Eiger BioPharmaceuticals, Inc.

Protocol EIG-LMD-001

A Phase 2 Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of Pegylated Interferon Lambda Monotherapy in Patients with Chronic Hepatitis Delta Virus Infection (LIMT-1)

FINAL v3
Statistical Analysis Plan

June 25, 2019
Revised: April 1, 2020

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Eiger BioPharmaceuticals, Inc.

Protocol EIG-LMD-001 (Amendment 5)
Statistical Analysis Plan

Final (version 3)

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Document history

Document	Date of Issue	Summary of Key Changes
Statistical Analysis Plan (SAP) v1	June 25, 2019	Not applicable (original SAP)
Revised SAP v2	September 19, 2019	Reference to Week 96 hepatitis delta virus (HDV) ribonucleic acid (RNA) assessment was added. Virologic response at Week 48 and sustained virologic response (SVR) were added as endpoints, and the definition of durable virologic response (DVR) was clarified and limited to the 24-week post-treatment visit (Week 72). Hepatitis B surface antigen (HBsAg) categories were updated. Proportion of patients with alanine aminotransferase (ALT) normalization was added as an endpoint at Weeks 48, 72, and 96. The analysis population section was edited to (a) clarify that analyses of the modified intention-to-treat (MITT) population will be considered sensitivity analyses, and (b) add the treatment completer population, defined as patients who received study therapy at the Week 48 visit. Visit windows were added between Weeks 72 and 96; the Week 72 imputation rule now follows the same rule as other visits bracketed by adjacent visits on both sides. Among patients who do not meet MITT criteria, dose reduction and treatment through Week 48 were added to the patient disposition summary. "Relevant protocol deviations" was changed to "important protocol deviations," and the list of important protocol deviations was expanded to include all programmable eligibility deviations and additional on-study deviations.

Document history, continued

Revised SAP v2	September 19, 2019	Descriptive statistics for baseline ALT and HBsAg as well as proportion of patients with ALT ≤ and > upper limit of normal (ULN) were added. Prothrombin time was added to baseline laboratory summaries. The term "compliance" has been replaced by "adherence." Summary of dose modifications was added for patients who did not meet the MITT criteria. A sentence was added to make clear that efficacy analyses of HDV RNA should first transform the HDV RNA values to the $\log_{10}$ IU/mL scale. Efficacy analyses were defined for the MITT and treatment completer populations. Sensitivity analyses of DVR and SVR have been added: (a) excluding patients with baseline HDV RNA below the lower limit of quantification (LLOQ) from the denominator of each proportion calculation, and (b) excluding responders with virologic failure from the numerator of each proportion calculation. It was clarified that interim data snapshot for purposes of data review and presentation would occur and will not require multiplicity adjustment. The safety analysis section was edited to clarify that safety presentations will include data through the patient's last study visit. Reference to summaries of adverse events by study month was removed.
Revised SAP v3	April 1, 2020	The following were corrected: • References to pharmacokinetics and electrocardiogram (ECG) were removed. • Section 8.2: MITT analyses will be limited to the primary efficacy endpoint and a select set of exploratory efficacy endpoints. Reference to other MITT analyses was deleted.

Document history, continued

Revised SAP v3	April 1, 2020	• The list of endpoints in Sections 3.6.1 and 8.2 were reconciled. • Virologic response rate at Week 48 included reference to "12 weeks" in the endpoint definition, which was deleted. • Reference to "ITT population" was removed and replaced with "randomized population." Clarifying edits were added to visit labels, e.g., "(Week 72)" was included after "24 weeks after Week 48." SVR24 and DVR24 were added to the study schema. The definition of ALT normalization was added. It was also clarified how patients with ALT<ULN at baseline would be handled in the analysis of the proportion of patients with ALT normalization at a given visit. "Treatment completer population" was changed to "treatment completion population." In Section 5.3: Because the SAP was written toward the completion of the study, the algorithms in the previous versions of the SAP did not match the investigator electronic case report form (eCRF) visit labels. Therefore, the following updates have been made to this section: • Header was changed from "Visit windows" to "Visit labels." • Derived visit windows were removed. All visit labels will come from eCRF pages. • Conventions were added for visit labels in patients who have early termination of treatment before Week 48. Because the last dose of study therapy is not captured on the eCRF, the patient visit date recorded in the patient registration portal and labeled as "Week 48 / EOT Date" will be used as the date of last dose. This convention was added to the study therapy administration and adherence section.

Document history, continued

Revised SAP v3	April 1, 2020	In addition to patient disposition, a summary of analysis populations was added. Baseline HDV RNA level as a continuous measure with descriptive statistics was added to the list of analyses for baseline disease characteristics. Reason for dose reduction was removed as it was not collected. Proportion of patients with virologic failure was added to Section 8.2 (Efficacy exploratory endpoints) and refined to align with definitions in FDA's guidance document. Rash was removed as an adverse event (AE) of special interest. Safety presentations will include AEs up to 28 days after the last dose of study treatment. Anti-hepatitis B virus (anti-HBV) therapies other than entecavir and tenofovir were removed in the protocol deviation table. Also, the derivation for absolute neutrophil count (ANC) was added, as ANC was not provided by the central laboratory.

Contents

Contents, continued

Exhibits

Abbreviations

Ab	antibody
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
CrCl	creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
DR	dose reduction (DR1 = first DR; DR2 = second DR)
DVR	durable virologic response
ECG	electrocardiogram
eCRF	electronic case report form
EOFU	end of follow-up
EOS	end of study
EOT	end of treatment
ET	early termination
FU	follow-up
GGT	gamma-glutamyl transferase
HBV	hepatitis B virus
HBsAb	hepatitis B surface antibody
HBeAb	hepatitis B envelope antibody
HBeAg	hepatitis B envelope antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDV	hepatitis delta virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IFN	interferon
IFN-α	interferon alpha

(continued)

Abbreviations, continued

INR	international normalized ratio
IUD	intrauterine device
IWRS	interactive web response system
LOD	limit of detection
LLOQ	lower limit of quantification
mcg	micrograms
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intention-to-treat
NCI	National Cancer Institute
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PT	preferred term
qPCR	quantitative polymerase chain reaction
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia formula
QW	once a week
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SVR	sustained virologic response
TBILI	total bilirubin
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
ULN	upper limit of the normal range
WBC	white blood cell
WHO	World Health Organization
WHODDE	World Health Organization Drug Dictionary Enhanced

1. Introduction

Peginterferon lambda-1a (Lambda) is a well-characterized, late-stage, first-in-class, type III interferon (IFN) that has demonstrated activity and favorable tolerability as compared to pegylated alfa interferon (Alfa) in human studies against hepatitis B and C viruses (HBV, HCV, respectively). Lambda exerts its antiviral effects through direct inhibitory and indirect immune-mediated mechanisms of action. In proof of concept preclinical studies, Lambda has demonstrated activity against hepatitis D virus (HDV) that is comparable to Alfa. Accordingly, Lambda is postulated to induce HDV ribonucleic acid (RNA) decline in humans, but with fewer adverse events (AEs) than Alfa.

EIG-LMD-001 is the first study of Lambda in patients with chronic HDV infection. The primary aims of the study are to define the safety, tolerability, and pharmacodynamics (PD)/efficacy of Lambda monotherapy in patients with chronic HDV infection. The Lambda doses chosen for this study were based on the results from studies in healthy volunteers and in patients with chronic HBV or chronic HCV infection.

This statistical analysis plan (SAP) is based on the protocol for study EIG-LMD-001 (Amendment 5), dated April 18, 2019. The SAP summarizes key aspects of the study to provide context for statistical methods and presents details of the planned statistical methods addressing the study aims. This analysis plan will serve as the final documentation for the planned statistical analyses for study EIG-LMD-001 and will supersede the protocol if there are any discrepancies.

