind patients how to administer study drugs.
- Review returned bottles of study drugs for drug accountability.
- Dispense 2-week supply of study drugs.

### 4.2.6 Treatment Visits – Weeks 8, 12, and 16; Days 57, 85, and 113 (±5 Days): PK Sampling

All Day 57, 85, and 113 procedures *except* postdose PK blood sample collection must be performed before administration of study treatment.

- Review concomitant medications.
- Conduct brief physical examination.
- Record ECGs (12-lead, serial ECGs in triplicate 2 to 3 minutes apart). Patients should rest in a supine position for ≥5 minutes before the ECG recording is made.
- Measure vital signs (heart rate, blood pressure, respiratory rate, and body temperature) and weight. Blood pressure and heart rate should be measured after 5 minutes in a sitting position.
- Obtain blood samples for
  - Clinical laboratory assessments, including hematology, serum chemistries, serologic tests (HDV, HBsAg, reproductive).
  - PBMC analysis (Week 12 only ).
  - Quantitative PCR (HBV DNA, HDV RNA).
  - Genotypic analysis of sequences of large HDV antigen (analyzed only in case of viral load rebound).
- Obtain urine sample for pregnancy test for women of childbearing capacity.
- Obtain urine sample for urinalysis.
- Obtain blood samples for either trough or full PK analysis. If the patient has been on a stable dose for the previous 2 weeks, samples for full PK analysis should be obtained at the following time points: within 30 minute before the first dose of drug, and 0.5, 1, 2, 3, 4, 6, 8,10 and 12 hours. The second daily dose of drug should not be taken until after the 12 hour time point. If the patient has not been at a stable dose for the 2 weeks before the study visit, obtain a single trough sample, and conduct full PK sampling at a future visit, after the patient has been on a stable dose for at least 2 weeks.
- Inquire about AEs.
- Review patient diary and remind patients how to administer study drugs.
- Review returned bottles of study drugs for drug accountability.
- Dispense 4-week supply of study drugs.

### 4.2.7 Treatment Visit – Week 20; Day 141 (±5 Days)

All Day 141 procedures must be performed before administration of study treatment.

- Review concomitant medications.
- Conduct brief physical examination.
- Record ECGs (12-lead, serial ECGs in triplicate 2 to 3 minutes apart). Patients should rest in a supine position for ≥5 minutes before the ECG recording is made.
- Measure vital signs (heart rate, blood pressure, respiratory rate, and body temperature) and weight. Blood pressure and heart rate should be measured after 5 minutes in a sitting position.
- Obtain blood samples for
  - Clinical laboratory assessments, including hematology, serum chemistries, serologic tests (HDV, HBsAg, reproductive).
  - Quantitative PCR (HBV DNA, HDV RNA).
  - Genotypic analysis of sequences of large HDV antigen (analyzed only in case of viral load rebound).
- Obtain urine sample for pregnancy test for women of childbearing capacity.
- Obtain urine sample for urinalysis.
- Inquire about AEs.
- Review patient diary and remind patients how to administer study drugs.
- Review returned bottles of study drugs for drug accountability.
- Dispense 4-week supply of study drugs.

### 4.2.8 Treatment Visit – Week 24, Day 169 (±5 Days): End of Treatment Period

All Day 169 procedures must be performed before administration of study treatment.

- Review concomitant medications.
- Conduct brief physical examination.
- Conduct genital examination.
- Conduct ophthalmic examination and obtain retinal photographs.
- Record ECGs (12-lead, serial ECGs in triplicate 2 to 3 minutes apart). Patients should rest in a supine position for ≥5 minutes before the ECG recording is made.
- Measure vital signs (heart rate, blood pressure, respiratory rate, and body temperature) and weight. Blood pressure and heart rate should be measured after 5 minutes in a sitting position.
- Conduct Fibroscan (patients must fast for at least 3 hours before the Fibroscan is performed).
- Obtain blood samples for
  - Clinical laboratory assessments, including hematology, serum chemistries, serologic tests (HDV, HBsAg, HBeAb, HBeAg, reproductive), prothrombin time and INR.

  - PBMC analysis.
  - Quantitative PCR (HBV DNA, HDV RNA).
  - Genotypic analysis of sequences of large HDV antigen (analyzed only in case of viral load rebound).
- Obtain urine sample for pregnancy test for women of childbearing capacity.
- Obtain urine sample for urinalysis.
- Inquire about AEs.
- Collect and review patient diary.
- Review returned bottles of study drugs for drug accountability.

### 4.2.9 Follow-up Visit – Week 28, Day 197 (±5 Days)

- Review concomitant medications.
- Conduct brief physical examination.
- Record ECGs (12-lead, serial ECGs in triplicate 2 to 3 minutes apart). Patients should rest in a supine position for ≥5 minutes before the ECG recording is made.
- Measure vital signs (heart rate, blood pressure, respiratory rate, and body temperature) and weight. Blood pressure and heart rate should be measured after 5 minutes in a sitting position.
- Obtain blood samples for
  - Clinical laboratory assessments, including hematology, serum chemistries, serologic tests (HDV, HBsAg, reproductive), prothrombin time and INR.
  - Quantitative PCR (HBV DNA, HDV RNA).
  - Genotypic analysis of sequences of large HDV antigen (analyzed only in case of viral load rebound).
  - PBMC analysis
- Obtain urine sample for pregnancy test for women of childbearing capacity.
- Obtain urine sample for urinalysis.
- Inquire about AEs.

### 4.2.10 Follow-up Visits – Weeks 32, 36, 40, 44, and 48; Days 225, 253, 281, 309, and 337 (±5 Days)

- Review concomitant medications.
- Conduct brief physical examination.
- Record ECGs (12-lead, serial ECGs in triplicate 2 to 3 minutes apart). Patients should rest in a supine position for ≥5 minutes before the ECG recording is made.
- Measure vital signs (heart rate, blood pressure, respiratory rate, and body temperature) and weight. Blood pressure and heart rate should be measured after 5 minutes in a sitting position.
- Obtain blood samples for

  - Clinical laboratory assessments, including hematology, serum chemistries, serologic tests (HDV, HBsAg, reproductive), prothrombin time and INR.
  - Quantitative PCR (HBV DNA, HDV RNA).
  - Genotypic analysis of sequences of large HDV antigen (analyzed only in case of viral load rebound).
  - PBMC analysis (Weeks 36 & 48 only)
- Obtain urine sample for pregnancy test for women of childbearing capacity.
- Obtain urine sample for urinalysis.
- Inquire about AEs.

### 4.2.11 Unscheduled Visits

Unscheduled visits may occur as needed, for example, to assess a viral or hepatic flare, during the study. The following procedures should be performed during an unscheduled visit:

- Review concomitant medications.
- Conduct brief physical examination.
- Record ECGs (12-lead, serial ECGs in triplicate 2 to 3 minutes apart). Patients should rest in a supine position for ≥5 minutes before the ECG recording is made.
- Measure vital signs (heart rate, blood pressure, respiratory rate, and body temperature) and weight. Blood pressure and heart rate should be measured after 5 minutes in a sitting position.
- Obtain blood samples for
  - Clinical laboratory assessments, including hematology, serum chemistries, serologic tests (HDV, HBsAg, reproductive), prothrombin time and INR.
  - Quantitative PCR (HBV DNA, HDV RNA).
  - Genotypic analysis of sequences of large HDV antigen (analyzed only in case of viral load rebound).
- Obtain urine sample for pregnancy test for women of childbearing capacity.
- Obtain urine sample for urinalysis.
- Inquire about AEs.
- Review returned bottles of study drugs for drug accountability if patient is on study treatment.
- Review patient diary if unscheduled visit occurs during the Treatment Period.

### 4.2.12 Early Termination Visit

The following procedures should be performed if the patient discontinues treatment early:

- Review concomitant medications.
- Conduct brief physical examination.
- Conduct genital examination.

