2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Eiger BioPharmaceuticals, Inc.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Lonafarnib and Norvir® (ritonavir) Tablets</td></tr>
<tr><td>Name of Active Ingredient:
Lonafarnib and ritonavir</td></tr>
<tr><td colspan="3">Title of Study: A Phase 2, Open-Label Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic Activity of Titrating-Dose Lonafarnib in Combination with Ritonavir in Patients Chronically Infected with Hepatitis Delta Virus (LOWR-4)</td></tr>
<tr><td colspan="3">Principal Investigator: Heiner Wedemeyer, MD</td></tr>
<tr><td colspan="3">Study center: Medizinische Hochschule Hannover (MHH, Hannover Medical School), Carl-Neuberg-Straße 1, 30625 Hannover, Germany</td></tr>
<tr><td colspan="3">Publications (reference):
Wedemeyer H, Port K, Deterding K, Wranke A, Kirschner J, EB Martins, et al. A phase 2 study of titrating-dose lonafarnib plus ritonavir in patients with chronic hepatitis D: interim results from the Lonafarnib with ritonavir in HDV-4 (LOWR HDV-4) study (AASLD abstract 230). Hepatol 2016;64:121A.
Wedemeyer H, Port K, Deterding K, Wranke A, Kirschner J, EB Martins, et al. A phase 2 dose-escalation study of lonafarnib plus ritonavir in patients with chronic hepatitis D: final results from the Lonafarnib with ritonavir in HDV-4 (LOWR HDV-4) study (ILC abstract PS-039). J Hepatol 2017;66:S24.</td></tr>
<tr><td colspan="2">Studied period (years):
Date first patient enrolled: 06 January 2016
Date last patient completed: 09 February 2017</td><td>Phase of development:
2</td></tr>
</table>

Objectives:

Primary:

- Evaluate the safety and tolerability of the following dose-titration regimen of lonafarnib (LNF) in combination with ritonavir (RTV) over a 24-week treatment period: LNF/RTV starting at 50 mg bid/100 mg bid, escalated to LNF/RTV 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 LNF in combination with RTV over a 24-week treatment period

Secondary:

- Evaluate the effects of the dose-titration regimen of LNF/RTV on the following:
  - Pharmacokinetics
  - Change in alanine aminotransferase (ALT) levels
  - Change in HBV DNA levels

Exploratory:

- Evaluate the effect of the dose-titration regimen of LNF/RTV on immunologic parameters during treatment

Methodology: This Phase 2, open-label, single-arm study evaluated a dose-titration regimen of LNF/RTV starting at 50 mg twice daily (bid)/100 mg bid, escalated to 75 mg bid/100 mg bid, and then to 100 mg bid/100 mg bid as tolerated in patients chronically infected with hepatitis D virus (HDV). The study was designed to evaluate the safety and tolerability of the study drug regimens, the efficacy (as measured by change in HDV ribonucleic acid [RNA] viral load), the steady-state pharmacokinetics (PK) of LNF and RTV, and the effects on ALT levels, hepatitis B virus (HBV) deoxyribonucleic acid (DNA) levels, and immunologic parameters. The initial dose of LNF/RTV (50 mg bid/100 mg bid) was maintained for at least 4 weeks; subsequent dose escalation could occur at an interval of no less than 2 weeks after the patient had received the particular dose. The duration of the study for each patient was planned to be approximately 52 weeks (up to 4 weeks for screening, 24 weeks of treatment, 4 weeks for the primary follow-up visit, and safety follow-up visits every 4 weeks for 20 weeks thereafter).

Number of patients (planned and analyzed): Approximately 15 patients with chronic HDV infection with detectable HDV RNA by quantitative polymerase chain reaction (qPCR) were planned to be enrolled.

Enrolled and received at least one dose of study drug: 15

Primary pharmacodynamics (PD)/efficacy population: 13

PK population: 15

Diagnosis and main criteria for inclusion:

Inclusion criteria

A patient could have been included in this study if he or she met all of the following criteria:

1. Willing and able to comply with study procedures and provide written informed consent
2. Male or female patients, 18 to 65 years of age, inclusive
3. Had a body mass index (BMI) of $\geq$18 kg/m^2 and had a body weight of $\geq$45 kg
4. Chronic HDV infection documented by a positive HDV antibody 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 was available, the patient must have been willing to consent to and have no contraindication to liver biopsy. Liver biopsy was performed during screening.