The statistical principles applied in the design and planned analyses of this study are consistent with the International Conference on Harmonization (ICH) guidelines E9 (Statistical Principles for Clinical Trials) [1].

2. Study objectives

2.1. Primary objective

The primary objectives of the study are as follows:

- To evaluate the safety and tolerability of treatment with 2 dose levels of Lambda over a 48-week treatment period
- To evaluate the effect of treatment with two different doses of Lambda on HDV RNA levels

2.2. Secondary objectives

The secondary objectives of the study are as follows:

- To evaluate the proportion of patients with undetectable HDV RNA 12 weeks after the end of treatment
- To evaluate the proportion of patients with undetectable HDV RNA 24 weeks after the end of treatment
- To evaluate the proportion of patients with undetectable HDV RNA approx. 48 weeks after the end of treatment
- To evaluate the effect of treatment with two dose levels of Lambda on the following:
  - Alanine aminotransferase (ALT) levels including ALT levels at approx. 48 weeks after end of treatment
  - Hepatitis B surface antigen levels

    NOTE: This will be assessed by quantitative polymerase chain reaction (qPCR) assay (qHBsAg).
  - Gamma-glutamyl transferase (GGT) levels

2.3. Exploratory objective

An exploratory objective of the study is to evaluate the effect of treatment with two dose levels of Lambda on immunologic parameters. This analysis plan will focus only on immunogenicity analyses that will be included in the clinical study report. Other analyses related to immunologic parameters, if conducted, will not be included in the Clinical Study Report and are therefore not described in this SAP.

3. Study design and conduct

3.1. Study design

This Phase 2, randomized, open-label, two dose level study will assess the safety, tolerability, and PD/efficacy of Lambda in patients with chronic HDV infection. Up to 40 patients will be enrolled at approximately 6 study sites globally. Patients will be randomized 1:1 to receive one of the following treatments with open-label study drug:

- 120 mcg Lambda, weekly subcutaneous (SC) injection
- 180 mcg Lambda, weekly SC injection

Eligible patients will have chronic HDV infection (≥6 months) confirmed by positive HDV antibody (Ab) test and detectable HDV RNA by qPCR.

The study will consist of three periods (Exhibit 1):

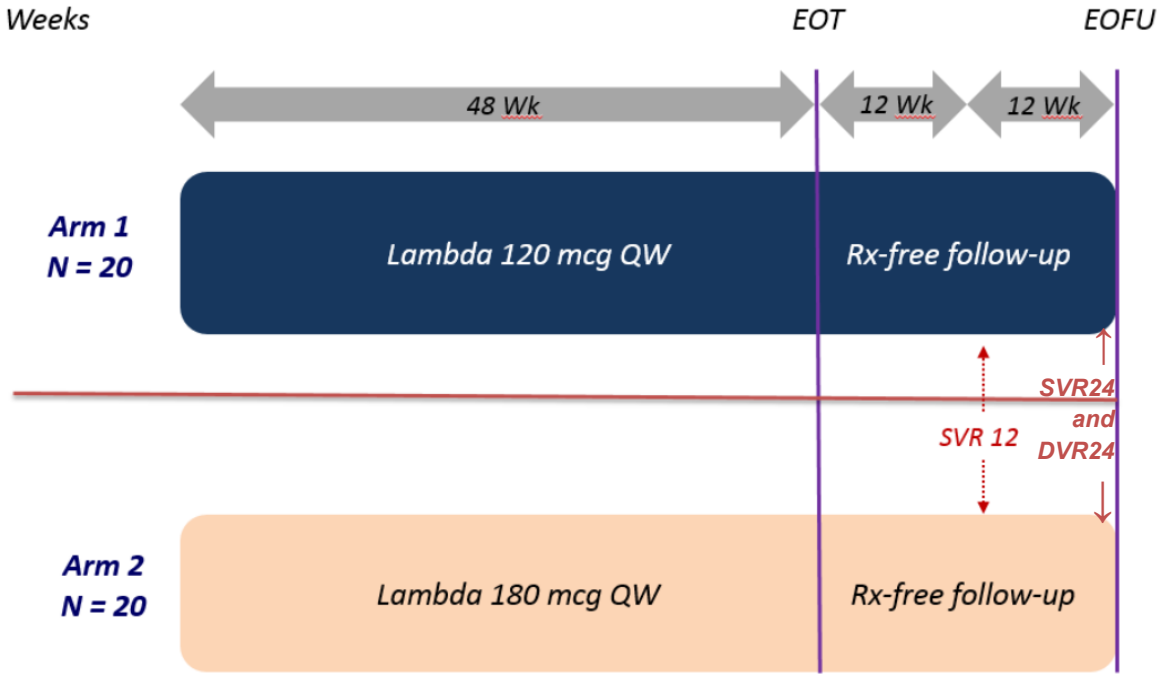
- Screening Period: Day -28 to Day 0 (maximum 4 weeks)
- Treatment Period: Day 1 (first day of treatment) through Week 48 (12 months)
- Follow-up (post-treatment) Period: Week 49 though Week 72 (6 months)

In addition, a Week 96 visit (Week 48 post-treatment) will occur to collect a blood sample for HDV RNA for qPCR and clinical laboratory tests; concomitant medications will also be captured at this visit. [The study schema shown in Exhibit 1 is taken from the protocol. See Section 3.6.1 for definitions of "sustained virologic response (SVR)" as well as the additional endpoint, "durable virologic response (DVR)."]All patients, whether they complete the treatment period or not, will be followed for 24 weeks in the post-dosing follow-up period with an additional visit at Week 96 to assess long-term durability of post-treatment endpoint

responses (HDV RNA and serum ALT). Therefore, the maximum anticipated time an individual patient will participate in the study will be 96 weeks after the screening is complete.

Patients will be required to take an anti-HBV nucleos(t)ide analog from baseline (Day 1) until the end of the study. Tenofovir disoproxil fumarate (TDF) will be prescribed for any patients not already taking one of these medications at baseline; if TDF is contraindicated then entecavir will be prescribed. This medication will protect patients from occurrences of HBV-related ALT flares related to unchecked HBV replication, with resulting secondary negative effects on the patient's HDV status (virologic control and hepatic status).

Exhibit 1. Study schema



EOT, end of treatment; EOFU, end of follow-up; QW, once a week; SVR 12, sustained virologic response at 12 weeks after treatment

Sustained virologic response and durable virologic response at 24 weeks after treatment, SVR24 and DVR24, will also be evaluated.

3.2. Study treatments

Patients will be randomly assigned 1:1 to receive either 120 mcg or 180 mcg open-label Lambda as SC weekly injection by the interactive web response system (IWRS). Lambda will be provided in ready-to-use syringes to be administered via SC injection.

Clinic staff will administer each patient's first dose of study drug in the clinic on Day 1. Clinic staff will train patients on SC administration of study drug on Day 1 and provide written instructions for drug administration and storage and safe handling of needles (including discarding instructions and provision of a sharps container). Patients will be given sufficient study drug at each visit for the number of weeks until the next visit.

Patients who require dose reduction in the 180 mcg/week dose group will be given 120 mcg/week in the first dose reduction (DR1) and 80 mcg/week in the second dose reduction (DR2); patients in the 120 mcg/week dose group will be given 80 mcg/week in DR1 and also in DR2; in effect, patients cannot be given a dose below 80 mcg/week.