- Record ECGs (12-lead, serial ECGs in triplicate 2 to 3 minutes apart). Patients should rest in a supine position for ≥5 minutes before the ECG recording is made.
- Measure vital signs (heart rate, blood pressure, respiratory rate, and body temperature) and weight. Blood pressure and heart rate should be measured after 5 minutes in a sitting position.
- Obtain blood samples for
  - Clinical laboratory assessments, including hematology, serum chemistries, serologic tests (HDV, HBsAg, reproductive), prothrombin time and INR.
  - PBMC analysis.
  - Quantitative PCR (HBV DNA, HDV RNA).
  - Genotypic analysis of sequences of large HDV antigen (analyzed only in case of viral load rebound).
- Obtain urine sample for pregnancy test for women of childbearing capacity.
- Obtain urine sample for urinalysis.
- Inquire about AEs.
- Collect and review patient diary if visit occurs during the Treatment Period.
- Opthalmic exam if patient discontinues treatment between weeks 12-24.

# 5 STATISTICAL CONSIDERATIONS

## 5.1 Analysis Objectives and Endpoints

The purpose of this study is to evaluate the safety and tolerability of the dose-titration regimen of lonafarnib in combination with ritonavir over the 24-week treatment period. In addition, the PD activity (ie, change in HDV viral load) of the lonafarnib/ritonavir dose-titration regimen over the 24-week Treatment Period will be evaluated.

Secondary evaluations will include the effect the lonafarnib/ritonavir dose-titration regimen on PK characteristics, ALT levels, and HBV DNA levels. Exploratory evaluations will include the effects of the lonafarnib/ritonavir dose-titration regimen on immunologic parameters during treatment.

## 5.2 Determination of Sample Size

A sample size of 15 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 tolerability to the same administered dose. In this study of approximately 15 patients, the probability of at least one patient experiencing an event with a true incidence rate of 1/100 is 14%, and the probability of at least one patient experiencing an event with a true incidence rate of 5/100 is 54%.

## 5.3 Analysis Populations

The safety population will consist of all patients who receive at least one dose of study drug.

The primary PD/efficacy population 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.

The PK population will 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.

## 5.4 Hypothesis Testing

No hypothesis will be tested during this clinical trial.

## 5.5 Analysis Plan

### 5.5.1 Demographic and Baseline Data

Descriptive statistics will be used to summarize demographic and baseline patient characteristics. Continuous-scaled variables (eg, age) will be summarized with means, medians, standard deviations, quartiles, and minimum and maximum values. Categorical variables (eg, sex) will be summarized using patient counts and percentages.

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

Medications taken after informed consent is signed and before randomization will be summarized by treatment group, based on mapping to drug classes and generic terms in the WHO Drug Dictionary.

### 5.5.2 Safety Analyses

A primary goal of this study is to evaluate the tolerability of the lonafarnib/ritonavir dose-titration regimen. The safety endpoints are as follows:

- Treatment-emergent AEs
- Treatment-emergent SAEs
- Treatment-emergent treatment-related AEs
- Treatment-emergent treatment-related SAEs and deaths
- AEs leading to early discontinuation of study treatment
- AEs leading to dose reduction
- Treatment-emergent changes in clinical laboratory findings and ECGs

AEs will be mapped to system organ classes and preferred terms in MedDRA. 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. TEAEs will be summarized by dose level, system organ class, and preferred term, and also by event severity and by 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. AEs will also be listed for individual patients, along with information regarding onset, duration, severity, and relationship to study drug. SAEs and AEs that lead to withdrawal from the study will be listed by individual patients. Events with missing severity will be classified as Grade 3; events with missing attribution will be classified as related to study drug.

Clinical laboratory data will be summarized at each measurement time point and for each patient's final postbaseline 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 postbaseline 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.

Actual values for vital signs and changes from baseline will be summarized and listed for each patient. No inferential statistics are planned for safety data. 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.

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).

### 5.5.3 Pharmacodynamics/Efficacy

Pharmacodynamic data will be presented by dose level in summary tabulations and listings that will display viral load data at each period/time point collected by patient. These data will also be presented graphically. Mean and median levels and change from baseline of the viral load 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 and 1 log reductions from baseline will be summarized at each time point. The number of patients with reduction in viral load below the limit of quantitation and the limit of detection will be summarized.

Results below the level of detection will be imputed as half the lower limit of detection (500 IU/mL).

Missing data will not be imputed. All summaries and figures will show the number of non-missing data at each visit.

### 5.5.4 Pharmacokinetics

The PK parameters listed in Table 8 will be derived from plasma concentrations for lonafarnib and ritonavir.

**Table 8 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:<br>dose/ $AUC_{0-\infty}$<br>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 $0.693/K_{el}$. |

Protocol-scheduled times will be used in the PK analyses 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 9.

**Table 9 Time Windows for Collection of Pharmacokinetic Samples**

| Nominal Time | Reporting Standards |
|---|---|
| Predose | Within 30 minutes before first dose |
| 0.0–2.0 hours | ≤ ±1 minute |
| >2.0–8.0 hours | ≤ ±2 minutes |
| >8.0-12 hours | ≤ ±5 minutes |

A noncompartmental method will be used to derive the PK parameters for lonafarnib and ritonavir. Additional PK parameters using noncompartmental methods may also be used if data permit. Plasma concentrations of lonafarnib and ritonavir and the generated PK parameters will be summarized descriptively by dose level and by patient. 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 may be performed include linearity and dose proportionality across the different lonafarnib dose levels. These analyses will be conducted for patients who receive titrated doses. 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.

### 5.5.5 Viral Resistance Analysis

Screening visit and baseline serum samples will be collected from all patients for HDV genotypic analysis to determine HDV subtypes (1–8) and to understand natural genetic polymorphisms of HDV.

For resistance surveillance, genotypic analysis of large HDV antigen 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. In vitro phenotypic analysis may be explored as necessary.

# 6 SAFETY EVENTS DOCUMENTATION AND REPORTING

## 6.1 Investigator's Responsibilities

Investigators are responsible for monitoring the safety of patients who have entered this study and for providing appropriate medical care. In addition, the Investigators are responsible for alerting Eiger BioPharmaceuticals or its designee to any event that seems unusual, even if the event may be considered an unanticipated benefit to the patient, and for reporting the event on the appropriate case report form (CRF) or safety report form.

A serious adverse event (SAE) should be reported to Eiger BioPharmaceuticals or its designee within 24 hours after becoming aware of its occurrence. Investigators must report all SAEs to their governing IEC as required by local regulations and guidelines. The Investigator is responsible for reporting the relationship to study drug for each adverse event (AE).

By exercising appropriate health-care options, the Investigator remains responsible for managing AEs that are serious or that cause the patients to withdraw before completing the study. Frequency of follow-up of any particular AE is left to the discretion of the Investigator. Duration of follow-up and requirements for *immediate* SAE reporting (within 24 hours of the event) are described below.

## 6.2 Monitoring Safety Data During Study

Safety results collected during the study (eg, AEs, laboratory test results, physical findings, ECGs) will be monitored on an ongoing basis by the Medical Monitor and Investigator.

## 6.3 Definitions of Types of Adverse Events

### 6.3.1 Adverse Events

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.

### 6.3.2 Suspected Adverse Reactions

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of investigational new drug (IND) or Investigational Medicinal Product (IMP) safety reporting, ‘‘reasonable possibility’’ means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

### 6.3.3 Life-Threatening Adverse Events

An AE or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not

include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### 6.3.4 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 (see Section 6.3.3)
- 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.

### 6.3.5 Unexpected Adverse Event

An AE or suspected adverse reaction is considered ‘‘unexpected’’ if it meets any of the following criteria:

- It is not listed in the Investigator’s Brochure or is not listed at the specificity or severity that has been observed.
- If an Investigator Brochure is not required or available, it is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.
- If it is not listed in the Summary of Product Characteristics for Norvir® [ritonavir] tablets, (2014)

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator’s Brochure listed only cerebral vascular accidents.

‘‘Unexpected,’’ as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator’s Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

## 6.4 Adverse Event Classification

### 6.4.1 Severity Grades of Adverse Events and Serious Adverse Events

The seriousness of an AE should not be confused with its intensity (severity). To describe the maximum intensity of the AE on the AE CRF, the Investigator will use the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 (CTCAE 2010). For events not listed in the CTCAE, the definitions from the CTCAE provided in Table 10 should be used to evaluate the grade of severity for the AE.