6. ALT <10 × upper limit of the normal range (ULN)
7. Electrocardiogram (ECG) demonstrating no acute ischemia or clinically significant abnormality and a QT interval corrected for heart rate [HR] using Fridericia correction (QTcF) of <450 ms.
8. Female patients who met the following criteria:

   Of non-childbearing potential—defined as women who were surgically sterile (had bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), had medically documented ovarian failure, or were postmenopausal (amenorrheic for more than 2 years, age appropriate, and confirmed by follicle-stimulating hormone [FSH] level indicating a postmenopausal state).
   Of childbearing potential—defined as women who had an intact uterus and ovaries and were within 1 year since the last menstrual period, and who met the following conditions:
   - Were not pregnant, and had a negative serum pregnancy test at screening and a negative urine pregnancy test on the Baseline/Day 1 Visit before randomization
   - Were not lactating or breastfeeding
   - Agreed to use 2 of the following contraceptive methods until at least 90 days after the last dose of study drug, of which at least 1 must be a barrier method:
     – Hormonal contraceptives for at least 3 months before the start of screening until at least 90 days after the last dose of study drug
     – Intrauterine device (IUD) in place for at least 3 months before the start of screening until at least 90 days after the 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 the last dose of study drug
     – Surgical sterilization of the partner (vasectomy for 1 month before the start of screening until at least 90 days after the last dose of study drug)
9. Male patients with female partners who were of childbearing potential (see above) who met the following criteria:
   - Were surgically sterile
     or
   - Agreed to practice 2 effective forms of birth control from those listed above from the start of screening until at least 90 days after the last dose of study drug, at least one of which must be a barrier method:
     – Consistently and correctly used a condom
       and
     – Their partner agreed to use a hormonal contraceptive or a non-hormonal barrier method (IUD or diaphragm with spermicide or cervical cap with spermicide).

Exclusion criteria

A patient was to be excluded from this study if he or she met any of the following criteria:

General Criteria

1. Participation in a clinical trial with or use of any investigational agent within 30 days before start of screening
2. Pregnant or lactating/breastfeeding

3. Previous use of LNF
   However, patients who previously participated in a clinical trial of LNF but were confirmed to have received placebo were 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 antibody test at screening. Patients with a positive HCV antibody test at screening were allowed if they had completed a curative antiviral regimen and were 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 Child-Turcotte-Pugh (CTP) 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), T4, or T3 levels, unless the patient was stable on thyroid hormone replacement therapy
11. Significant renal dysfunction, defined as serum creatinine concentration ≥1.5 × 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 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 would 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 required more than intermittent nonsteroidal anti-inflammatory medications for management or that required use of systemic corticosteroids in prior 6 months (note: inhaled asthma medications were allowed)
    b. History of or evidence of retinal disorder or clinically relevant ophthalmic disorder
    c. Any malignancy within 5 years before the start of screening. Exceptions were 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 were 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 as allowed (ie, ondansetron)
    c. Receipt of systemic immunosuppressive therapy within the 3 months before the start of screening
    d. Statins, due to inhibition of mevalonate synthesis, which reduces protein prenylation
    e. Medications contraindicated in the prescribing information for RTV:
        – $Alpha_1$-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 (GI) 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 LNF, RTV, or other substances that are part of the study medication

Other Medical Conditions

21. Other significant medical condition that could have required intervention during the duration of the study. Patients with any serious condition that, in the opinion of the investigator, would have precluded evaluation of response or made it unlikely that the contemplated course of therapy and follow-up could be completed or increased the risk to the patient of participation in the trial.