3.3. Study visits and assessments

The following assessments are planned:

- Inclusion/exclusion criteria (baseline)
- Demography, including age, sex, race, and ethnicity (baseline)
- Medical history (baseline)
- Retinal examination (within 1 year of screening and at Week 48)
- Blood sampling for the following efficacy testing:
- HDV RNA viral load analysis using RoboGene® [2] HDV RNA Quantification Kit (baseline and all visits starting with Week 4, including all on-treatment and post-treatment follow-up visits)
- HBV deoxyribonucleic acid (DNA) analysis using Aptima HBV Quant DX assay via the fully automated Hologic Panther system (baseline and all visits starting with Week 4, including all on-treatment and post-treatment follow-up visits)
- HBsAg levels by Architect (Abbott) quantitative HBsAg (qHBsAg) assay (baseline and all visits starting with Week 4, including all on-treatment and post-treatment follow-up visits)
- HBsAg status (positive or negative) by Architect (Abbott) qHBsAg assay and Hepatitis B surface antibody (HBsAb) by Elecsys (Roche) qualitative antibody assay (baseline and at the Week 48 visit in the treatment period and at the Week 72 visit in the post-treatment follow-up period)

- Hepatitis B envelope antigen (HBeAg), and hepatitis B envelope antibody (HBeAb) by Elecsys (Roche) qualitative antigen and antibody assays (baseline, at the Week 24 and 48 visits in the treatment period, and at the Week 60 and 72 visits in the post-treatment follow-up period)
- Fibroscan testing (baseline and Week 48 [end of treatment, EOT])
- AEs (collected at baseline and throughout the study through the follow-up period)
- Patient reported outcomes (Day 2 through post-treatment follow-up period)
- Laboratory assessments
- HCV and human immunodeficiency virus (HIV) testing (baseline)
- Blood samples for hematology, coagulation, thyroid panel, and clinical chemistry (baseline and every subsequent visit during treatment and post-treatment follow-up periods)
- Urine samples (baseline, Week 8, 16, 24, 32, 40, and 48 visits in the treatment period and the Week 60, 72, and 96 visits in the post-treatment follow-up period)
- Vital signs, including body weight, blood pressure, heart rate, respiratory rate, and body temperature (baseline and every subsequent visit during treatment and follow-up periods); height and body mass index (BMI) (baseline)
- Concomitant medications (baseline and every subsequent visit during treatment and post-treatment follow-up periods)

Refer to Appendix 1 of the protocol for the Schedule of Assessments and Procedures.

3.4. Eligibility

Patients must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for enrollment into the study.

Exhibit 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Willing and able to comply with study procedures and provide written informed consent • Male or female, 18 to 65 years of age, inclusive • Chronic HDV infection of at least 6 months' duration documented by a positive HDV Ab test; detectable and quantifiable HDV RNA by qPCR at study entry • Serum ALT > upper limit of the normal range (ULN) and <10 × ULN at screening • ECG demonstrating no acute ischemia or clinically significant abnormality and a QT interval corrected for heart rate (QTcF) <450 ms for male patients and <460 ms for female patients • Thyroid stimulating hormone (TSH) and/or free T4 within 0.8 to 1.2 × ULN, or adequately controlled thyroid function as assessed by the investigator • Dilated retinal examination ≤1 year before screening: For patients with diabetes, hypertension, or other risk factors for retinal disease, performed by a licensed ocular specialist; for all other patients, a normal retinal examination as assessed by the investigator or a licensed ocular specialist	*General exclusions* • Participation in a clinical trial with, or use of, any investigational agent within 30 days of start of screening, or treatment with IFNs or immunomodulators within 12 months of start of screening • Previous use of Lambda. Patients who previously participated in a clinical trial of Lambda but are confirmed to have received placebo or other non-Lambda IFNs are allowed. • History or evidence of any intolerance or hypersensitivity to IFNs or other substances contained in the study medication. • Female patients who are pregnant or breastfeeding. Male patients must confirm that their female sexual partners are not pregnant. Female patients must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) within 24 hours prior to the start of investigational product. *Exclusions based on disease-related criteria (abbreviated)* • Current or previous history of decompensated liver disease • Co-infected with HIV or HCV • Past history or current evidence of decompensated liver disease • Evidence of significant portal hypertension; current presence or history of variceal bleeding • Current evidence or history of ascites requiring diuretics or paracentesis, or hepatic encephalopathy

(continued)

Exhibit 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• 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 through 90 days after the last dose of study medication. Female patients of childbearing potential are all those except patients who are surgically sterile, who have medically documented ovarian failure, or who are at least one year postmenopausal. o **For females**, 2 of the following contraceptive methods, with at least 1 being a barrier method: Hormonal contraceptives for ≥27 days before dosing; intrauterine device (IUD) in place ≥27 days before dosing; double-barrier methods (use of condom [male partner] with either diaphragm with spermicide or cervical cap with spermicide) from screening; or surgical sterilization of the partner (vasectomy ≥1 month before screening). o **For males**, surgical sterilization (vasectomy ≥1 month before screening) or both consistent and correct use of condoms and partner must use a hormonal contraceptive or a nonhormonal barrier method (IUD or diaphragm with spermicide or cervical cap with spermicide) • Willing and able to provide written informed consent • Willing and able to comply with all study procedures	• Patients with any of the following abnormalities at screening: platelet count <90,000 cells/mm^3; white blood cell (WBC) count <3,000 cells/mm^3; absolute neutrophil count (ANC) <1,500 cells/mm^3; hemoglobin <11 g/dL for women and <12 g/dL for men; serum creatinine concentration ≥1.5 × ULN; or creatinine clearance (CrCl) <50 mL/min by Cockroft-Gault • Evidence of another form of viral hepatitis or another form of liver disease • History of hepatocellular carcinoma • Patients with any of the following: current eating disorder or alcohol abuse; excessive alcohol intake; alcohol use that will interfere with study conduct; or drug abuse within the previous 6 months before the screening visit with the exception of cannabinoids and their derivatives • Prior history or current evidence of any of the following: immunologically mediated disease; retinal disorder or clinically relevant ophthalmic disorder; any malignancy within five years before screening; cardiomyopathy or significant ischemic cardiac or cerebrovascular disease; chronic pulmonary disease associated with functional impairment; pancreatitis; severe or uncontrolled psychiatric disorder; active seizure disorder; or bone marrow or solid organ transplantation • Other significant medical condition that may require intervention during the study.

(continued)

Exhibit 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
	Exclusions related to use of selected medications • Therapy with an immunomodulatory agent; IFN-α (IFN alfa-2a or IFN alfa-2b, or pegylated IFN alfa-2a or alfa-2b); cytotoxic agent, or systemic corticosteroids within 12 months before screening • Use of telbivudine within three months before screening or during the study • Current use of Heparin or Coumadin • Received blood products within 30 days prior to study randomization • Use of hematologic growth factors within 30 days prior to study randomization • Systemic antibiotics, antifungals, or antivirals for treatment of active infection other than HBV within 14 days of study randomization • Any prescription or herbal product that is not approved by the investigator • Long-term treatment (>2 weeks) with agents that have a high risk for nephrotoxicity or hepatotoxicity, should be discussed with the medical monitor • Receipt of systemic immunosuppressive therapy within the three months before start of screening

3.5. Sample size

A sample size of 40 was chosen to allow assessment of the safety, tolerability, and PD/efficacy of Lambda at 120 vs. 180 mcg/week. The sample size was not formally calculated using power analysis.

3.6. Study endpoints

3.6.1. Efficacy endpoints

The primary endpoints and additional exploratory efficacy endpoints are listed in this section. All efficacy endpoints are defined in Sections 8.1 and 8.2.