**Table 10 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 (CTCAE 2010)

### 6.4.2 Relationship of Adverse Event to Investigational Products

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 11. For a particular AE, the Investigator will assess both the relationship to lonafarnib and the relationship to ritonavir.

**Table 11 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 |

## 6.5 Documentation of Adverse Events

Patients will be evaluated and questioned generally to identify AEs during the study. Any events occurring before administration of the first dose of study drug will be recorded on the Medical History CRF. Events occurring after administration of the first dose of study drug will be recorded on the AE CRF. Adverse events that occur up to and including 28 days after administration of the last dose of study drug will be considered treatment-emergent AEs. Any AEs reported more than 28 days after the last dose of study drug will be considered posttreatment AEs.

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the AE CRF for that visit. Any clinically relevant deterioration in laboratory assessments or other clinical findings will be considered an AE and must be recorded on the AE CRF. In addition, an abnormal test finding will be classified as an AE if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention, including significant additional concomitant drug treatment or other therapy. Note: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE.
- The test finding leads to a change in study drug dosing or discontinuation of patient participation in the clinical research study.
- The test finding is considered an AE by the Investigator.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE. Laboratory data are to be collected as stipulated in this protocol.

Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (eg, diabetes mellitus rather than hyperglycemia).

For SAEs, an SAE Form must also be completed with as much information as possible and submitted in the time frame described in Section 6.6.1. When new significant information is obtained as well as when the outcome of an event is known, the Investigator should record the information on a new SAE Form. If the patient was hospitalized, then a copy of the discharge summary and any other relevant hospital records (eg, admission report, laboratory test results) must be included as part of the patient medical file.

All AEs considered to be related (definitely or probably related, see Section 6.4.2) to study drug and all SAEs will be followed until resolved or until a stable status has been achieved.

### 6.5.1 Study Drug Action Taken

The action taken for each study drug should be classified according to the categories shown in Table 12.

**Table 12 Classifications for Study Drug Action Taken with Regard to an Adverse Event**

| Action | Definition |
|---|---|
| Drug interrupted | Study drug administration interrupted in response to an AE. |
| Drug withdrawn | Study drug administration permanently discontinued in response to an AE |
| Dose not changed | Study drug dose not changed in response to the AE. |
| Dose reduced | Study drug dose reduced in response to an AE. |
| Not applicable | Action taken regarding study drug administration does not apply. “Not applicable” should be used in circumstances such as when the investigational treatment had been completed before the AE began and no opportunity to decide whether to continue, interrupt or withdraw treatment is possible. |
| Unknown | Action taken is unknown (eg,, a patient hospitalized at a hospital not under the case of the Investigator and the Investigator has no knowledge whether study drugs were continued or not). |

### 6.5.2 Outcome of Adverse Event

The outcome should be classified according to the categories shown in Table 13. All AEs considered to be related (definitely or probably related, see Section 6.4.2) to study drug and all SAEs will be followed until resolved or until a stable status has been achieved.

**Table 13 Classifications for Outcome of an Adverse Event**

| Outcome | Definition |
|---|---|
| Recovered/resolved | Resolution of an AE with no residual signs or symptoms. |
| Recovered/resolved with sequelae | Resolution of an AE with residual signs or symptoms. |
| Not recovered/not resolved (continuing) | Either incomplete improvement or no improvement of an AE, such that it remains ongoing. |
| Fatal | Outcome of an AE is death. "Fatal" should be used when death is at least possibly related to the AE. |
| Unknown | Outcome of an AE is not known. e.g. a patient lost to followup |

## 6.6 Reporting Serious Adverse Events

### 6.6.1 Reporting to Sponsor

All SAEs that occur during the study must be reported by the Investigator to the Sponsor and to the Medical Monitor within 24 hours via eCRF, facsimile (ie, fax) or email. The SAE Form should be submitted within 1 working day from the point in time when the Investigator becomes aware of the SAE. In addition, all SAEs that occur up to and including 1 month (28 days) after administration of the last dose of study drug must be reported to the Sponsor within 1 working day from when the Investigator becomes aware of the SAE. Any SAEs reported more than 1 month (28 days) after the last dose of study drug will be considered posttreatment SAEs.

Investigators must report to the Sponsor any SAE, whether or not considered drug related, including those listed in the protocol or Investigator Brochure. The report must include an assessment of causality.

For all SAEs, the Investigator is obligated to obtain and provide information to the Sponsor in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE CRF. In general, this information will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the AE, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designated representative.

SAE reporting contact information:

Eduardo Martins, MD, DPhil
SVP, Liver and Infectious Diseases
Eiger BioPharmaceuticals, Inc.
350 Cambridge Avenue, Suite 350
Palo Alto, CA 94306 USA
Telephone: +1-650-867-7111
Fax: +1-650-618-1608
email address: eigersafety@eigerbio.com

Alternate:

Shelly Xiong, PhD
Vice President, Regulatory Affairs
Eiger BioPharmaceuticals, Inc.
350 Cambridge Avenue, Suite 350
Palo Alto, CA 94306 USA
Telephone: +1-408-230-1668
Fax: +1-650-618-1608
email address: eigersafety@eigerbio.com

### 6.6.2 Reporting to Regulatory Agencies and Independent Ethics Committee

If there is a suspected, unexpected, serious adverse reaction (SUSAR), the Sponsor or designee will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis.

It is the responsibility of the Investigator to promptly notify the IEC of all SUSARs involving risk to patients.

### 6.6.3 Emergency Contact

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a patient, operation of the clinical study, and/or the use of investigational product), study site personnel will apply appropriate medical intervention according to current standards of care and contact the Medical Monitor :

Frank Tschubar, MD
Cato Europe GmbH
Hertzstrasse 7
50859 Cologne,
Germany
Telephone: +49-2234-37944-10
Fax: +49-2234-37944-25
Email: f.tschubar@cato-europe.com

## 6.7 Pregnancy

The patient will be instructed to notify the Investigator if the patient or the patient's partner becomes pregnant during the study. The Investigator must notify the Sponsor or designee within 24 hours via fax or e-mail and must complete the Pregnancy Notification Form and submit it to the Sponsor within 1 working day of being notified. The Investigator should obtain informed consent from the patient or the patient's partner allowing the Investigator to obtain information regarding the pregnancy and its outcome, and record the informed consent in the patient's source documents. If the patient or the patient's partner provides informed consent, the Investigator should follow the pregnancy until outcome. A final Pregnancy Notification Form should be completed when the outcome of the pregnancy is known.

## 6.8 Overdose

### 6.8.1 Lonafarnib Overdose

A small number of cancer patients in clinical trials have received an overdose of lonafarnib as a single agent or in combination therapy. The highest dosage was 800 mg/day. The resulting AEs (anorexia, fatigue, diarrhea, vomiting, dehydration, and AST and ALT elevation) were expected and known to be associated with lonafarnib when administered at the recommended dose. Given the limited experience with overdoses with this drug, it is recommended that general supportive measures and close monitoring of blood counts, electrolytes, and renal function be employed. It is unknown if lonafarnib binds to activated charcoal. As lonafarnib is absorbed slowly, induction of emesis or administration of activated charcoal may limit absorption of drug from the GI tract. There is no evidence of abuse potential based on the nonclinical pharmacology of lonafarnib.

### 6.8.2 Ritonavir Overdose

**Human Experience—**According to the prescribing information for ritonavir (Prescribing Information for Norvir® [ritonavir] Tablets, 2015; Summary of Product Characteristics for Norvir® [ritonavir] tablets, 2014), human experience of acute overdose with ritonavir is limited. One patient in clinical trials took ritonavir 1500 mg per day for 2 days. The patient reported paresthesias which resolved after the dose was decreased. A postmarketing case of renal failure with eosinophilia has been reported with ritonavir overdose. The approximate lethal dose was found to be greater than 20 times the related human dose in rats and 10 times the related human dose in mice.