Test product, dose and mode of administration, lot number:
Lonafarnib Capsules, 50 mg, for oral administration, Lot No. L262-01A005BOT35
Lonafarnib Capsules, 75 mg, for oral administration, Lot No. L262-01A006BOT35
Norvir® Ritonavir Tablets, 100 mg, for oral administration, Lot No. 1039671

Duration of treatment: Approximately 52 weeks (up to 4 weeks for screening, 24 weeks of treatment, 4 weeks for the primary follow-up visit, and safety follow-up visits every 4 weeks for 20 weeks thereafter)

Reference therapy, dose and mode of administration, lot number: Not applicable

Criteria for evaluation:

Efficacy:

- Change from baseline in HDV RNA viral load by dose level and time point (change to Week 24 is the primary PD endpoint)
- Number (percent) of patients with 1 log reduction from baseline in HDV RNA viral load by dose level and time point
- Number (percent) of patients with HDV RNA viral load below the lower limit of quantitation (BLQ) by dose level and time point
- Number (percent) of patients with HDV RNA viral load below the limit of detection (BLD) by dose level and time point
- HBV DNA viral load by dose level and time point
- HBV and HDV serology by dose level and time point

Pharmacokinetics:

- Steady-state PK parameters for LNF and RTV included the following: C_{max}, T_{max}, $AUC_{0-\tau}$, C_{avg}, C_{min}, K_{el}, V_{area}/F, CL/F, and $T_{1/2}$.
- Trough plasma concentrations of LNF and RTV

Safety:

- Adverse events (AEs)
- Vital signs
- Clinical laboratory results, including ALT and other liver enzymes
- ECG results
- Concomitant medication usage
- Ophthalmic examination results
- Reproductive serology results

Virology:

- HDV genotypic analysis of screening and baseline serum samples
- For resistance surveillance, genotypic analysis of large HDV antigen in any patients with virologic failure

Exploratory immunology:

- Analysis of PBMC samples

Statistical Methods:

The following analysis sets were used:

- Efficacy analysis set (EAS): consisted of patients who received study drug throughout the entire 24-week treatment period and for whom viral load data were available from baseline and end-of-treatment (Week 24) study visits
- PK analysis set: consisted of 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
- Safety analysis set: included all patients who receive at least 1 dose of study drug

All efficacy and safety data were analyzed based on the applicable protocol-specified dose regimen at the time point.

Efficacy: HDV RNA viral load data in $\log_{10}$ IU/mL were presented in summary tabulations by dose level and time point and in listings by patient. Absolute and change-from-baseline summary statistics (mean, standard deviation [SD], median, minimum, and maximum) were calculated at each time point. HDV RNA mean absolute and change-from-baseline titers by dose level at each time point were presented graphically. Individual patient plots of absolute and change-from-baseline HDV RNA over time were also presented graphically. A spaghetti plot of HDV RNA over time was provided. The number of patients with 1 $\log_{10}$ IU/mL reduction from baseline was summarized by dose level at each time point. The numbers of patients with HDV RNA concentrations that were BLQ (<14 IU/mL) and BLD (<8 IU/mL) were each summarized by dose level at each time point. Viral serology data were listed by patient. The number and percentage of patients who experienced virologic failure was summarized by dose level.

PK: For both trough and serial PK sampling, plasma LNF and RTV concentrations were summarized using summary statistics by dose level and time point and listed by patient. Steady-state plasma LNF and RTV concentrations following serial sampling were also plotted by dose level over time. The following steady-state PK parameters were derived from the serial plasma concentrations using a noncompartmental method: C_{max}, T_{max}, $AUC_{0-\tau}$, C_{avg}, C_{min}, K_{el}, V_{area}/F, CL/F, and $T_{1/2}$. These PK parameters were summarized using summary statistics (arithmetic mean, SD, median, minimum, and maximum, coefficient of variation [%CV]) by dose level and time point and listed by patient. Linearity and dose proportionality were planned to be performed across LNF dose levels. HDV RNA (absolute and change-from-baseline) values were plotted with LNF plasma concentrations over time to examine possible correlations.

Safety: AEs that started after administration of the first dose of study drug up to and including 28 days after administration of the last dose of study drug were considered treatment emergent (TEAE). Any AEs that started more than 28 days after the last dose of study drug were considered posttreatment AEs.

