Supplemental Table 1: Univariable analysis of the baseline characteristics associated with response at 72 weeks.

Characteristic	**Responders** N=11	**Non responders** N=22	**p-value**
Age, years (range)	42.9 (26, 63)	38 (20, 63)	0.31
Male, n (%)	6 (54.5)	16 (72.7)	0.44
Prior Interferon Use (%)	3 (27.3)	13 (59.1)	0.14
Cirrhosis (%)	0 (0%)	3 (14%)	0.53
Liver stiffness, kPa	11.8 (4.6, 27.4)	11.6 (6.5, 20)	0.92
HDV RNA, log_{10} IU/mL (range)[1]	3.45 (0.47, 7.31)	4.28 (3.3, 6.1)	0.17
ALT, U/mL (range)[2]	95 (55, 147)	116 (35, 364)	0.46
Total Bilirubin, mcmol/L (range)[2]	7.55 (4, 13)	9.36 (3, 20)	0.26
Albumin, g/L (range)[2]	45 (37, 49)	43 (37, 52)	0.22
INR (range)[2]	1.22 (1.1, 1.5)	1.24 (1, 1.6)	0.68
Platelets, $x10^9$/L (range)[2]	181 (95, 303)	184 (99, 281)	0.89

* HDV RNA BLQ or >2 log decline in HDV RNA compared to baseline values at week 72

Supplemental Table 2: Response to treatment in patients with high vs low baseline viral load

A: 180 mcg arm

			48 Week End of Treatment		**24 Week Post-Treatment**
Dose		N	Mean Log10 Decline	#BLQ	#BLQ
180 mcg	All	14	-2.3	5 / 14 36%	5 / 14 36%
	High BL VL	8		3 / 8 38%	2 / 8 25%
	Low BL VL	6		2 / 6 33%	3 / 6 50%

B: 120 mcg arm

			48 Week End of Treatment		24 Week Post-Treatment
Dose		N	Mean Log10 Decline	#BLQ	#BLQ
120 mcg	All	19	-1.3	3 / 19 16%	3 / 19 16%
	[1]High BL VL	12		2 / 12 17%	1/ 12 8%
	[2]Low BL VL	7		1 / 7 14%	2 / 7 29%

Abbreviations: BL = baseline; BLQ = below limit of quantification; VL= viral load.

[1] ≥ 4 $\log_{10}$

[2] <4 $\log_{10}$

	Baseline	Week 48	Week 72	p-value
120 mcg	11.0 (7.1, 17.3)	12.4 (6.7, 20.2)	11.9 (5.5, 23.4)	0.232
180 mcg	12.7 (4.6, 27.4)	19.2 (3, 36.3)	16.3 (4.4, 64)	0.178

Supplemental Table 3: Changes in liver stiffness over the course of the study

A: Liver stiffness (kPa) at baseline, week 48 and week 72 in the 2 treatment arms

B: Liver stiffness (kPa) at baseline, week 48 and week 72 in responders and non-responders

	Baseline	Week 48	Week 72	p-value
*Responders	11.8 (4.6, 27.4)	17.7 (3, 36.3)	13.5 (4.4, 23.4)	0.234
Non-responders	11.6 (6.5, 20)	13.4 (6.7, 31.5)	14.3 (5.5, 64)	0.292

*Patients achieving HDV RNA BLQ or >2 log decline in HDV RNA compared to baseline values at week 72

Supplemental Table 4: Adverse events by system organ class and severity

System Organ Class & CTCAE Grade	Number of Patients Experiencing Adverse Event[1]		
	120 mcg (N = 19) (%)	180 mcg (N = 14) (%)	Total (N = 33) (%)
Endocrine disorders	1 (5.3)	1 (7.1)	2 (6.1)
Grade 1	1 (5.3)	1 (7.1)	2 (6.1)
Eye disorders	0	2 (14.3)	2 (6.1)
Grade 1	0	1 (7.1)	1 (3.0)
Grade 2	0	1 (7.1)	1 (3.0)
Gastrointestinal disorders	11 (57.9)	11 (78.6)	22 (66.7)
Grade 1	4 (21.1)	5 (35.7)	9 (27.3)
Grade 2	7 (36.8)	6 (42.9)	13 (39.4)
General disorders	13 (68.4)	12 (85.7)	25 (75.8)
Grade 1	10 (52.6)	5 (35.7)	15 (45.5)