**Management—**According to the prescribing information for ritonavir (Prescribing Information for Norvir® [ritonavir] Tablets, 2015; Summary of Product Characteristics for Norvir® [ritonavir] tablets, 2014), treatment of overdose with ritonavir consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with ritonavir. If indicated, elimination of unabsorbed drug should be achieved by gastric lavage; usual precautions should be observed to maintain the airway. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since ritonavir is extensively metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug. A Certified Poison Control Center should be consulted for up-to-date information on the management of overdose with ritonavir.

# 7 DATA QUALITY CONTROL AND ASSURANCE

## 7.1 Overview

The Sponsor is responsible for implementing and maintaining quality assurance (QA) and quality control (QC) systems with written standard operating procedures (SOPs). Accurate, consistent, and reliable data will be ensured through the use of standard Good Clinical Practices (GCPs). Local monitors and representatives of the Sponsor will monitor the study for compliance with appropriate regulations, International Conference on Harmonisation (ICH) and GCP guidelines, and requirements of individual countries.

The Investigator at each investigational site is responsible for the quality of all study data from that site. This includes but is not limited to adherence to the study protocol and study procedure manual, review of the results of all study evaluations to ensure quality, and accurate data entry. A list of individuals who will have key positions in this study will be saved in the Trial Master File. This list will include names, titles, and roles of selected individuals from the Sponsor and the contract research organization (CRO) that will contribute to this study.

Quality control will be applied to each stage of data handling. The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting
- Site initiation visit
- Routine site monitoring
- Ongoing site communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data

In addition, the Sponsor's or its designee's Clinical QA Department may conduct periodic audits of the study processes, including but not limited to study site, site visits, vendors, and clinical database. When audits are conducted, the Sponsor's representatives and authorized regulatory representatives must be allowed access to all study-related documents, including medical history and concomitant medication documentation. If the site is informed of an inspection by any regulatory authority, the Investigator should notify the Sponsor immediately.

## 7.2 Study Monitoring

The Sponsor has engaged the services of a CRO to perform all monitoring functions for this clinical study. Monitors will work in accordance with Sponsor's and CRO's SOPs and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator or a designee and the Sponsor.

Monitors will evaluate the competence of each study site, informing the Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study, monitors will

- Check that written informed consent has been correctly obtained from each patient in the study
- Data are recorded correctly and completely on the CRFs
- Compare entries in CRFs with corresponding source data and inform the Investigator or a designee of any errors or omissions
- Review adherence to the protocol and to regulatory requirements at the study site and discuss and deviations noted with the Investigator or a designee.

Monitors will arrange for the study site to receive an adequate supply of investigational products and ensure that appropriate storage conditions are maintained.

Monitoring visits will be conducted according to the US CFR Title 21 parts 50, 56, and 312; EU_Directive 2005/28/EC; and International Conference on Harmonisation (ICH) Guideline for GCP. The monitor will submit written reports to the Sponsor following each contact with the Investigator or a designee, regardless of whether it is by phone or in person.

## 7.3 Data Management

Study data will be handled according to the relevant SOPs of the data management and biostatistics departments of the Sponsor or CRO.

## 7.4 Quality Assurance Audit

Study sites, the study database, and study documentation may be subject to a QA audit during the study by the Sponsor or its designee on behalf of the Sponsor. In addition, inspections may be conducted by regulatory agencies at their discretion.

## 7.5 Data Handling and Recordkeeping

### 7.5.1 Case Report Form Completion

Case report forms will be completed for each patient enrolled in the study. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's CRF. Source documentation supporting the CRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status. Study monitors will discuss instances of missing or uninterpretable data with the Investigator for resolution. Any changes to study data will be made to the CRF according to SOP specifications.

For patients who discontinue treatment or withdraw from the study, the CRFs will be completed as much as possible, and the reason for the discontinuation or withdrawal clearly and concisely specified on the appropriate CRF.

If electronic CRFs (eCRFs) are used, data will be entered into the CRF by site personnel using a secure, validated web-based electronic data capture (EDC) application. Any data not entered by the site will be entered into an eCRF by trained data entry staff using a secure, validated, web-based EDC application. The Sponsor will have access to all data on entry in the EDC application.

### 7.5.2 Data Handling

If data are transformed during processing, records will be maintained so that it will be possible to compare the original data and observations with the processed data.

An unambiguous patient identification code will be used that allows identification of all the data reported for each patient.

### 7.5.3 Study Files and Retention of Study Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential study documents (protocol and protocol amendments, completed CRFs, signed ICFs, relevant correspondence, and all other supporting documentation) must be maintained until at least 15 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 15 years after the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Patient identification codes (patient names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator or designee must contact the Sponsor before disposing of any study records.

Biological samples at the conclusion of this study may be retained in storage by the Sponsor for a period up to 10 years. Samples may be retained for future determination of active metabolite concentrations, HDV and HBV analyses, and host DNA analyses of polymorphisms that may impact drug response (refer to Section 8.4 for information regarding written informed consent for permission to retain the samples).

## 7.6 Drug Accountability

It is the responsibility of the Investigator to maintain drug accountability at the study site and ensure that a current record of investigational product disposition is maintained. It is the responsibility of the Investigator to ensure that the investigational product is used only in accordance with the approved protocol. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from Eiger BioPharmaceuticals and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the drug. At the end of the study, after final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to standard procedures.

In this study, drug accountability will be ascertained through assessment of the study drug both dispensed and returned at each study visit during the Treatment Period, as well as review of the patient diary. Patients will be instructed to bring any bottles of study drug and the patient diary to each study visit during the Treatment Period.

# 8 ETHICAL AND LEGAL CONSIDERATIONS

## 8.1 Ethical Conduct and Good Clinical Practice

This study will be conducted in compliance with GCP as described in the ICH document "Guidance for Industry—E6 Good Clinical Practice: Consolidated Guidance," dated June 1996. These practices are consistent with the principles stated in the Declaration of Helsinki (version as currently endorsed by the European Medicines Evaluation Agency and the US FDA). The study will also be performed in keeping with local legal and regulatory requirements of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a United States Investigational New Drug (IND) application, the Investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in the US Code of Federal Regulations (CFR) Title 21, Part 312 Subpart D "Responsibilities of Sponsors and Investigators", Part 50 "Protection of Human Subjects", and Part 56 "Institutional Review Boards" are adhered to. For studies conducted in the EU the GCP requirements are outlined in Directive 2005/28/EC. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical trial, the Investigator will ensure that 21 CFR, Part 54 "Financial Disclosure by Clinical Investigators", is adhered to. A "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that Investigators and all subinvestigators must provide documentation of their financial interest or arrangements with Eiger BioPharmaceuticals, or proprietary interests in the drug being studied. This documentation must be provided before participation of the Investigator and any subinvestigator. The Investigator and subinvestigator agree to notify Eiger BioPharmaceuticals of any change reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol defined activities.

## 8.2 Independent Ethics Committee

All IECs will meet all FDA requirements governing Investigational Review Boards (21 CFR Part 56 "Institutional Review Boards") and the EU requirements outlined in Directive 2001/20/EC.

The protocol and informed consent forms that will be used must be approved by the IEC before the study is initiated; documentation of this approval (ie, a copy of the document showing IEC approval including the chairperson's signature and the date of approval) must be provided to the Sponsor or its designee and made available during an inspection by regulatory agency inspectors.

Other Investigator responsibilities relative to the IEC's requirements include the following:

- Submit to the IEC/IRB and to the Sponsor or its designee for review any advertisements that will be used to recruit patients or any other relevant materials intended or directed to patients
- During the conduct of the study, submit timely and accurate progress reports to the IEC/IRB, if required, and request re-review of the study at least once a year

- Report, in writing, to the IEC/IRB any SAEs that occur during the study or SAEs reported in other studies using pirfenidone, per local IEC/IRB regulations
- Inform the IEC/IRB of any changes in the protocol and obtain documented IEC/IRB approval of the changes
- Provide the IEC/IRB with any other information it requests before or during the conduct of the study
- Maintain a file of study-related information, including all correspondence with the IEC/IRB

## 8.3 Patient and Data Confidentiality

**Patient Data--**The Investigator must ensure that the patient's confidentiality is maintained. All CRFs, study drug accountability records, study reports, and communications will identify the patient by the assigned patient number. Patients should not be identified by name, social security number, or medical record number on any documents or materials (samples, slides) sent to Eiger BioPharmaceuticals or its representatives (eg, data management organization) or during verbal communications. The Investigator will maintain a list of patient identification numbers and names to enable identification of patient records. Only the patient's identification number and initials will be recorded in the CRFs, and if a patient's name appears on any other document, it must be obliterated on copies provided to the Sponsor.