The primary efficacy endpoints are as follows:

- Change from baseline in HDV viral load at Week 48 (EOT)
- Change from baseline in HDV viral load at Week 72

The following additional efficacy endpoints will also be analyzed:

- Virologic response rate at Week 48 (EOT): Proportion of patients with HDV RNA below LLOQ at Week 48 (EOT)
- DVR rate: Proportion of patients with HDV RNA below LLOQ 24 weeks after Week 48 (Week 72)
- Virologic response rate at 12 weeks post-treatment (Week 60): Proportion of patients with HDV RNA below LLOQ 12 weeks after Week 48 (Week 60)
- Virologic response rate at 48 weeks post-treatment (Week 96): Proportion of patients with HDV RNA below LLOQ 48 weeks after Week 48 (Week 96)
- Sustained virologic response rate at 12 weeks post-treatment (SVR-12): Proportion of patients with HDV RNA below the LLOQ at Week 48 (EOT) and 12 weeks after Week 48 (Week 60)
- Sustained virologic response rate at 24 weeks post-treatment (SVR-24): Proportion of patients with HDV RNA below the LLOQ at Week 48 (EOT) and 24 weeks after Week 48 (Week 72)

- Sustained virologic response rate at 48 weeks post-treatment (SVR-48): Proportion of patients with HDV RNA below the LLOQ at Week 48 (EOT) and 48 weeks after Week 48 (Week 96)
- Proportion of patients with virologic failure (defined in Section 8.2)
- Change from baseline in HDV viral load by visit
- Change from baseline in HBV viral load by visit
- Change from baseline in HBsAg levels by visit
- Proportion of patients with clearance of HBsAg, where clearance is defined as undetectable HBsAg by current quantitative assay
- Proportion of patients with change from baseline in HBsAg categories on $\log_{10}$ scale (<0.25, 0.25 to <0.5, 0.5 to <0.75, 0.75 to <1, 1 to <1.25, 1.25 to <1.5, and ≥1.5) by visit
- Proportion of patients falling within HBsAg categories (<100 IU/mL, 100 to <200 IU/mL, 200 to <500 IU/mL, 500 to <1000 IU/mL, 1000 to <2000 IU/mL, 2000 to <10,000 IU/mL, ≥10,000 IU/mL) at each of the following times: Weeks 12, 24, and 48; at 12 and 24 weeks after EOT (Weeks 60 and 72)
- Proportion of patients with clearance of HBsAg at Weeks 12, 24, and 48; at 12 and 24 weeks after EOT (Weeks 60 and 72)
- Change from baseline in Fibroscan results at Week 48 (EOT) and 24 weeks after EOT (Week 72)
- Change from baseline in ALT at Week 48 (EOT), 24 weeks after EOT (Week 72), and 48 weeks after EOT (Week 96)
- Proportion of patients with ALT normalization (i.e., ALT ≤ULN) at Week 48 (EOT), 24 weeks after EOT (Week 72), and 48 weeks after EOT (Week 96). Note: A patient who has baseline ALT ≤ ULN cannot qualify for assessment of ALT normalization. Therefore, two separate analyses will be performed: (a) patients with baseline ALT ≤ ULN will be included in the denominator and considered "non-responders" in the proportion calculation, and (b) patients with baseline ALT ≤ ULN will be excluded altogether from the proportion calculation.

(Note: After finalization of the protocol, the sponsor has clarified the definition of "sustained virologic response [SVR]" and included "durable virologic response [DVR]" as an additional endpoint. The introduction of DVR is intended to differentiate the endpoint from SVR, which has historically been used in clinical trials of therapeutic agents for the treatment of chronic HCV infection.)

HDV RNA was measured using the RoboGene® [2] HDV RNA Quantification Kit 2.0 reverse transcription-polymerase chain reaction assay. The assay is designed to detect eight HDV genotypes, applying probes and primers specific for a subsequence of the hepatitis D antigen. The assay has a LLOQ of 14 IU/mL and limit of detection (LOD) of 6 IU/mL based on calibrated standards using a reference HDV GT-1 positive serum.

The Architect (Abbott) quantitative assay will be used to measure HBsAg (both quantitative and qualitative assessments and presence of antigen [positive, negative]), given the LLOQ of this assay is lower than that of the Architect (Abbott) qualitative assay. The HBsAg levels will be measured at screening, Day 1, and Weeks 12, 24, and 48 during the treatment period, and 12 and 24 weeks post-treatment (Weeks 60 and 72). HBsAg values will be converted to the $\log_{10}$ scale for purposes of analysis and summarization.

HBsAb, HBeAg and HBeAb will be measured using Elecsys (Roche) qualitative assays.

HBV DNA will be measured by the Aptima quantitative nucleic acid amplification assay [Hologic]. The linear range is 10 to 1,000,000,000 IU/mL (or 1 to 9 $\log_{10}$ IU/mL).

3.6.2. Safety endpoints

Safety endpoints include the following:

- Treatment-emergent AEs and serious adverse events (SAEs)
- Treatment-emergent treatment-related AEs and SAEs
- AEs leading to early discontinuation of study treatment
- AEs leading to dose reduction
- AEs leading to dose interruption

- ALT flares
- Treatment-emergent changes in clinical laboratory findings
- Anti-drug antibodies, neutralizing and non-neutralizing
- Treatment-emergent changes in vital signs
- Treatment-emergent changes in ECG findings
- Treatment-emergent changes in physical examination results
- Usage of concomitant medications during the study

4. Analysis populations

All enrolled population is defined as patients who signed the informed consent form and were assigned a patient identification number. Patient disposition and protocol deviations will be analyzed in this population.

Randomized population is defined as patients who are enrolled, randomized, and assigned to a treatment group using the IWRS system. Patients are classified according to the randomized treatment group. Note: An exception to this classification will be patients who were randomized to 180 mcg but were moved to the 120 mcg group before receiving their first dose of study drug; these patients will be included in the 120 mcg treatment group and are identified in the manually identified (non-programmable) protocol deviation spreadsheet. Analyses of baseline characteristics and efficacy will be performed on this population.

Modified intention-to-treat (MITT) population is defined as those patients in the randomized population who receive at least 80% of the total planned number of study drug doses for this protocol throughout the entire 48 week treatment period and for whom HDV viral load data are available for the Day 1 (baseline) and EOT (Week 48) study visits. Patients who receive less than 80% of the assigned dose on any given treatment day (e.g., dose missed, interrupted, or reduced to DR1 or DR2) will be excluded from this analysis population. Sensitivity analyses of efficacy and safety may be performed on patients in the MITT population; this is an update to what is stated in the protocol.

Treatment completion population is defined as randomized patients who were treated to Week 48, i.e., received a dose of study therapy in the Week 48 visit window, irrespective of dose modifications between Day 1 and Week 48. Patients in this population are classified according to treatment received.

Safety population is defined as randomized patients who received at least one dose of study therapy. Patients who receive at least one dose of assigned study therapy will be analyzed as randomized; otherwise, patients are analyzed with the treatment group that corresponds to actual treatment received as their first dose. Exposure and safety analyses will be performed on this population.

5. General conventions and statistical considerations

Categorical variables will be summarized as counts and percentages. Continuous variables will be summarized using number of patients (n), mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum.

All summaries will be presented by treatment group. Medical history, concomitant medications, and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®) and World Health Organization Drug Dictionary Enhanced (WHODDE), as applicable.

Tabular presentations will display two columns to summarize results for each of the two dose regimens; by-patient listings will present relevant electronic case report form (eCRF) data. All data listings, summaries, and statistical analyses will be generated using SAS® Version 9.1 or higher [3] or other validated software.

The following sections describe additional conventions to be used for the analyses.

5.1. Study days

For the purpose of efficacy analyses and study visits, the date of randomization will be considered Day 1, and study day will be calculated relative to the date of randomization. Specifically: Study day = date of visit/test/procedure – Day 1 date + 1.

For the purpose of safety analyses, study day will be calculated relative to the date of first dose of study therapy. Specifically: Study day = date of adverse event or laboratory abnormality – date of first dose + 1.

The following conversion factors will be used to convert days to months or years:
1 month = 30.4375 days and 1 year = 365.25 days.

5.2. Baseline

Baseline measures for non-safety evaluations are defined as the last measure on or before the date of randomization. Baseline measures for safety evaluations of laboratory tests, pulse oximetry, and vital signs are defined as the last measure on or before the date of first dose of study therapy; see Section 9.1 for the definition of a treatment-emergent adverse event.

5.3. Visit labels

All analyses requiring measurements at a specified visit (e.g., baseline, Week 48, Week 72, etc.) will use the eCRF visit label as the basis for the visit classification. In addition, the following conventions will be applied to the final visit label for each assessment date.