System Organ Class & CTCAE Grade	Number of Patients Experiencing Adverse Event[1]		
	120 mcg (N = 19) (%)	180 mcg (N = 14) (%)	Total (N = 33) (%)
Grade 2	3 (15.8)	6 (42.9)	9 (27.3)
Grade 3	0	1 (7.1)	1 (3.0)
Hepatobiliary disorders	6 (31.6)	3 (21.4)	9 (27.3)
Grade 1	4 (21.1)	2 (14.3)	6 (18.2)
Grade 2	0	1 (7.1)	1 (3.0)
Grade 3	2 (10.5)	0	2 (6.1)
Infections and infestations	8 (42.1)	4 (28.6)	12 (36.4)
Grade 1	5 (26.3)	1 (7.1)	6 (18.2)
Grade 2	2 (10.5)	3 (21.4)	5 (15.2)
Grade 3	1 (5.3)	0	1 (3.0)
Investigations	10 (52.6)	8 (57.1)	18 (54.5)
Grade 1	3 (15.8)	0	3 (9.1)
Grade 2	1 (5.3)	1 (7.1)	2 (6.1)
Grade 3	5 (26.3)	5 (35.7)	10 (30.3)
Grade 4	1 (5.3)	2 (14.3)	3 (9.1)
Metabolism and nutrition disorders	0	5 (35.7)	5 (15.2)
Grade 1	0	5 (35.7)	5 (15.2)
Musculoskeletal and connective tissue disorders	10 (52.6)	9 (64.3)	19 (57.6)
Grade 1	7 (36.8)	5 (35.7)	12 (36.4)

System Organ Class & CTCAE Grade	Number of Patients Experiencing Adverse Event[1]		
	120 mcg (N = 19) (%)	**180 mcg (N = 14) (%)**	**Total (N = 33) (%)**
Grade 2	3 (15.8)	3 (21.4)	6 (18.2)
Grade 3	0	1 (7.1)	1 (3.0)
Nervous system disorders	10 (52.6)	12 (85.7)	22 (66.7)
Grade 1	9 (47.4)	6 (42.9)	15 (45.5)
Grade 2	0	5 (35.7)	5 (15.2)
Grade 3	1 (5.3)	1 (7.1)	2 (6.1)
Psychiatric disorders	0	1 (7.1)	1 (3.0)
Grade 1	0	1 (7.1)	1 (3.0)
Renal and urinary disorders	2 (10.5)	1 (7.1)	3 (9.1)
Grade 1	0	0	0
Grade 2	2 (10.5)	1 (7.1)	3 (9.1)
Reproductive system and breast disorders	1 (5.3)	1 (7.1)	2 (6.1)
Grade 1	1 (5.3)	1 (7.1)	2 (6.1)
Respiratory, thoracic, and mediastinal disorders	3 (15.8)	3 (21.4)	6 (18.2)
Grade 1	2 (10.5)	3 (21.4)	5 (15.2)
Grade 2	1 (5.3)	0	1 (3.0)
Skin and subcutaneous tissue disorders	4 (21.1)	6 (42.9)	10 (30.3)
Grade 1	3 (15.8)	2 (14.3)	5 (15.2)

System Organ Class & CTCAE Grade	Number of Patients Experiencing Adverse Event[1]		
	120 mcg (N = 19) (%)	180 mcg (N = 14) (%)	Total (N = 33) (%)
Grade 2	1 (5.3)	4 (28.6)	5 (15.2)
Vascular disorders	0	1 (7.1)	1 (3.0)
Grade 1	0	1 (7.1)	1 (3.0)

[1] AE counts are presented irrespective of investigator classified relationship to treatment.