The patients will be informed in writing that representatives of the Sponsor, IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations. If results of the study are published, subject identity will remain confidential.

**Other Study Information—**All information regarding the investigational product supplied by the Sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of the investigational product and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

## 8.4 Informed Consent

The Investigator or designee is responsible for the content of the informed consent form (ICF), but the content must be approved by the IEC/IRB and the Sponsor or designee. The content of the ICF must comply with FDA regulations (21 CFR Part 50.25), Directive 2001/20/EC, and the ICH document "Guidance for Industry—E6 Good Clinical Practice: Consolidated Guidance," dated June 1996. It should also include any additional information required by local laws relating to institutional review. The content of the ICF must not be altered without the prior agreement of the relevant IEC and the Sponsor.

The ICF will be used to explain the risks and benefits of study participation in simple terms before the patient will be entered into the study. The ICF will contain a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time. The ICF must include information about the possible retention of biological samples at the conclusion of this study; with the patient's permission, samples may be retained for future determination of active metabolite concentrations, HDV and HBV analyses and host DNA analyses of polymorphisms that may impact drug response.

The Investigator is responsible for obtaining written informed consent from each patient participating in the study. If there are amendments to the ICF, patients should be re-consented in a timely fashion. Informed consent must be obtained from the patient before any screening activity or treatment is undertaken that is not part of routine care. This includes, but is not limited to, the performance of diagnostic or therapeutic procedures and the administration of the first dose of the study drug. Before a patient's participation in the study, the written ICF should be signed and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion.

The ICF must be written in a language understandable to the patient or to his or her representative. The Investigator is responsible for keeping the original signed and dated ICF in a secure place. A signed and dated copy of the ICF must be given to the person signing the document. This document should not be displayed or made accessible to any third party except for Eiger BioPharmaceuticals or regulatory agency representative.

If a patient permanently revokes informed consent, recording of study data will stop.

## 8.5 Protocol Amendments

Protocol amendments should be approved by the Sponsor and the IEC before implementation, except when necessary to eliminate immediate hazards to the patients or when the changes involve only logistical or administrative aspects of the study (eg, change of monitor, telephone numbers). In this case, the Sponsor will amend and implement the protocol change and subsequently notify the regulatory authorities and/or the IEC, as appropriate.

## 8.6 Delegation of Responsibilities of the Principal Investigator

The Investigator should ensure that all persons involved in the conduct of the study are informed about the protocol, protocol amendments, study procedures, and any study-related duties. The Principal Investigator (PI) is also responsible for ensuring that the study is being conducted by qualified personnel. Documentation of these qualifications must be retained with the Regulatory Binder.

Any study-related responsibilities that are delegated to a subinvestigator or other person should be clearly documented in the Delegation of Authority Log. The designee should be appropriately trained and where necessary certified or licensed to perform the task.

## 8.7 Coordinating Investigator

The Principal Investigator will be responsible for signing the final clinical study report and assuring that the study has been executed according to the protocol.

## 8.8 Compensation, Insurance, and Indemnity

Information regarding compensation, insurance, and indemnity will be provided to the Investigator in a separate document.

## 8.9 Publication Policy

The data generated by this study are considered confidential information and the property of Sponsor and shall not be published or disclosed without the prior written consent of Sponsor.

## 8.10 Direct Access to Source Data

The Investigator/institution and study site will permit study-related monitoring, audits, IEC review, and regulatory inspections as requested by regulatory authorities and the Sponsor or its designee, including direct access to source data/documents (eg, original medical records, laboratory reports, hospital documents, progress reports, and signed ICFs) in addition to CRFs..

The Investigator or a designee will prepare and maintain adequate and accurate source documents to support all observations and other pertinent data recorded on the CRFs for patient enrolled in the study.

# 9 REFERENCES

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Yurdaydin C, Idilman R, Choong I, Kalkan C, Keskin O, Karakaya MF, et al. 2015. Optimizing the prenylation inhibitor lonafarnib using ritonavir boosting in patients with chronic delta hepatitis. J Hepatology. Suppl 2, vol 62: S252. European Association for the Study of the Liver 50th Annual Meeting 2015, Abstract 0118, oral presentation.

# APPENDIX A 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 | | | X [h] |
| 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 |
| T3, T4, TSH | | 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 | | 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 | | | | | | 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 | | | | | | | | | | |
| Blood alcohol test | | X | | | | | | | | | | |
| PBMC collection [x] | | | X | | X | X | X | | X | X | X | |
| PK sampling [y] | | | | | X | X | X [y] (Collect full PK once at either Wk 8, 12, or 16) | | | | | |
| Evaluate for dose escalation | | | | | | X | | | | | | |
| Dispense study drug [z] | | | X | | X | X | X | X | | | | |
| Study drug administration | | | X | X | X | X | X | X | X | | | |
| Study drug accountability [z] | | | | X | X | X | X | X | X | | | |
| Provide patient diary/patient information sheet | | | X | | | | | | | | | |
| Review patient diary | | | | X | X | X | X | X | X | | | X [aa] |
| 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 as soon as possible 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)
[e] See Section 3.8.2 and Appendix C 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/$m^2$
[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. An early termination visit ophthalmic exam is only required if the early termination occurs between weeks 12 and 24 of the dosing period
[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 cannabinoids, opiates, amphetamines, barbiturates, benzodiazepenes, and cocaine.

[x] PBMC will be drawn at baseline, Weeks 2, 4, 12, 24, 28, 36, and 48.

[y] Collect trough PK blood samples at Weeks 2, 4, 6, 8, 12, and 16. Trough PK sample is collected within 30 minutes prior to study drug administration. At either Week 8, 12, or 16 *if the patient is on a stable dose for the prior 2 weeks,* full PK sampling should be performed. The time points for full 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. On the day that full PK sampling is collected, patients will remain in clinic at least 13 hours. 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. On all days that trough PK sampling is done patients should not take the morning dose; the morning dose should be administered after the trough PK sample is taken. On the day full PK is performed, patients should take the morning dose after the pre-dose PK sample is obtained, and the second dose after the final 12 hour PK sample is obtained. *Note:* For any lonafarnib dose adjustments that occur due to patient tolerability issues (refer to Section 3.6.2), full 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, full PK sampling will be performed at a future visit, after the patient has been on a stable dose for at least 2 weeks.

[z] 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.

[aa] Collect and review the patient diary if the visit occurs during the Treatment Period.