All reported AEs were mapped to standard coding terms (Medical Dictionary for Regulatory Activities [MedDRA], Version 18.1) and grouped by system organ class (SOC) and preferred term (PT). The following AE summaries (number and percent of patients) by SOC, PT, and dose level were provided:

- All TEAEs
- All serious adverse events (SAEs)
- All treatment-emergent SAEs (TESAEs)
- All treatment-related TEAEs (LNF-related and RTV-related presented separately)
- All treatment-related TESAEs
- All TEAEs by severity
- All TEAEs that led to early discontinuation of study treatment
- All TEAEs that led to dose reduction in study drug

The following by-patient data listings were provided:

- All AEs (with an indicator whether the event was treatment emergent)
- SAEs
- Deaths
- TEAEs that led to discontinuation of study drug

Laboratory results were summarized using summary statistics (absolute and change-from-baseline values) by dose level and time point. All Grade 3 and Grade 4 laboratory values were summarized

categorically by dose level. Liver enzyme results (ALT, aspartate aminotransferase [AST], total bilirubin, and alkaline phosphatase) were summarized by Common Terminology Criteria for Adverse Events (CTCAE; Version 4.03) grade.

Actual and change-from-baseline vital sign values (blood pressure [BP], HR, respiration rate, and body temperature) were summarized at each time point by dose level. Vital signs were listed by patient.

ECG intervals were summarized by visit and dose level using summary statistics for actual values and change-from-baseline values (average of 3 readings). ECG data and clinical interpretations were listed by patient.

Concomitant medications were defined as non-study medications that were started on or after the first day of study drug dosing. Concomitant medications were mapped to drug classes and generic terms using the World Health Organization Drug Dictionary Enhanced (WHO-DD Enhanced), Version WHO2015SEP and summarized by dose level. Prior and concomitant medications were also listed by patient. Previous hepatitis medications were listed by patient separately.

Results of the slit lamp and dilated fundus examinations and retinal photography were summarized as normal or abnormal (nonclinically significant or clinically significant) using number (%) of patients by dose level and time point. Results of the visual acuity examination provided number (%) of patients with discrete visual acuity values (eg, 20/15, 20/20) by dose level and time point.

Results of male and female reproductive hormone tests were summarized by dose and time point and listed by patient. Physical examination findings (comprehensive exam at screening, brief exams at each subsequent visit, and genital exams at screening and Week 24 or early termination) were listed by patient.

SUMMARY – CONCLUSIONS

Fifteen patients were enrolled in the study. The majority of patients were male (73.3%) and identified as White (80.0%). The mean (SD) age was 42 (12.6) years. Thirteen patients (86.7%) completed study drug through Week 24.

All patients (15, 100%) received the first study drug regimen (LNF/RTV 50 mg bid/100 mg bid). Thirteen patients (86.7%) were titrated up to the second study drug regimen (LNF/RTV 75 mg bid/100 mg bid). Ten patients (66.7%) were titrated up to the third study drug regimen (LNF/RTV 100 mg bid/100 mg bid). Five patients (33.3%) maintained at the LNF/RTV 100 mg bid/100 mg bid dosing regimen through Week 24.

Nine of 13 patients (69.2%) demonstrated a >1 log decline in HDV RNA at Week 24 (end of treatment).

Four of 13 patients (30.7%) demonstrated a >2 log decline in HDV RNA at Week 24 (end of treatment).

Eight of 13 patients (61.5%) normalized ALT levels at Week 24 (end of treatment).

Eight patients (53.3%) required dose reduction during the study. Although only lonafarnib was indicated to be reduced per protocol, some of these patients also dose reduced ritonavir from 100 mg bid to 100 mg qd. Two patients (13.3%) discontinued study treatment before Week 24 due to AEs: Patient No. 301-007 had Grade 2 abdominal pain while taking LNF 50 mg qd/RTV 100 mg bid, and Patient No. 301-008 had decreased appetite that worsened from Grade 1 to Grade 2 while taking LNF/RTV 100 mg bid/100 mg bid. Both events were considered related to both LNF and RTV.

Efficacy Results: In this study that evaluated a LNF/RTV dose titration regimen, patients experienced a mean decrease from baseline in HDV RNA of 1.62 $\log_{10}$ IU/mL (SD 1.4) at Week 24 (primary efficacy endpoint). Patients who reached maximum doses of 50 mg bid/100 mg bid, 75 mg bid/100 mg bid, and 100 mg bid/100 mg bid LNF/RTV at Week 24 demonstrated similar mean HDV RNA reductions of 1.51, 1.23, and 1.88 $\log_{10}$ IU/mL, respectively.