Supplemental Table 5: Summary of frequent adverse events, by system organ class and preferred term[1]

System Organ Class & Preferred Term	Number of Patients Experiencing Adverse Event		
	120 mcg (N = 19) (%)	180 mcg (N = 14) (%)	Total (N = 33) (%)
Overall	19 (100)	14 (100)	33 (100)
Eye disorders	0	2 (14.3)	2 (6.1)
Eye pruritis	0	2 (14.3)	2 (6.1)
Gastrointestinal disorders	11 (57.9)	11 (78.6)	22 (66.7)
Abdominal pain	2 (10.5)	1 (7.1)	3 (9.1)
Abdominal pain upper	2 (10.5)	3 (21.4)	5 (15.2)
Diarrhea	5 (26.3)	5 (35.7)	10 (30.3)
Dyspepsia	6 (31.6)	7 (50.0)	13 (39.4)
Gastritis	0	2 (14.3)	2 (6.1)
Gastroesophageal reflux disease	0	2 (14.3)	2 (6.1)

System Organ Class & Preferred Term	Number of Patients Experiencing Adverse Event		
	120 mcg (N = 19) (%)	180 mcg (N = 14) (%)	Total (N = 33) (%)
Nausea	1 (5.3)	5 (35.7)	6 (18.2)
Vomiting	3 (15.8)	2 (14.3)	5 (15.2)
General disorders	13 (68.4)	12 (85.7)	25 (75.8)
Asthenia	1 (5.3)	2 (14.3)	3 (9.1)
Chills	5 (26.3)	3 (21.4)	8 (24.2)
Fatigue	3 (15.8)	8 (57.1)	11 (33.3)
Feeling cold	2 (10.5)	1 (7.1)	3 (9.1)
Influenza like illness	4 (21.1)	1 (7.1)	5 (15.2)
Injection site erythema	1 (5.3)	5 (35.7)	6 (18.2)
Injection site pain	1 (5.3)	5 (35.7)	6 (18.2)
Injection site pruritis	2 (10.5)	5 (35.7)	7 (21.2)
Pyrexia	8 (42.1)	7 (50.0)	15 (45.5)
Hepatobiliary disorders	6 (31.6)	3 (21.4)	9 (27.3)
Jaundice	4 (21.1)	2 (14.3)	6 (18.2)
Infections and infestations	8 (42.1)	4 (28.6)	12 (36.4)
Urinary tract infection	3 (15.8)	0 (0.0)	3 (9.1)
Investigations	10 (52.6)	8 (57.1)	18 (54.5)
Alanine aminotransferase increased	3 (15.8)	5 (35.7)	8 (24.2)
Aspartate aminotransferase increased	2 (10.5)	5 (35.7)	7 (21.2)

System Organ Class & Preferred Term	Number of Patients Experiencing Adverse Event		
	120 mcg (N = 19) (%)	180 mcg (N = 14) (%)	Total (N = 33) (%)
Blood bilirubin increased	2 (10.5)	4 (28.6)	6 (18.2)
Gamma-glutamyl transferase increased	2 (10.5)	2 (14.3)	4 (12.1)
International normalized ratio increased	2 (10.5)	1 (7.1)	3 (9.1)
Liver function test abnormal	0 (0.0)	2 (14.3)	2 (6.1)
Neutrophil count decreased	1 (5.3)	2 (14.3)	3 (9.1)
Weight decreased	2 (10.5)	0 (0.0)	2 (6.1)
Metabolism and nutrition disorders	0 (0.0)	5 (35.7)	5 (15.2)
Decreased appetite	0 (0.0)	4 (28.6)	4 (12.1)
Musculoskeletal and connective tissue disorders	10 (52.6)	9 (64.3)	19 (57.6)
Arthralgia	8 (42.1)	7 (50.0)	15 (45.5)
Back pain	5 (26.3)	2 (14.3)	7 (21.2)
Muscle spasms	0 (0.0)	2 (14.3)	2 (6.1)
Musculoskeletal pain	2 (10.5)	0 (0.0)	2 (6.1)
Myalgia	5 (26.3)	7 (50.0)	12 (36.4)
Nervous system disorders	10 (52.6)	12 (85.7)	22 (66.7)
Dizziness	1 (5.3)	3 (21.4)	4 (12.1)
Dysgeusia	0	3 (21.4)	3 (9.1)
Headache	9 (47.4)	12 (85.7)	21 (63.6)