# APPENDIX B 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. Patients with a total CTP score of 7 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 | 1.72–20 | >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

Patients with assessments of stage 1–4 are *not* eligible to participate in this study.

| 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

# APPENDIX C PROHIBITED CONCOMITANT DRUGS OR DRUGS THAT MAY HAVE SIGNIFICANT INTERACTIONS WITH STUDY DRUGS

**Table 14 Drugs That Are Contraindicated with Use of Ritonavir**

| Class | Drug | Clinical Outcome/Rationale |
|---|---|---|
| Alpha$_1$- adrenoreceptor antagonist | Alfuzosin HCL | Potential for hypotension. Increased plasma concentrations of alfuzosin which may lead to severe hypotension |
| Analgesics* | Pethidine*, piroxicam*, propoxyphene* | Increased plasma concentrations of norpethidine, piroxicam and propoxyphene. Thereby, increasing the risk of serious respiratory depression or haematologic abnormalities, or other serious adverse effects from these agents. |
| Antiarrhythmics | Amiodarone, bepridil*, encainide*, flecainide, propafenone, quinidine | Potential for cardiac arrhythmias. Increased plasma concentrations of amiodarone, bepridil, encainide, flecainide, propafenone, quinidine. Thereby, increasing the risk of arrhythmias or other serious adverse effects from these agents. |
| Antibiotic* | Fusidic acid* | Increased plasma concentrations of fusidic acid and ritonavir. |
| Antifungal | Voriconazole | Co-administration of voriconazole with ritonavir 400 mg every 12 hours significantly decreases voriconazole plasma concentrations and may lead to loss of antifungal response. Voriconazole is contraindicated with ritonavir doses of 400 mg every 12 hours or greater |
| Antihistamines* | Astemizole*, terfenadine* | Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents. |
| Antimycobacterial* | Rifabutin* | Concomitant use of ritonavir dosed as an antiretroviral agent (600 mg twice daily) and rifabutin due to an increase of rifabutin serum concentrations and risk of adverse reactions |

| Class | Drug | Clinical Outcome/Rationale |
|---|---|---|
| | | including uveitis (see section 4.4). Recommendations regarding use of ritonavir dosed as a pharmacokinetic enhancer with rifabutin are noted in section 4.5 |
| Antipsychotics*/Neuroleptics | Clozapine*, pimozide | Potential for cardiac arrhythmias. Increased plasma concentrations of clozapine and pimozide. Thereby, increasing the risk of serious haematologic abnormalities, or other serious adverse effects from these agents. |
| | Quetiapine* | Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated |
| Ergot Derivatives | Dihydroergotamine, ergonovine, ergotamine, methylergonovine | Potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system. |
| Gastrointestinal Motility Agent | Cisapride | Increased plasma concentrations of cisapride. Potential for cardiac arrhythmias. |
| Herbal Products | St. John's Wort (hypericum perforatum) | Co-administration of NORVIR with St. John’s Wort may result in decreased ritonavir plasma concentrations and may lead to loss of virologic response and possible resistance to NORVIR or to the class of protease inhibitors. |
| HMG-CoA Reductase Inhibitors: | Lovastatin, simvastatin | Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis |
| PDE5 enzyme inhibitor | Avanafil* | Increased plasma concentrations of avanafil |
| | Sildenafil (Revatio®) only when used for the treatment of pulmonary arterial hypertension (PAH) | A safe and effective dose has not been established when used with ritonavir. There is an increased potential for sildenafil- associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope. |
| | Vardenafil* | Increased plasma concentrations of vardenafil |

| Class | Drug | Clinical Outcome/Rationale |
|---|---|---|
| Sedative/hypnotics | Clorazepate*, diazepam*, estazolam*, flurazepam*, oral midazolam, triazolam | Prolonged or increased sedation or respiratory depression. Thereby, increasing the risk of extreme sedation and respiratory depression from these agents |

Source: Prescribing Information for Norvir® [ritonavir] Tablets, 2015. *Additional terms from the Summary of Product Characteristics for Norvir® [ritonavir] tablets, 2014

## Table 15 Established and Other Potentially Significant Drug Interactions with Use of Ritonavir

| Concomitant Drug Class: Drug Name | Effect on Concentration of Ritonavir or Concomitant Drug | Clinical Comments |
|---|---|---|
| **HIV-Antiviral Agents** | | |
| HIV-1 Protease Inhibitor: atazanavir | When co-administered with reduced doses of atazanavir and ritonavir ↑ atazanavir (↑ AUC, ↑ $C_{max}$, ↑ $C_{min}$) | Atazanavir plasma concentrations achieved with atazanavir 300 mg once daily and ritonavir 100 mg once daily are higher than those achieved with atazanavir 400 mg once daily. See the complete prescribing information for Reyataz® (atazanavir) for details on co-administration of atazanavir 300 mg once daily with ritonavir 100 mg once daily. |
| HIV-1 Protease Inhibitor: darunavir | When co-administered with reduced doses of ritonavir ↑ darunavir (↑ AUC, ↑ $C_{max}$, ↑ $C_{min}$) | See the complete prescribing information for Prezista® (darunavir) for details on co-administration of darunavir 600 mg twice daily with ritonavir 100 mg twice daily or darunavir 800 mg once daily with ritonavir 100 mg once daily. |
| HIV-1 Protease Inhibitor: fosamprenavir | When co-administered with reduced doses of ritonavir ↑ amprenavir (↑ AUC, ↑ $C_{max}$, ↑ $C_{min}$) | See the complete prescribing information for Lexiva® (fosamprenavir) for details on co-administration of fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily, fosamprenavir 1400 mg once daily with ritonavir 200 mg once daily or fosamprenavir 1400 mg once daily with ritonavir 100 mg once daily. |
| HIV-1 Protease Inhibitor: indinavir | When co-administered with reduced doses of indinavir and ritonavir ↑ indinavir (↔ AUC, ↓ $C_{max}$, ↑ $C_{min}$) | Alterations in concentrations are noted when reduced doses of indinavir are co-administered with NORVIR. Appropriate doses for this combination, with respect to efficacy and safety, have not been established. |
| HIV-1 Protease Inhibitor: nelfinavir* | When co-administered with ritonavir, ↑ nelfinavir (↑ AUC) | Ritonavir increases the serum levels of nelfinavir as a result of CYP3A4 inhibition. Appropriate doses for this combination, with respect to efficacy and safety, have not been established. |
| HIV-1 Protease Inhibitor: saquinavir | When co-administered with reduced doses of ritonavir ↑ saquinavir (↑ AUC, ↑ $C_{max}$, ↑ $C_{min}$) | See the complete prescribing information for Invirase® (saquinavir) for details on co-administration of saquinavir 1000 mg twice daily with ritonavir 100 mg twice daily. Saquinavir/ritonavir should not be given together with rifampin, due to the risk of severe hepatotoxicity (presenting as increased hepatic transaminases) if the three drugs are given together. |
| HIV-1 Protease Inhibitor: tipranavir | When co-administered with reduced doses of ritonavir ↑ tipranavir (↑ AUC, ↑ $C_{max}$, ↑ $C_{min}$) | See the complete prescribing information for Aptivus® (tipranavir) for details on co-administration of tipranavir 500 mg twice daily with ritonavir 200 mg twice daily. There have been reports of clinical hepatitis and hepatic decompensation including some fatalities. All patients should be followed closely with clinical |

| Concomitant Drug Class: Drug Name | Effect on Concentration of Ritonavir or Concomitant Drug | Clinical Comments |
|---|---|---|
| | | and laboratory monitoring, especially those with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity. Liver function tests should be performed prior to initiating therapy with tipranavir/ritonavir, and frequently throughout the duration of treatment. |
| Nucleoside Reverse Transcriptase Inhibitor: didanosine* | ↓ didanosine (↓AUC) | Based on comparison to historical data, the pharmacokinetics of delavirdine did not appear to be affected by ritonavir. When used in combination with delavirdine, dose reduction of ritonavir may be considered. |
| Non-Nucleoside Reverse Transcriptase Inhibitor: delavirdine | ↑ ritonavir (↑AUC, ↑$C_{max}$, ↑ $C_{min}$) | Appropriate doses of this combination with respect to safety and efficacy have not been established. |
| Non-Nucleoside Reverse Transcriptase Inhibitor: efavirenz* | ↑ ritonavir (↑AUC), ↑ efavirenz (↑AUC) | A higher frequency of adverse reactions (eg, dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes) have been observed when efavirenz is co-administered with ritonavir dosed as an antiretroviral agent. |
| HIV-1 CCR5 – antagonist: maraviroc | ↑ maraviroc | Concurrent administration of maraviroc with ritonavir will increase plasma levels of maraviroc. For specific dosage adjustment recommendations, please refer to the complete prescribing information for Selzentry® (maraviroc). |
| Integrase Inhibitor: Raltegravir | ↓ raltegravir | The effects of ritonavir on raltegravir with ritonavir dosage regimens greater than 100 mg twice daily have not been evaluated, however raltegravir concentrations may be decreased with ritonavir coadministration. |
| **Other Agents** | | |
| Analgesics, Narcotic: tramadol, propoxyphene | | A dose decrease may be needed for these drugs when co-administered with ritonavir. |
| Anesthetic: meperidine | ↓ meperidine/ ↑ normeperidine (metabolite) | Dosage increase and long-term use of meperidine with ritonavir are not recommended due to the increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g., seizures). |
| Antialcoholics: disulfiram/metronidazole | | Ritonavir formulations contain alcohol, which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole). |
| Antiarrhythmics: disopyramide, lidocaine, mexiletine | ↑ antiarrhythmics | Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when co-administered with ritonavir, if available. |
| Anticancer Agents: dasatinib, nilotinib, vincristine, vinblastine | ↑ anticancer agents | Concentrations of these drugs may be increased when co-administered with ritonavir resulting in the potential for increased adverse events usually |