In this study, HDV RNA viral load sharply dropped in the first weeks of treatment; then the decline slowed and reversed at the end of treatment (after dosing completed) and throughout the follow-up period. The mean HDV RNA titer at baseline was 4.58 $\log_{10}$ IU/mL. After 4 weeks of treatment at LNF/RTV 50 mg bid/100 mg bid, mean HDV RNA was 3.12 $\log_{10}$ IU/mL, a mean decrease of 1.47 $\log_{10}$ IU/mL. Overall, mean HDV RNA titer continued to decrease, to 2.88, 2.79, 2.60, and 2.51 $\log_{10}$ IU/mL at Weeks 6, 8, 12, and 16, respectively. Mean HDV RNA titers then increased to 2.82 and 2.96 $\log_{10}$ IU/mL for the last 2 visits in the treatment period at Weeks 20 and 24, respectively. After patients stopped study drug, mean HDV RNA values returned to levels close to baseline (4.40 $\log_{10}$ IU/mL at Week 28 and 4.20 $\log_{10}$ IU/mL at Week 48).

A 1 $\log_{10}$ IU/mL reduction from baseline in HDV RNA titer was demonstrated in approximately half of the patients at Weeks 1 and 2 and 76.9% at Week 4. At all subsequent on-treatment measurements, the majority of patients had a 1 $\log_{10}$ IU/mL reduction: 84.6% at Week 6, 76.9% at Week 8, 92.3% at Weeks 12 and 16, 76.9% at Week 20, and 69.2% at Week 24. HDV RNA concentrations were BLQ (<14 IU/mL) in 2 patients (15.4%) at Week 4, in 1 patient (7.7%) each at Weeks 8, 12, and 16, and in 2 patients (15.4%) at Week 20. At Week 24, 2 patients (15.4%) had HDV RNA concentrations BLQ, 1 patient's value was BLQ and 1 patient's value was BLD.

Five patients (38.5%) had an increase in serum HDV RNA of at least 1 $\log_{10}$ IU/mL above their nadir value on 2 consecutive visits. Earlier, these patients each had a >1 $\log_{10}$ IU/mL decrease from baseline and 2 achieved HDV RNA BLQ. The virologic failures occurred at 6, 8, 16, 18, and 20 weeks after the patient's nadir time point.

Small decreases from baseline in mean HBV DNA titer were seen in the treatment period (maximum: 0.78 $\log_{10}$ IU/mL at Week 24). None of the 11 patients who were taking hepatitis antivirals at study entry had notable HBV DNA increases (confirmed >2,000 IU/mL). Three of the 4 patients who had not been taking hepatitis antivirals at study entry had on-treatment increases in HBV DNA titer; subsequently they each started Viread 245 mg once daily (qd), and their HBV DNA titers dropped to BLQ or BLD. The fourth patient had HBV DNA titers generally BLQ or BLD throughout the study.

PK Results:

Mean maximal LNF plasma concentrations (C_{max}) were 1595 and 3085 ng/mL in the 50 mg qd and bid dose groups, respectively; 1820 and 3730 ng/mL in the 75 mg qd and bid dose groups, respectively; and 3889 ng/mL in the 100 mg bid dose group. The median T_{max} values ranged from 2 to 8 hours for all LNF dose groups; T_{max} was independent of dose level. The mean extent of absorption to LNF over the dosing interval ($AUC_{0-\tau}$) values were 16,517 and 33,755 ng·h/mL in the 50 mg qd and bid dose groups, respectively; 19,140 and 42,215 ng·h/mL in the 75 mg qd and bid dose groups, respectively; and 42,701 ng·h/mL in the 100 mg bid dose group. The overall variability in LNF exposure, measured as %CV for C_{max} and $AUC_{0-\tau}$, ranged from 9.3% to 72.2% and from 11.0% to 74.1%, respectively. Formal dose linearity and proportionality analyses could not be performed because incorrect RTV dosing (RTV dose reduced in some patients to qd outside of protocol) led to inadequately sized dosing samples. However, increases in LNF exposure were less than dose-proportional as the dose increased from 50 to 100 mg bid. The qd LNF PK data were difficult to interpret and did not reflect a once-daily PK profile; this is because of the truncated interval in which they were collected (ie, 0–12 hours vs. 0–24 hours). LNF plasma concentrations did not reach terminal elimination in the 12-hour sampling window.