System Organ Class & Preferred Term	Number of Patients Experiencing Adverse Event		
	120 mcg (N = 19) (%)	**180 mcg (N = 14) (%)**	**Total (N = 33) (%)**
Renal and urinary disorders	2 (10.5)	1 (7.1)	3 (9.1)
Nephrolithiasis	2 (10.5)	0 (0.0)	2 (6.1)
Respiratory, thoracic, and mediastinal disorders	3 (15.8)	3 (21.4)	6 (18.2)
Oropharyngeal pain	2 (10.5)	1 (7.1)	3 (9.1)
Rhinorrhea	0	3 (21.4)	3 (9.1)
Skin and subcutaneous tissue disorders	4 (21.1)	6 (42.9)	10 (30.3)
Erythema	2 (10.5)	2 (14.3)	4 (12.1)
Pruritis	1 (5.3)	4 (28.6)	5 (15.2)

[1] Frequent TEAEs are defined as those occurring in more than 2 patients, in which case data from both groups are presented.

Supplemental Table 6: Treatment Adjustments (Interruption, Reduction, Discontinuation)

	Lambda 120 mcg, N = 19 (%)	**Lambda 180 mcg, N = 14(%)**	**Total, N = 33(%)**
Patients who were discontinued from treatment	4 (21.1)	4 (28.6)	8 (24.2)
Patients who were dose reduced	6 (31.6)	7 (50.0)	13 (39.4)
Patients who underwent a dose interruption	1 (5.3)	1 (7.1)	2 (6.1)

Supplemental Table 7 : Baseline, peak, EOT and EOFU values of biochemical indices of patients who discontinued treatment

Pt ID	Sex	Baseline					
		Total Bilirubin (0-20 umol/L)	Direct Bilirubin (0-5 umol/L)	Indirect Bilirubin (0-14 umol/L)	ALT (10-50, 10-35 IU/L)	AST (0-37, 0-31 IU/L)	Al (40-12 104 I
601-004	M	14	6	8	197	97	6
601-017	M	6	3	3	68	34	8
701-001	F	7	4	3	51	40	4
701-011	F	6	3	3	75	53	6
501-011	M	16	6	10	147	70	1(
601-003	M	5	No data	No data	56	38	1
601-007	M	20	14	6	92	89	1(
601-012	M	8	3	5	109	61	1(

Pt ID	Sex	Peak					
		Total Bilirubin (0-20 umol/L)	Direct Bilirubin (0-5 umol/L)	Indirect Bilirubin (0-14 umol/L)	ALT (10-50, 10-35 IU/L)	AST (0-37, 0-31 IU/L)	Al (40- 35- IU/
601-004	M	530	465	65	91	108	1(
601-017	M	15	9	6	335	255	48
701-001	F	62	56	6	258	421	3
701-011	F	132	115	17	434	798	42
501-011	M	27	11	16	80	68	3
601-003	M	54	47	7	496	677	3
601-007	M	96	86	10	118	136	3
601-012	M	41	35	6	132	240	3

Pt ID	Sex	End of Treatment								End of 24 weeks			
		Total Bilirubin (0-20 umol/L)	Direct Bilirubin (0-5 umol/L)	Indirect Bilirubin (0-14 umol/L)	ALT (10-50, 10-35 IU/L)	AST (0-37, 0-31 IU/L)	ALP (40-129, 35-104 IU/L)	GGT (10-71, 6-42 IU/L)	INR (0,9 - 1,2)	Total Bilirubin (0-20 umol/L)	Direct Bilirubin (0-5 umol/L)	Indirect Bilirubin (0-14 umol/L)	Al (1 50 10 3 IU