- If the assessment date was recorded as an unscheduled visit according to the eCRF label, then the visit label will be "Unscheduled Visit X" as noted in the eCRF label, where "X" is the unscheduled visit number.
- For patients who have early termination (ET) of treatment before Week 48, then the visit label associated with EOT should be labeled as "Week X / ET" where Week X is the next scheduled 4-week visit. If a patient discontinues treatment prior to Week 48 and between regularly scheduled visits, then the follow-up visits will be derived and labeled in four-week increments from the date of treatment discontinuation as

"Week X / FU". If the patient completes treatment to Week 48, then the eCRF visit labels for "Follow-Up 1 (Week 52)," "Follow-Up 2 (Week 56)," etc. will be relabeled as "Week X / FU," where X is the applicable week of the visit in the follow-up period.

5.4. Imputation rules for partial or missing data

5.4.1. Partial or missing efficacy measurements

This section describes imputation rules for addressing missing values. For graphical displays, imputed data will be shown only for partially missing data. By-patient listings will show raw, un-imputed results.

For the purpose of calculating endpoints involving HDV RNA measurements, values deemed less than the limit of detection (<LOD) or less than the lower limit of quantitation (<LLOQ) will be imputed as follows.

- If the HDV RNA value is "<LOD" or "<6 IU/mL", then the RNA value will be imputed as the midpoint between 0 and 6: 6/2 = 3.0 IU/mL.
- If the HDV RNA value is "<LLOQ" or "<14 IU/mL", then the RNA value will be imputed as the midpoint between 6 and 14: [(14-6)/2] + 6 = 10 IU/mL.

Several planned endpoints require measurements at specified visits – e.g., change from baseline in HDV viral load at Weeks 48 and 72; proportion of patients with durable virologic response at 24 weeks after EOT (DVR); virologic response at Week 48 (EOT), at 12 weeks post-treatment, and at 48 weeks post-treatment; SVR-12, SVR-24, and SVR-48; and change from baseline in ALT 24 and 48 weeks after EOT. The specified visits may have missing data for one of the following reasons:

- A visit occurred, but the relevant data were not collected
- A visit occurred, and data were collected, but the visit fell outside of the visit window defined in Section 5.3
- A visit did not occur
- The patient withdrew from the study or was lost to follow-up before reaching the visit window

A missing HDV RNA value at the Week 48 visit and Week 60 visit (12 weeks after EOT) will be imputed as follows:

- A missing value bracketed by prior and subsequent values of "<LOD" from the adjacent visit windows will be imputed as 3.0 IU/mL.
- A missing value bracketed by prior and subsequent values of "<LLOQ" will be imputed as 10 IU/mL.
- A missing value bracketed by a prior value of "<LOD" and a subsequent value of "<LLOQ", or vice versa, will be imputed as 10 IU/mL.
- For virologic response at Week 48, DVR, virologic response at 12 weeks post-treatment, virologic response at 48 weeks post-treatment, SVR-12, SVR-24, and SVR-48, a missing value at the timepoint of interest bracketed by non-missing values from adjacent visits will be imputed as a responder if both adjacent values show HDV RNA values below LLOQ. Otherwise, the missing value will result in the patient being counted as a non-responder.
- If the Week 96 value is missing and the prior adjacent visit has a non-missing value, then the prior value will be carried forward to Week 96.
- For a given HDV RNA endpoint, if the Week 96 value is missing, the adjacent visit prior to Week 96 is a response (as defined for the HDV RNA endpoint), and a visit occurred within -1 month and +6 months of Week 96 showing response, then the endpoint will be imputed as a responder; otherwise, it will not be imputed. A patient with a missing value at this visit will be counted as a non-responder in the calculation of the endpoint.
- A missing value due to early treatment discontinuation, study withdrawal, or loss to follow-up will result in the patient being counted as a non-responder in the calculation of virologic response at Week 48, DVR, virologic response 12 weeks post-treatment, virologic response 48 weeks post-treatment, SVR-12, SVR-24, and SVR-48.

5.4.2. Partial or missing dates

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the first of the month will be used to replace the missing day. The imputed date will be compared to the last known alive date + 1 and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known alive date + 1.
- If the date is completely missing but a reason for death is present, the death date will be imputed as the last known alive date + 1.

For other partially missing dates, the following conventions will be used:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, July 1st will replace the missing information.
- Exception: If an AE has a partially missing date with missing day and the month is the same month as first dose date, then the date will be imputed to be the first dose date so that the AE is considered treatment-emergent.

If a date is completely missing, it will be considered as missing.

5.5. Software

All data listings, summaries, figures, and statistical analyses will be generated using SAS Version 9.1 or higher [3] or other validated software.

6. Study population summaries

6.1. Patient disposition

The total number of patients enrolled (randomized or not randomized) will be presented along with the reason for not being randomized. The number and percentage of randomized patients who were treated and not treated and who withdrew early from the study will be presented

by treatment group (as randomized), along with the reason for not receiving treatment and reason for study withdrawal. The number and percentage of treated patients who had early treatment discontinuation will be presented by treatment, along with the reason for treatment discontinuation. The number and percentage of patients in each analysis population will also be presented.

The number and percentage of patients in each of the analysis populations will be summarized in a separate table. The populations are as follows:

- All enrolled population
- Randomized population
- MITT population
- Treatment completion population
- Safety population.

Patients who do not meet the criteria for the MITT population will be further classified as follows: the number and percentage who had a dose reduction and continued treatment to Week 48, and the number and percentage who had a dose reduction and discontinued treatment prior to Week 48.

6.2. Protocol deviations

The programmable deviations from the eligibility criteria and on-study requirements as shown in the appendix (Section 11) will be considered important protocol deviations. (Note: ICH E3 defines "important protocol deviations" as a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a patient's rights, safety, or well-being.)

Non-programmable important eligibility and on-treatment protocol deviations will be identified through manual reviews and recorded separately for inclusion in the clinical study report.

6.3. Demographics and baseline characteristics

The following demographic and baseline characteristics will be summarized. Unless otherwise noted, the analyses will be performed for randomized population by treatment group as randomized.

Demography:

- Age (descriptive statistics)
- Age (65, ≥65 – <75, ≥ 75)
- Gender, race/ethnicity, region

Physical measurements:

- Height (descriptive statistics, in meters)
- Weight (descriptive statistics, in kilograms)
- BMI (descriptive statistics, in kg/m^2)
- BMI (<25, 25 – < 30, ≥ 30 kg/m^2)

Disease characteristics:

- Baseline HDV RNA level (descriptive statistics)
- Baseline HDV RNA category (≤ 4 log_{10} IU/mL or > 4 log_{10} IU/mL)
- Baseline ALT threshold (< 2×ULN, ≥ 2×ULN and ≤ 5×ULN, > 5×ULN and ≤ 10×ULN, > 10×ULN)
- Baseline ALT category (≤ ULN, > ULN)
- Baseline ALT level (descriptive statistics)
- Baseline HBsAg and HBeAg status (positive, negative)
- Baseline HBsAg category (>1500 IU/mL, 1500–20,000 IU/mL, >20,000 IU/mL)
- Baseline HBsAg level (descriptive statistics)
- Baseline Fibroscan exam (2–7 kPa, >7 kPa; summary statistics for ratio of interquartile range liver stiffness to median liver stiffness [%])
- Baseline retinal exam results (normal vs. abnormal), by eye (left, right)

Other commonly collected baseline laboratory measurements will be summarized for all randomized patients by treatment group as treated and grade (0, 1, 2, 3, 4). These tests include, but are not limited to:

- Hepatobiliary: albumin, alkaline phosphatase, aspartate aminotransferase (AST), direct bilirubin, indirect bilirubin, total bilirubin, and GGT
- Hematology: ANC, hemoglobin, international normalized ratio (INR), prothrombin time, lymphocytes (absolute), platelets, WBC count

6.4. Prior medications

The following will be summarized by treatment group as randomized:

- Prior treatment with HBV or HDV medication (yes/no)
- Prior HBV or HDV treatments (drug name, number of HBV or HDV treatments received)

6.5. Medical history

General medical history will be summarized and listed by patient.