	Steady-State Lonafarnib Pharmacokinetic Parameters				
	Study Drug Dose Level (LNF/RTV)				
Parameter	**50 mg qd/ 100 mg qd (N=2)[a]**	**50 mg bid/ 100 mg bid (N=2)**	**75 mg qd/ 100 mg qd (N=1)[a]**	**75 mg bid/ 100 mg bid (N=1)**	**100 mg bid/ 100 mg bid (N=9)**
T_{max} (h)	6.0 (4.0, 8.0)	8.0 (8.0, 8.0)	6.0	2.0	6.0 (2.0, 8.0)
C_{max} (ng/mL)	1595 (9.3)	3085 (72.2)	1820	3730	3889 (35.0)
C_{trough} (ng/mL)	1345 (1.6)	2705 (81.3)	1670	3550	3393 (36.9)
C_{avg} (ng/mL)	1376 (11.0)	2813 (74.1)	1595	3518	3558 (36.7)
$AUC_{0-\tau}$ (ng· h/mL)	16517 (11.0)	33755 (74.1)	19140	42215	42701 (36.7)
CL/F (L/h)	3.0 (11.0)	2.0 (74.1)	3.9	1.8	2.6 (32.9)

All values are mean (%CV) except T_{max}, which is median (min, max).
a These patients received RTV on a qd instead of bid basis in error.

All patients were to receive RTV 100 mg bid, but since 3 patients were incorrectly dosed at RTV 100 mg qd during the serial PK sampling, 2 RTV dose groups were examined. For the RTV 100 mg bid dose group, the mean maximum RTV plasma concentration (C_{max}) was 1914 ng/mL; the median T_{max} value was 3 hours and ranged from 1–6 hours across the different LNF dose levels. The mean extent of absorption for RTV over the dosing interval ($AUC_{0-\tau}$) was 13,566 ng·h/mL for RTV 100 mg bid. Overall exposure variability for RTV was high (%CV for C_{max} 61.1% and %CV for $AUC_{0-\tau}$ 61.6%).

	Steady-State Ritonavir Pharmacokinetic Parameters	
	Study Drug Dose Level (RTV)	
Parameter	**100 mg qd (N=3)[a]**	**100 mg bid (N=12)[b]**
T_{max} (h)	4.0 (3.0, 8.0)	3.0 (1.0, 6.0)
C_{max} (ng/mL)	1221 (60.7)	1914 (61.1)
C_{trough} (ng/mL)	324 (25.8)	558.3 (63.1)
C_{avg} (ng/mL)	540.4 (38.7)	1131 (61.6)
$AUC_{0-\tau}$ (ng· h/mL)	6484 (38.7)	13566 (61.6)
CL/F (L/h)	17.0 (35.7)	11.3 (77.2)
t½ (h)	5.5 (41.8)	5.3 (61.7)
AUC_{inf} (ng· h/mL)	6856 (50.1)	13562 (64.6)
Ke (1/h)	0.138 (42.0)	0.160 (37.6)
Extrapolated (%)	0.868 (81.6)	0.492 (83.4)
V_{area}/F (L)	146.5 (83.4)	80.3 (82.8)

a N=3 (LNF 50 mg qd, RTV 100 mg qd for 2 patients; LNF 75 mg qd, RTV 100 mg qd for 1 patient)
b N=12 (LNF 50 mg bid, RTV 100 mg bid for 2 patients; LNF 75 mg bid, RTV 100 mg bid for 1 patient; and LNF 100 mg bid, RTV 100 mg bid for 9 patients)
Values are mean (%CV) except T_{max}, which is median (min, max).