| Concomitant Drug Class: Drug Name | Effect on Concentration of Ritonavir or Concomitant Drug | Clinical Comments |
|---|---|---|
| | | associated with these anticancer agents. For vincristine and vinblastine, consideration should be given to temporarily withholding the ritonavir containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when ritonavir is administered concurrently with vincristine or vinblastine. Clinicians should be aware that if the ritonavir containing regimen is withheld for a prolonged period, consideration should be given to altering the regimen to not include a CYP3A or P-gp inhibitor in order to control HIV-1 viral load. A decrease in the dosage or an adjustment of the dosing interval of nilotinib and dasatinib may be necessary for patients requiring co-administration with strong CYP3A inhibitors such as NORVIR. Please refer to the nilotinib and dasatinib prescribing information for dosing instructions. |
| Anticoagulant: warfarin | ↓ R-warfarin ↓↑ S-warfarin | Initial frequent monitoring of the INR during ritonavir and warfarin co-administration is indicated. |
| Anticoagulant: rivaroxaban | ↑ rivaroxaban | Avoid concomitant use of rivaroxaban and ritonavir. Co-administration of ritonavir and rivaroxaban is expected to result in increased exposure of rivaroxaban which may lead to risk of increased bleeding. |
| Anticonvulsants: carbamazepine, clonazepam, ethosuximide | ↑ anticonvulsants | Use with caution. A dose decrease may be needed for these drugs when co-administered with ritonavir and therapeutic concentration monitoring is recommended for these anticonvulsants, if available. |
| Anticonvulsants: divalproex, lamotrigine, phenytoin | ↓ anticonvulsants | Use with caution. A dose increase may be needed for these drugs when co-administered with ritonavir and therapeutic concentration monitoring is recommended for these anticonvulsants, if available. |
| Antidepressants: nefazodone; selective serotonin reuptake inhibitors (SSRIs): eg, fluoxetine, paroxetine, sertraline*; tricyclics: eg, amitriptyline, imipramine*, nortriptyline | ↑ antidepressants | A dose decrease may be needed for these drugs when co-administered with ritonavir. |
| Antidepressant: bupropion | ↓ bupropion ↓ active metabolite, hydroxybupropion | Concurrent administration of bupropion with ritonavir may decrease plasma levels of both bupropion and its active metabolite (hydroxybupropion). Patients receiving ritonavir |

| Concomitant Drug Class: Drug Name | Effect on Concentration of Ritonavir or Concomitant Drug | Clinical Comments |
|---|---|---|
| | | and bupropion concurrently should be monitored for an adequate clinical response to bupropion. |
| Antidepressant: desipramine | ↑ desipramine | Dosage reduction and concentration monitoring of desipramine is recommended. |
| Antidepressant: trazodone | ↑ trazodone | Concomitant use of trazodone and NORVIR increases plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and NORVIR. If trazodone is used with a CYP3A4 inhibitor such as ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered. |
| Antiemetic: dronabinol | ↑ dronabinol | A dose decrease of dronabinol may be needed when co-administered with ritonavir. |
| Antifungal: ketoconazole, itraconazole, voriconazole | ↑ ketoconazole<br>↑ itraconazole<br>↓ voriconazole | High doses of ketoconazole or itraconazole (greater than 200 mg per day) are not recommended. Co-administration of voriconazole and ritonavir doses of 400 mg every 12 hours or greater is contraindicated. Co-administration of voriconazole and ritonavir 100 mg should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. |
| Anti-gout: colchicine | ↑ colchicine | Patients with renal or hepatic impairment should not be given colchicine with ritonavir.<br><br><u>Treatment of gout flares-co-administration of colchicine in patients on ritonavir:</u><br>0.6 mg (one tablet) for one dose, followed by 0.3 mg (half tablet) one hour later. Dose to be repeated no earlier than three days.<br><br><u>Prophylaxis of gout flares-co-administration of colchicine in patients on ritonavir:</u><br>If the original colchicine regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day.<br>If the original colchicine regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day.<br><u>Treatment of familial Mediterranean fever (FMF)-co-administration of colchicine in patients on ritonavir:</u><br>Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day). |
| Antihistamines: fexofenadine, loratadine | ↑ fexofenadine<br>↑ loratadine | Ritonavir may modify P-glycoprotein mediated fexofenadine efflux when dosed as an antriretroviral agent or as a pharmacokinetic |

| Concomitant Drug Class: Drug Name | Effect on Concentration of Ritonavir or Concomitant Drug | Clinical Comments |
|---|---|---|
| | | enhancer resulting in increased concentrations of fexofenadine. Increased fexofenadine levels may lessen over time as induction develops.<br>Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is r ecommended when loratidine is concomitantly administered with ritonavir. |
| Anti-infective: clarithromycin | ↑ clarithromycin | For patients with renal impairment the following dosage adjustments should be considered:<br>• For patients with $CL_{CR}$ 30 to 60 mL per min the dose of clarithromycin should be reduced by 50%.<br>• For patients with $CL_{CR}$ less than 30 mL per min the dose of clarithromycin should be decreased by 75%.<br><br>No dose adjustment for patients with normal renal function is necessary. |
| Antimycobacterial: rifabutin, erythromycin* | ↑ rifabutin and rifabutin metabolite<br>↑ erythromycin | Dosage reduction of rifabutin by at least three-quarters of the usual dose of 300 mg per day is recommended (eg, 150 mg every other day or three times a week). Further dosage reduction may be necessary.<br>Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of erythromycin. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin is used concomitantly administered with ritonavir. |
| Antimycobacterial: rifampin | ↓ ritonavir | May lead to loss of virologic response. Alternate antimycobacterial agents such as rifabutin should be considered (see Antimycobacterial: rifabutin, for dose reduction recommendations). |
| Antiparasitic: atovaquone | ↓ atovaquone | Clinical significance is unknown; however, increase in atovaquone dose may be needed. |
| Antiparasitic: quinine | ↑ quinine | A dose decrease of quinine may be needed when co-administered with ritonavir. |
| Antipsychotics: quetiapine, haloperidol* | ↑ quetiapine<br>↑ haloperidol | Initiation of NORVIR in patients taking quetiapine: Consider alternative antiretroviral therapy to avoid increases in quetiapine exposures. If coadministration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine |

| Concomitant Drug Class: Drug Name | Effect on Concentration of Ritonavir or Concomitant Drug | Clinical Comments |
|---|---|---|
| | | prescribing information for recommendations on adverse reaction monitoring.<br><br>Initiation of quetiapine in patients taking NORVIR: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.<br><br>Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of haloperidol. Careful monitoring of therapeutic and adverse effects is recommended when concomitantly administered with antiretroviral doses of ritonavir |
| β-Blockers: metoprolol, timolol | ↑ Beta-Blockers | Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with ritonavir. |
| Bronchodilator: theophylline | ↓ theophylline | Increased dosage of theophylline may be required; therapeutic monitoring should be considered. |
| Calcium channel blockers: diltiazem, nifedipine, verapamil, amlodipine* | ↑ calcium channel blockers | Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with ritonavir. |
| Digoxin | ↑ digoxin | Concomitant administration of ritonavir with digoxin may increase digoxin levels. Caution should be exercised when co-administering ritonavir with digoxin, with appropriate monitoring of serum digoxin levels. |
| Endothelin receptor antagonists: bosentan | ↑ bosentan | Co-administration of bosentan in patients on ritonavir: In patients who have been receiving ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability.<br><br>Co-administration of ritonavir in patients on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of ritonavir. After at least 10 days following the initiation of ritonavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability. |
| HCV-Protease Inhibitor: simeprevir | ↑simeprevir | It is not recommended to co-administer ritonavir with simeprevir. |
| HMG-CoA Reductase Inhibitor: atorvastatin rosuvastatin, fluvastatin*, pravastatin* | ↑ atorvastatin [a] ↑ rosuvastatin [a]<br>↑ fluvastatin [a] ↑pravastatin [a] | Titrate atorvastatin and rosuvastatin dose carefully and use the lowest necessary dose. If NORVIR is used with another protease inhibitor, see the complete prescribing information for the |