7. Exposure

Extent of exposure will be summarized for the safety population by treatment group as treated.

7.1. Administration of study therapy and adherence

Site staff will count syringes to monitor study treatment adherence. The number of doses of each Lambda treatment will be summarized by treatment group with descriptive statistics.

For each patient, the number of expected doses of an assigned treatment component is the total number of days from Day 1 to the last scheduled day for treatment administration. For a patient who discontinued from a treatment component permanently, the number of expected doses for that treatment component is the total number of days from Day 1 to the date of the last dose of study medication. Percent adherence will be calculated as follows.

Percent adherence = 100 × (Number of Actual Doses / Number of Expected Doses)

Because the last dose of study therapy is not captured on the eCRF, the patient visit date recorded in the patient registration portal and labeled as "Week 48 / EOT Date" will be used as the date of last dose.

7.2. Discontinuation of study therapy

The reason for discontinuation of study therapy will be summarized by study therapy and component of the regimen. In addition, duration of treatment (time to last dose) will be presented by treatment group as a Kaplan-Meier analysis, where the last dose date for a study drug within the treatment regimen will be the event date. The study has a 48 week fixed treatment period. Therefore, all patients will have a last dose date, i.e., there should be no censoring, and the curves will represent the cumulative treatment discontinuation rate over time. The median duration of treatment and associated 95% CI will be presented.

7.3. Dose reduction and dose interruption

The following analyses will summarize timing of first dose relative to randomization, dose interruptions and dose reductions:

- Time from randomization to first dose of study therapy (0–3, > 3 to 7, > 7 to 14, > 14 to 21, > 21 to 28, > 28 days)
- Number and percentage of patients with at least one interrupted dose
- Reason for first dose interruption
- Number and percentage of patients with a dose reduction
- Total number of dose reductions (descriptive statistics)
- Total number of dose interruptions (descriptive statistics)

The analyses described in this section will also be produced for patients who did not meet the MITT criteria.

7.4. Concomitant medications

Concomitant medications are summarized by treatment group for patients in the safety population. These are medications taken any time on or after the first dose of study therapy and on or before the last dose of study therapy. Medications will be presented alphabetically by anatomic class, therapeutic class and generic name using the World Health Organization (WHO) dictionary.

8. Efficacy analyses

All efficacy analyses of HDV RNA will transform the raw values to the $\log_{10}$ IU/mL scale before conducting the analyses. Listings will include both the raw and transformed values.

8.1. Primary efficacy endpoint

The primary endpoints are change from baseline in HDV viral load at Week 48 and change from baseline in HDV viral load at Week 72. The primary endpoints for each treatment group will be summarized by visit with descriptive statistics (n, mean, median, standard deviation, 25th quartile, 75th quartile, minimum, and maximum).

The primary efficacy analysis will compare the treatment group differences in means of the Lambda dose groups against each other using an analysis of covariance model (ANCOVA) with treatment group as a covariate. The difference in the mean differences for each comparison will be calculated and reported along with their 95% confidence intervals (CIs).

The primary analyses will be performed for the randomized, MITT, and treatment completion populations.

8.2. Efficacy exploratory endpoints

Additional efficacy analyses will evaluate the following endpoints for the randomized populations:

- Virologic response rate at Week 48: Proportion of patients with HDV RNA below LLOQ at Week 48 (EOT)

- DVR rate: Proportion of patients with HDV RNA below LLOQ 24 weeks after Week 48 (Week 72)
- Virologic response rate at 12 weeks post-treatment (Week 60): Proportion of patients with HDV RNA below LLOQ 12 weeks after Week 48 (Week 60)
- Virologic response rate at 48 weeks post-treatment (Week 96): Proportion of patients with HDV RNA below LLOQ 48 weeks after Week 48 (Week 96)
- Sustained virologic response rate at 12 weeks post-treatment (SVR-12): Proportion of patients with HDV RNA below the LLOQ at Week 48 (EOT) and 12 weeks after Week 48 (Week 60)
- Sustained virologic response rate at 24 weeks post-treatment (SVR-24): Proportion of patients with HDV RNA below the LLOQ at Week 48 (EOT) and 24 weeks after Week 48 (Week 72)
- Sustained virologic response rate at 48 weeks post-treatment (SVR-48): Proportion of patients with HDV RNA below the LLOQ at Week 48 (EOT) and 48 weeks after Week 48 (Week 96)
- Proportion of patients with virologic failure, defined as any of the following occurring during or post-treatment: (a) serum HDV RNA increases at least 1 $\log_{10}$ above the nadir value on two consecutive visits in patients who are on Lambda treatment; (b) serum HDV RNA detectable by qPCR (≥ LLOQ) in patients who had undetectable HDV RNA (< LLOQ) during therapy (breakthrough) or during the follow-up period (relapse); or (c) serum HDV RNA ≤ 1 $\log_{10}$ reduced from the baseline value through EOT (virologic non-response).
- Change from baseline in HDV viral load
- Change from baseline in HBV viral load
- Change from baseline in HBsAg levels
- Proportion of patients with clearance of HBsAg, where clearance is defined as undetectable HBsAg by current quantitative HBsAg assay
- Proportion of patients with change from baseline in HBsAg categories on $\log_{10}$ scale (<0.25, 0.25 to <0.5, 0.5 to <0.75, 0.75 to <1, 1 to <1.25, 1.25 to <1.5, and ≥ 1.5) by visit

- Proportion of patients within each HBsAg category (<100 IU/mL, 100 to <200 IU/mL, 200 to <500 IU/mL, 500 to <1000 IU/mL, 1000 to <2000 IU/mL, 2000 to <10,000 IU/mL, ≥10,000 IU/mL) at each of the following times: Weeks 12, 24, and 48; at 12 and 24 weeks after EOT (Weeks 60 and 72)
- Proportion of patients with clearance of HBsAg at Weeks 12, 24, or 48 during the treatment period; at 12 and 24 weeks after EOT (Weeks 60 and 72)
- Change from baseline in Fibroscan results at Week 48 (EOT) and 24 weeks after EOT (Week 72)
- Change from baseline in ALT at Week 48 (EOT), 24 weeks after EOT (Week 72), and 48 weeks after EOT (Week 96)
- Proportion of patients with ALT normalization (i.e., ALT ≤ ULN) at Week 48 (EOT), 24 weeks after EOT (Week 72), and 48 weeks after EOT (Week 96). Note: A patient who has baseline ALT ≤ ULN cannot qualify for assessment of ALT normalization. Therefore, two separate analyses will be performed: (a) patients with baseline ALT ≤ ULN will be included in the denominator and considered "non-responders" in the proportion calculation, and (b) patients with baseline ALT ≤ ULN will be excluded altogether from the proportion calculation.

All exploratory efficacy endpoints will be analyzed in the randomized population. The following endpoints will also be analyzed in the MITT population and the treatment completion population:

- Change from baseline in HDV viral load at Week 48
- Change from baseline in HDV viral load at Week 72
- Virologic response rate at Week 48
- DVR rate
- SVR-24 rate

Each proportion endpoint will be presented as the frequency and percentage for each treatment group along with the exact 95% CI. The difference in the proportions will be presented along with the exact 95% CI.

The change from baseline endpoints by visit for all visits will be presented as longitudinal plots of the mean change from baseline by visit and treatment group with error bars representing the associated 95% CIs. In addition, boxplots will also be shown by visit and treatment group.