Safety Results:

Adverse Events

All patients reported TEAEs, and almost all reported TEAEs were categorized as expected events with LNF treatment (DCSI, 19 Sept 2016). Exceptions included several instances of alopecia, acne, pruritus, chest pain, back pain, and rash. GI events were the most common type of TEAE (100.0% of patients). Overall, the most frequently reported TEAEs were diarrhea (100.0%); nausea, vomiting, decreased

appetite, and weight decreased (53.3% each); abdominal pain (40.0%); and fatigue, dizziness, and dysgeusia (26.7% each). While diarrhea had the highest rate of incidence, the majority of events occurred in the first 2 weeks of treatment with the remaining events spread out over the next 22 weeks, occurring sparsely across the 15 patients. The average time to last event for a patient demonstrates that most patients acclimate by approximately 6 weeks of treatment. In the majority of patients (60%), TEAEs were at worst Grade 2. Reported Grade 3 TEAEs included diarrhea in 2 patients (13.3%) and asthenia, hepatic enzyme increased, and weight decreased, each in 1 patient (6.7%). There were no Grade 4 or 5 events and no treatment-emergent SAEs (1 patient was hospitalized for a fractured jaw due to an altercation more than 5 months after his last dose of study treatment). Two patients (13.3%) discontinued study treatment early because of a Grade 2 TEAE (abdominal pain and decreased appetite, both considered related to LNF and RTV). Overall, 10 patients (66.7%) experienced TEAEs that led to study drug dose reduction, with percentages that increased with LNF dose: 13.3%, 23.1%, and 50.0% at the LNF/RTV 50/100, 75/100, and 100/100 mg dose levels, respectively.

Grade 1 decreased weight (in 53.3% of patients) was first reported at Week 6 in 5 patients, at Week 8 in 2 patients, and at Week 12 in 1 patient. In 5 of these 8 patients, the event worsened (to Grade 2 in 4 patients, to Grade 3 in 1 patient) and was ongoing at the end of the study. All decreased weight events were considered related to LNF and RTV; study drug dose was not reduced because of these events.

Three TEAEs (Grade 2, 3, 3) of increased hepatic enzymes were reported for 1 patient (6.7%). This patient's ALT and AST values were above the respective normal range from screening through the end of the study; however, the values increased rapidly at Week 4 and then continued to fluctuate well above the normal range through the treatment period, returning to Grade 1 in the follow-up period. The highest values (ALT 954 IU/L; AST 676 IU/L) occurred at Week 24.

Anemia was reported in 2 patients (13.3%), one Grade 1 and one Grade 2 event. Both anemia events were considered possibly related to LNF and RTV treatment, and both resolved without treatment.

Grade 1 eye-related TEAEs were reported in 3 patients (20.0%). Eye pain, keratitis, ocular hyperemia, and reduced visual acuity were each reported in 1 patient. All of these events were considered related to LNF and RTV. No study drug doses were reduced as a result of these events, and all of these events resolved.

Clinical Laboratory Results

No clinically significant changes from baseline in clinical laboratory test results were seen in this study, with the exception of liver enzymes. On-treatment Grade 3 or 4 clinical chemistry findings were seen in 6 patients (40%), ALT in 4 patients, and AST, phosphate, and creatine kinase (CK) in 1 patient each. In 1 patient, the ALT/AST events were reported as a TEAE of increased hepatic enzyme. The incidence of Grade 3/4 laboratory abnormalities did not increase with increasing dose (26.7%, 23.1%, and 20.0% of patients at the LNF/RTV 50/100 mg, 75/100 mg, and 100/100 mg dose levels, respectively).

At baseline, all ALT and AST concentrations were above the respective normal range as per protocol, and they were highly variable at all subsequent assessments. Mean ALT concentrations remained close to baseline values at Week 1, then gradually increased to approximately 40 IU/L above baseline levels at Week 6, then decreased to approximately 50 IU/L below baseline levels at Week 20. In the follow-up period, mean ALT concentrations increased to 128 IU/L above baseline at Week 32, and then fluctuated above and below the baseline level. Mean AST concentrations remained at or below baseline values except at Week 6 (mean increase of 8.1 IU/L) and from Week 24 through the end of the study (maximal increase of 63.9 IU/L at Week 32). Mean alkaline phosphatase values increased steadily from baseline through Week 28, then decreased during the follow-up period. Mean bilirubin concentrations fluctuated within the normal range.

Liver enzyme concentrations stayed at the CTCAE baseline grade or worsened by 1 grade in all patients except the following: ALT 1 patient Grade 1 to 3, 2 patients Grade 1 to 4; AST 1 patient Grade 0 to 3, 5 patients Grade 1 to 3, 1 patient Grade 1 to 4.