| Concomitant Drug Class: Drug Name | Effect on Concentration of Ritonavir or Concomitant Drug | Clinical Comments |
|---|---|---|
| | | concomitant protease inhibitor for details on co-administration with atorvastatin and rosuvastatin.<br><br>The metabolism of pravastatin and fluvastatin is not dependent on CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended. |
| Immunosuppressants: cyclosporine, tacrolimus, sirolimus (rapamycin) | ↑ immunosuppressants | Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with ritonavir. |
| Inhaled or Intranasal Steroid: e.g. fluticasone budesonide | ↑ glucocorticoids | Concomitant use of ritonavir and fluticasone or other glucocorticoids that are metabolized by CYP3A is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. Concomitant use may result in increased steroid concentrations and reduced serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients when ritonavir has been coadministered with fluticasone propionate or budesonide. |
| Long-acting beta-adrenoceptor agonist: salmeterol | ↑ salmeterol | Concurrent administration of salmeterol and ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. |
| Narcotic Analgesic: methadone, fentanyl, morphine* | ↓ methadone ↑ fentanyl<br>↓ morphine | Dosage increase of methadone may be considered. Concentrations of fentanyl are expected to increase. Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with NORVIR.<br><br>Morphine levels may be decreased due to induction of glucuronidation by co-administered ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. |
| Neuroleptics: perphenazine, risperidone, thioridazine | ↑ neuroleptics | A dose decrease may be needed for these drugs when co-administered with ritonavir. |
| Oral Contraceptives or Patch Contraceptives: ethinyl estradiol | ↓ ethinyl estradiol | Alternate methods of contraception should be considered. |

| Concomitant Drug Class: Drug Name | Effect on Concentration of Ritonavir or Concomitant Drug | Clinical Comments |
|---|---|---|
| PDE5 Inhibitors:<br>avanafil,<br>sildenafil,<br>tadalafil,<br>vardenafil | ↑ avanafil<br>↑ sildenafil<br>↑ tadalafil<br>↑ vardenafil | Do not use ritonavir with avanafil because a safe and effective avanafil dosage regimen has not been established.<br><br>Particular caution should be used when prescribing sildenafil, tadalafil or vardenafil in patients receiving ritonavir. Coadministration of ritonavir with these drugs is expected to substantially increase their concentrations and may result in an increase in PDE5 inhibitor associated adverse events, including hypotension, syncope, visual changes, and prolonged erection.<br><br>Use of PDE5 inhibitors for pulmonary arterial hypertension (PAH):<br>Sildenafil (Revatio®) is contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) because a safe and effective dose has not been established when used with ritonavir.<br>The following dose adjustments are recommended for use of tadalafil (Adcirca™) with ritonavir:<br><br>Co-administration of ADCIRCA in patients on ritonavir: In patients receiving ritonavir for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.<br><br>Co-administration of ritonavir in patients on ADCIRCA: Avoid use of ADCIRCA during the initiation of ritonavir. Stop ADCIRCA at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.<br><br>Use of PDE5 inhibitors for the treatment of erectile dysfunction: It is recommended not to exceed the following doses:<br>• Sildenafil: 25 mg every 48 hours<br>• Tadalafil: 10 mg every 72 hours<br>• Vardenafil: 2.5 mg every 72 hours<br>Use with increased monitoring for adverse events. |
| Psychoanaleptics:<br>Amphetamine* | — | Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of therapeutic and adverse effects is recommended when these |

| Concomitant Drug Class: Drug Name | Effect on Concentration of Ritonavir or Concomitant Drug | Clinical Comments |
|---|---|---|
| | | medicines are concomitantly administered with antiretroviral doses of ritonavir. |
| Sedatives/Hypnotics: alprazolam* | | Alprazolam metabolism was inhibited following the introduction of ritonavir. After ritonavir use for 10 days, no inhibitory effect of ritonavir was observed. Caution is warranted during the first several days when alprazolam is co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops. |
| Steriods: fluticasone propionate aqueous nasal spray* | | Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression (plasma cortisol levels were noted to be decreased 86% in the study) have been reported in patients receiving ritonavir and inhaled or intranasal fluticasone propionate; similar effects could also occur with other corticosteroids metabolized by CYP3A, eg, budesonide.<br>Consequently, concomitant administration of ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (eg, beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a longer period. |

[a] As noted in Section 3.8.2, statins are prohibited due to inhibition of mevalonate synthesis, which reduces protein prenylation.

Source: Prescribing Information for Norvir® [ritonavir] Tablets, 2015. *Additional terms from the Summary of Product Characteristics for Norvir® [ritonavir] tablets, 2014

# APPENDIX D SAMPLE PATIENT DIARY— LONAFARNIB/RITONAVIR DOSAGE: 50 MG BID/100 MG BID

**Please complete this diary every time you take a dose of lonafarnib and ritonavir.**
**Study medication should be taken each morning and each night between HH:MM–HH:MM.**

| Day | Date of Dose (YYYY/MM/DD) | Time of dosing (24-hour clock) (HH:MM) | | Study Medication (LNF = lonafarnib RTV = ritonavir) | Check if Taken |
|---|---|---|---|---|---|
| 1 | \|__\|__\|__\|__\|/\|__\|__\|/\|__\|__\| | Morning | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| | | Evening | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| 2 | \|__\|__\|__\|__\|/\|__\|__\|/\|__\|__\| | Morning | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| | | Evening | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| 3 | \|__\|__\|__\|__\|/\|__\|__\|/\|__\|__\| | Morning | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| | | Evening | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| 4 | \|__\|__\|__\|__\|/\|__\|__\|/\|__\|__\| | Morning | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| | | Evening | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| 5 | \|__\|__\|__\|__\|/\|__\|__\|/\|__\|__\| | Morning | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| | | Evening | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| 6 | \|__\|__\|__\|__\|/\|__\|__\|/\|__\|__\| | Morning | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| | | Evening | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| 7 | \|__\|__\|__\|__\|/\|__\|__\|/\|__\|__\| | Morning | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| | | Evening | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |

| Day | Date of Dose (YYYY/MM/DD) | Time of dosing (24-hour clock) (HH:MM) | | Study Medication (LNF = lonafarnib RTV = ritonavir) | Check if Taken |
|---|---|---|---|---|---|
| 8 | \|__\|__\|__\|__\|/\|__\|__\|/\|__\|__\| | Morning | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| | | Evening | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| 9 | \|__\|__\|__\|__\|/\|__\|__\|/\|__\|__\| | Morning | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| | | Evening | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| 10 | \|__\|__\|__\|__\|/\|__\|__\|/\|__\|__\| | Morning | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| | | Evening | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| 11 | \|__\|__\|__\|__\|/\|__\|__\|/\|__\|__\| | Morning | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| | | Evening | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| 12 | \|__\|__\|__\|__\|/\|__\|__\|/\|__\|__\| | Morning | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| | | Evening | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| 13 | \|__\|__\|__\|__\|/\|__\|__\|/\|__\|__\| | Morning | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| | | Evening | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| 14 | \|__\|__\|__\|__\|/\|__\|__\|/\|__\|__\| | Morning | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |
| | | Evening | \|__\|__\|:\|__\|__\| | LNF (1 x 50-mg capsule)<br>RTV (1 x 100-mg tablet) | ☐<br>☐ |