Change in ALT at Week 48 (EOT), 24 weeks after EOT (Week 72), and 48 weeks after EOT (Week 96) will be shown as a lab shift table with baseline vs. Week 48, Week 72, and Week 96 (as applicable) categorized ALT values (< 2×ULN, ≥ 2×ULN and ≤ 5×ULN, > 5×ULN and ≤ 10×ULN, > 10×ULN).

8.3. Sensitivity analyses

The following sensitivity analyses will be performed:

- DVR and SVR accounting for HDV RNA level at baseline: The DVR and SVR endpoints will also be performed in randomized population and treatment completion population *excluding* patients with HDV RNA level below LLOQ at baseline from the denominator of each proportion calculation.
- DVR and SVR accounting for virologic failure: The DVR and SVR endpoints will also be performed in the randomized population and treatment completion population *excluding* responders with virologic failure from the numerator of each proportion calculation (see Section 8.2 for the definition of virologic failure).

8.4. Interim analyses and data monitoring

The study will have interim data snapshots for review and presentation.

8.5. Multiplicity

As there are no formal statistical tests and all analyses are descriptive, interim analyses will not require multiplicity adjustments.

9. Safety summaries

9.1. Adverse events

Adverse events (AEs) will be coded by the most current version of MedDRA at the time of the database lock for the final analysis and summarized by system organ class, preferred term (PT), and worst National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03) grade per patient. Adverse events will be summarized by patient, not event.

Investigators will assess the relationship of each AE to study drug. The relationship of each AE to study drug will be categorized as not related, unlikely related, possibly related, probably related, and definitely related.

All AE presentations will summarize treatment-emergent adverse events (TEAEs), defined as AEs with onset on or after first dose date or onset prior to first dose date but with worsened grade on or after first dose date. AEs without a severity rating that are reported post-randomization will be considered treatment-emergent. Presentations will include all AEs up to 28 days after the last dose of study treatment. All SAEs and deaths will be summarized, i.e., no window will be applied to SAEs and deaths.

The following presentations of TEAEs will be generated:

- SAEs
- All AEs
- AEs ≥Grade 3 in severity
- AEs related to study drug (i.e., AEs classified as possibly, probably, and definitely related)
- AEs leading to treatment discontinuation
- AEs of special interest: flu-like symptoms (PT), musculoskeletal symptoms (PTs: arthralgia, myalgia, and back pain), constitutional symptoms (PTs: fatigue and asthenia), neurologic symptoms (PTs: headache and dizziness), psychiatric symptoms (PTs: depression, irritability, and insomnia). In addition, a sensitivity

analysis will be performed to assess flulike symptoms by presence of ≥2 of the following PTs: pyrexia, chills, arthralgia, and myalgia.

All adverse events will be listed with MedDRA coding, onset and resolution dates, seriousness, severity, relationship, actions, and outcome.

9.2. Deaths

The number of patients who died will be summarized by treatment group. A by-patient listing of deaths including death date, cause of death, and relationship to study treatment.

9.3. Vital signs

Vital signs (blood pressure, heart rate, temperature, and respiratory rate) are collected according to the schedule in Section 3.3. These data may be analyzed using summary statistics on changes from baseline or distribution of worst on-study value based on CTCAE grade. Figures rather than tabular presentation may be used if appropriate.

9.4. Laboratory parameters

Presentations will include all laboratory data after a patient discontinues from the study. A by-patient listing of laboratory parameters will be provided.

9.4.1. Hematology

The following will be summarized by treatment group as worst CTC grade on-treatment per patient and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per patient: hemoglobin, platelets, WBCs, ANC, and lymphocyte count.

ANC is defined as WBC x(%PMN +%Bands) x 10, where PMN refers to the polymorphonuclear cell family and includes neutrophils, basophils, and eosinophils.

9.4.2. Serum chemistry

The following will be summarized by treatment group as worst CTC grade on-treatment per patient and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per patient: ALT, AST, alkaline phosphatase, total bilirubin, and creatinine.

9.4.3. Electrolytes

The following will be summarized by treatment group as worst CTC grade on-treatment per patient and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per patient: sodium (high and low), potassium (high and low), calcium (high and low), and magnesium (high and low).

9.4.4. Hepatic function and ALT flares

The number of patients with the following laboratory abnormalities from on-treatment evaluations will be summarized by treatment group:

- ALT or AST >5 x ULN, >10 x ULN and >20 x ULN
- Total bilirubin >2 x ULN
- Concurrent (within 1 day) ALT or AST >5 x ULN and total bilirubin >2 x ULN
- Concurrent (within 30 days) ALT or AST >5 x ULN and total bilirubin >2 x ULN

The following scatterplots will be produced for the following hepatic laboratory parameters:

- Total bilirubin peak vs. AST peak
- Total bilirubin peak vs. ALT peak

ALT flares are events of special interest. ALT flare definitions are specific to study periods as follows:

- On-treatment ALT flare is defined as an ALT measurement >2 × baseline and >10 × ULN occurring between the start of study treatment and the end of study therapy plus 10 days.
- Post-treatment ALT flare is defined as an ALT measurement >2 × reference and >10 x ULN occurring between the end of study treatment plus 11 days to the end of

off-treatment follow-up, where the reference is the minimum of the baseline and last ALT value up to the end of study treatment plus 10 days.

Summaries of ALT flares will be presented separately for the on-treatment and follow-up periods. The number and percent of patients with one or more ALT flare will be summarized by treatment group. Graphical longitudinal displays of ALT flares with HDV RNA changes may also be presented.

Among patients with ALT flares, the number and percent of patients with and without concurrent post-baseline laboratory abnormalities (occurring ± 30 days of an ALT flare, regardless of study period) will also be summarized. The post-baseline concurrent laboratory abnormalities of interest include:

- INR >2 x ULN or prothrombin time >1.5 x ULN
- Total bilirubin >2.5 x ULN

Patients with missing ALT data in a given period will be excluded from the analysis**.**

9.5. Immunogenicity analyses

Immunogenicity results will be summarized for patients in the safety population who have at least one post-baseline test result. Patients who have detectable anti-Lambda antibodies at baseline will be assessed for an on-study increase in antibody titer. Patients who lack detectable anti-Lambda antibodies at baseline will be assessed for the development of an on-study antibody response (anti-drug antibody seroconversion).

For patients with antibodies at baseline, the number and percent of patients who have measurable (defined as ≥5-fold) increases in titer will be reported by treatment group. The number and percent of patients who develop anti-drug antibodies to Lambda will be summarized by treatment group and scheduled visit. The following will be summarized:

- Incidence of patients who seroconverted (only patients without antibodies at baseline);

- Incidence of patients with neutralizing and non-neutralizing antibodies for patients who seroconvert.

10. References

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Statistical principles for clinical trials (E9). ICH Harmonized Tripartite Guideline; 1998.

2. Analytikjena. RoboGene HDV RNA quantification kit 2.0. 2017: https://www.analytik-jena.com/fileadmin/content/products/02_Kits/RoboGene_HDV_RNA_Quantification_Kit_2_0/Manual_RoboGene_HDV_RNA_Quantification_Kit_2_0_CE.pdf.

3. *SAS*, Version 9.1, Cary NC: SAS Institute; 2002.

11. Appendix: Important protocol deviations

Exhibit 3 shows the important protocol deviations pertaining to the inclusion and exclusion criteria as well as on-study important protocol deviations.