Vital Signs, Physical Findings, and Other Observations

No clinically significant changes in mean vital signs were seen. No physical examination findings were noteworthy, and all genital exams were normal.

No clinically significant changes from baseline in mean ECG results (QTcF and HR) were seen. The only QTcF prolongations reported were in the range of 450–480 ms in 2 patients (13.3%), 1 at Weeks 12 and 40, 1 at Weeks 44 and 48; the maximum value was 453 ms. No QTcF increases from baseline exceeded 30 ms.

Visual acuity examination results demonstrated no evidence of a worsening trend during the study. Results of the dilated fundus exams revealed that 1 patient had myopic degeneration of both retinas at screening and Week 24; at screening this finding was considered clinically significant only on the left side, whereas at Week 24, the findings on both sides were considered clinically significant. In the slit lamp examination, 1 patient had clinically significant bilateral corneal keratitis at Week 24 that was not present at screening. No evidence of treatment-related ophthalmic abnormalities was seen in the retinal photographs.

Analysis of reproductive hormone results showed no clinically significant patterns in the small group of female patients. In the male patients, increases in FSH and decreases in inhibin B were seen but were not thought to be clinically significant.

CONCLUSIONS:

Dose escalation of the LNF/RTV regimen was shown to be feasible. In the 15 treated patients, 10 (66.7%) were able to escalate to LNF/RTV 100 mg bid/100 mg bid.

Patients receiving the LNF/RTV dose titration regimen in this study experienced substantial decreases in HDV RNA viral load in the 24-week treatment period. At Week 24, mean decreases from baseline were 1.62 $\log_{10}$ IU/mL overall and 1.51, 1.23, and 1.88 $\log_{10}$ IU/mL for those at the 50 mg bid/100 mg bid, 75 mg bid/100 md bid, and 100 mg bid/100 mg bid LNF/RTV dose levels, respectively. HDV RNA viral load sharply dropped in the first weeks of treatment (maximal decrease from baseline was 2.08 $\log_{10}$ IU/mL at Week 16); then the decline slowed and reversed at the end of treatment (upon dosing completion) and throughout the follow-up period.

Five patients (38.5%) experienced virologic failure at least 6 weeks after their HDV RNA nadir.

Three of the 4 patients who had not been taking hepatitis antivirals at study entry had on-treatment increases in HBV DNA titer up to Week 12; subsequently they each started Viread 245 mg qd, and their HBV DNA titers dropped to BLQ or BLD.

Overall, LNF exposures were highly variable (>30% CV), which is not unusual for a pharmacokinetically boosted drug. LNF exposure for LNF/RTV 100 mg bid/100 mg bid in this study were similar to those of LNF-only dosing at 300 mg bid in a previous study (LOWR HDV-1), indicating that RTV seemed to successfully boost LNF PK. Although the LNF 50 and 75 mg qd and bid dose groups had few patients compared with the 100-mg bid dose group, a comparison of exposures (C_{max} and AUC) leads to the conclusion that LNF/RTV exposure is not linear over the dose range, suggesting a saturable absorption process.

Overall, there were no new, unexpected safety findings in this study examining a dose-titration regimen of LNF/RTV. Noteworthy expected safety findings included GI events (100%), decreased appetite/weight loss (53.3%), Grade 3/4 ALT or AST concentrations (26.7%), Grade 1/2 anemia (13.3%), and Grade 1 eye events (20.0%). Two patients had QTcF values > 450 ms (maximum value 453 ms).

In summary, LNF/RTV dose escalation led to on-therapy reductions in HDV RNA, with the most robust effect in the LNF/RTV 100 mg bid/100 mg bid dose regimen. Five patients tolerated this dosing regimen and maintained through Week 24 which allowed for 2 of 5 patients to achieve BLQ and 1 patient to achieve BLD. Given that the mean LNF exposures exceeded the previously determined maximum tolerated dose (MTD), together with the highly variable LNF exposures, the possible saturable absorption, and the safety profile, the data do not support exploring LNF/RTV doses higher than 50/100 mg bid. Future studies will explore lower LNF doses, including dose titration up to LNF/RTV 50 mg bid/100 mg bid.

Date of the report:

16 October 2017