Exhibit 3. Important protocol deviations

Protocol requirement	Programmable	Important deviation from criterion
Inclusion criteria:		
Willing and able to comply with study procedures and provide written informed consent	No	
Male or female, 18 to 65 years of age, inclusive	Yes	Patient's baseline age was not between 18 to 65 years, inclusive.
Chronic HDV infection of at least 6 months' duration documented by a positive HDV Ab test; detectable and quantifiable HDV RNA by qPCR at study entry	Yes	Patient did not have documented chronic HDV infection, defined as at least 6 months' duration by positive HDV Ab test.
Serum ALT > ULN and <10 × ULN at screening	Yes	Patient did not have a baseline serum ALT > ULN and < 10 × ULN.
ECG demonstrating no acute ischemia or clinically significant abnormality and a QTcF <450 ms for male patients and <460 ms for female patients	Yes	Patient had a baseline ECG showing a clinically significant abnormality.
TSH and/or free T4 within 0.8 to 1.2 × ULN, or adequately controlled thyroid function as assessed by the investigator	Yes	Patient had a baseline TSH or free T4 that is >1.2 times the normal limit.
Dilated retinal examination ≤1 year before screening: For patients with diabetes, hypertension, or other risk factors for retinal disease, performed by a licensed ocular specialist; for all other patients, a normal retinal examination as assessed by the investigator or a licensed ocular specialist	Yes	Patient had an abnormal retinal examination finding at baseline or did not have a baseline retinal examination performed.

(continued)

Exhibit 3. Important protocol deviations, continued

Protocol requirement	Programmable	Important deviation from criterion
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 through 90 days after the last dose of study medication. Female patients of childbearing potential are all those except patients who are surgically sterile, who have medically documented ovarian failure, or who are at least one year postmenopausal.	Yes	Female patient did not have evidence of a negative serum or urine pregnancy test.
Willing and able to provide written informed consent	No	
Willing and able to comply with all study procedures	No	
Exclusion criteria:		
Participation in a clinical trial with, or use of, any investigational agent within 30 days of start of screening, or treatment with IFNs or immunomodulators within 12 months of start of screening	Yes	Patient had prior treatment with an IFN therapy or regimen within 30 days of start of screening.
Previous use of Lambda. Patients who previously participated in a clinical trial of Lambda but are confirmed to have received placebo or other non-Lambda IFNs are allowed.	Yes	Patient had prior treatment with Lambda.
History or evidence of any intolerance or hypersensitivity to IFNs or other substances contained in the study medication.	No	
Female patients who are pregnant or breastfeeding. Male patients must confirm that their female sexual partners are not pregnant. Female patients must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to the start of investigational product.	Yes	Female patient did not have evidence of a negative serum or urine pregnancy test.

(continued)

Exhibit 3. Important protocol deviations, continued

Protocol requirement	Programmable	Important deviation from criterion
Current or previous history of decompensated liver disease	No	
Co-infected with HIV or HCV	Yes	Patient was HIV-positive at screening. Patient was HCV-positive at screening.
Past history or current evidence of decompensated liver disease	No	
Evidence of significant portal hypertension; current presence or history of variceal bleeding	No	
Current evidence or history of ascites requiring diuretics or paracentesis, or hepatic encephalopathy	No	
Patients with any of the following abnormalities at screening: platelet count <90,000 cells/mm3; WBC count <3,000 cells/mm3; ANC <1,500 cells/mm3; hemoglobin <11 g/dL for women and <12 g/dL for men; serum creatinine concentration ≥1.5 × ULN; or CrCl <50 mL/min by Cockroft-Gault	Yes	Patient had one of the following abnormalities at screening: (a) platelet count <90,000 cells/mm^3, (b) WBC count <3,000 cells/mm^3, (c) ANC <1,500 cells/mm^3, (d) hemoglobin <11 g/dL for women and <12 g/dL for men, (e) serum creatinine concentration ≥1.5 x ULN, or (f) CrCl <50 mL/min by Cockroft-Gault.
Evidence of another form of viral hepatitis or another form of liver disease	No	
History of hepatocellular carcinoma	Yes	Patient had a history of hepatocellular carcinoma.
Patients with any of the following: current eating disorder or alcohol abuse; excessive alcohol intake; alcohol use that will interfere with study conduct; or drug abuse within the previous 6 months before the screening visit with the exception of cannabinoids and their derivatives	No	

(continued)

Exhibit 3. Important protocol deviations, continued

Protocol requirement	Programmable	Important deviation from criterion
Prior history or current evidence of any of the following: immunologically mediated disease; retinal disorder or clinically relevant ophthalmic disorder; any malignancy within five years before screening; cardiomyopathy or significant ischemic cardiac or cerebrovascular disease; chronic pulmonary disease associated with functional impairment; pancreatitis; severe or uncontrolled psychiatric disorder; active seizure disorder; or bone marrow or solid organ transplantation	No	
Other significant medical condition that may require intervention during the study.	No	
Therapy with an immunomodulatory agent; IFN-α (IFN alfa-2a or IFN alfa-2b, or pegylated IFN alfa-2a or alfa-2b); cytotoxic agent, or systemic corticosteroids within 12 months before screening	No	
Use of telbivudine within three months before screening or during the study	Yes	Patient received telbivudine within 3 months prior to screening.
Current use of Heparin or Coumadin	Yes	Patient received Heparin or Coumadin within 3 months prior to screening.
Received blood products within 30 days prior to study randomization	No	
Use of hematologic growth factors within 30 days prior to study randomization	No	
Systemic antibiotics, antifungals, or antivirals for treatment of active infection other than HBV within 14 days of study randomization	No	

(continued)

Exhibit 3. Important protocol deviations, continued

Protocol requirement	Programmable	Important deviation from criterion
Any prescription or herbal product that is not approved by the investigator	No	
Long-term treatment (>2 weeks) with agents that have a high risk for nephrotoxicity or hepatotoxicity, should be discussed with the medical monitor	No	
Receipt of systemic immunosuppressive therapy within the three months before start of screening	No	
On-study criteria:		
Randomization vs. treatment	Yes	Patient received an incorrect study treatment, i.e., a treatment that is not what the patient was randomized to receive.
Randomization vs. treatment	No	Patient manually identified in protocol deviation spreadsheet who was randomized to 180 mcg but was moved to the 120 mcg group before receiving their first dose of study drug.
Anti-HDV therapy	Yes	Patient received alternative anti-HDV therapy.
Anti-HBV therapy	Yes	Patient did NOT receive one of the following medications from Day 1 to end of study: entecavir or tenofovir

(continued)

Exhibit 3. Important protocol deviations, continued

Protocol requirement	Programmable	Important deviation from criterion
Dose interruption, reduction, and discontinuation criteria, as defined in Section 5.4.3 of the protocol	Yes	Patient's dose was NOT reduced after any of the following events: • ANC ≥ 500/mm3 and < 750/mm3: reduce to DR1 • Platelets < 50,000: reduce to DR2 Patient's dose was NOT interrupted after any of the following events: • ANC < 500/mm3 • ALT (or AST) ≥ 15 × ULN and total bilirubin (TBILI) and/or INR < Grade 2 • TBILI > 2.5 × ULN and DB > 3 × ULN Patient's treatment was NOT discontinued after any of the following events: • ANC < 500/mm3 occurred and did not resolve within 4 weeks • ANC < 500/mm3 recurred at DR2 • Two consecutive occurrences of platelets < 25,000 ALT (or AST) ≥ 15 × ULN and TBILI and/or INR < Grade 2 occurred and did not resolve within 4 weeks

(continued)

Exhibit 3. Important protocol deviations, continued

Protocol requirement	Programmable	Important deviation from criterion
		• Two consecutive occurrences of ALT (or AST) ≥ 5×ULN **and** TBILI and/or INR ≥ Grade 2 • TBILI > 2.5 × ULN **and** DB > 3 × ULN occurred and did not resolve within 2 weeks • TBILI > 2.5 × ULN **and** DB > 3 × ULN recurred at DR2 • All of the following occurred simultaneously: o ALT > 10 × ULN o ALT > 5 × baseline or nadir, whichever is lower o Total bilirubin > 5 × ULN o INR > 1.5 × ULN confirmed with local confirmation
Efficacy labs	Yes	Patient did not have the following at baseline and Weeks 12, 24, 48, and 72: • HDV RNA levels • ALT values • HBsAg, HBsAb, HBeAg, and HBeAb levels. Patient did not have Fibroscan results at baseline and Weeks 48 and 72.