601-004	M	86	80	6	101	71	70	59	1.34	13	5	8	4
601-017	M	29	23	6	338	177	629	124	1.64	7	3	4	13
701-001	F	24	18	6	169	166	281	89	1.19	12	5	7	6
701-011	F	29	24	5	297	423	218	81	1.37	N/A	N/A	N/A	N/
501-011	M	16	7	9	59	42	424	94	1.0	22	8	14	9
601-003	M	21	18	3	154	180	273	155	1.39	6	3	3	4
601-007	M	36	34	2	73	90	305	199	1.33	61	50	11	13
601-012	M	49	38	11	289	449	249	189	1.71	19	8	11	6

Supplemental Table 8: Summary of treatment emergent serious adverse events (TESAEs) by meDRA system organ class and preferred term

System Organ Class Preferred Term		Lambda 120 mcg (N=19)	Lambda 180 mcg (N=14)	Overall (N=33)
TESAEs	n (%)	5 (26.3%)	2 (14.3%)	7 (21.2%)
Hepatobiliary disorders	n (%)	5 (26.3%)	2 (14.3%)	7 (21.2%)
DILI	n (%)	1 (5.3%)	0 (0%)	1 (3.0%)
Jaundice	n (%)	4 (21.1%)	2 (14.3%)	6 (18.2%)

CLINICAL STUDY PROTOCOL

EIG-LMD-001

Study Title	A Phase 2 Study to Eva**l**uate the Safety, Tolerab**i**lity, and Pharmacodynamics of Pegylated Interferon Lambda **M**onotherapy in Patients with Chronic Hepa**t**itis Delta Virus Infection (LIMT-1)
Study Phase	Phase 2
Investigational Product	Pegylated interferon lambda-1a (Lambda, PEG-IFN-λ) 120 or 180 μg
Indication	Chronic hepatitis D viral infection
IND Number	133743
Sponsor	Eiger BioPharmaceuticals, Inc. 350 Cambridge Ave., Suite 350 Palo Alto, CA 94306
Sponsor Clinical Program Manager	Robert Gish, MD Eiger BioPharmaceuticals
Medical Monitor	Hervé Mommeja Marin, MD Consultant Medical Monitor Eiger BioPharmaceuticals, Inc.
Version	Amendment 4
Original Protocol Date	14 March 2016
Amendment 1 Date	16 September 2016
Amendment 2 Date	22 February 2017
Amendment 3 Date	24 April 2017
Amendment 4 Date	11 December 2017

Conduct: In accordance with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

CONFIDENTIALITY STATEMENT

This document is the sole property of Eiger BioPharmaceuticals, Inc. This document and any and all information contained herein has to be considered and treated as strictly confidential. This document shall be used only for the purpose of the disclosure herein provided. No disclosure or publication shall be made without the prior written consent of Eiger BioPharmaceuticals, Inc.

SPONSOR SIGNATURE PAGE

Protocol Title	A Phase 2 Study to Eva**l**uate the Safety, Tolerab**i**lity, and Pharmacodynamics of Pegylated Interferon Lambda **M**onotherapy in Patients with Chronic Hepa**t**itis Delta Virus Infection (LIMT-1)
Protocol Number	EIG-LMD-001
Version	Amendment 4
Date	11 December 2017

APPROVAL STATEMENT

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

Signed:

Robert G. Gish M.D

December 11, 2017

Robert Gish, MD
Eiger BioPharmaceuticals

Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title	A Phase 2 Study to Eva**l**uate the Safety, Tolerab**i**lity, and Pharmacodynamics of Pegylated Interferon Lambda **M**onotherapy in Patients with Chronic Hepa**t**itis Delta Virus Infection (LIMT-1)
Protocol Number	EIG-LMD-001
Version	Amendment 4
Date Final	11 December 2017

INVESTIGATOR AGREEMENT

By my signature below, I attest to the following:

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

Signed:

Signature	Date
Name	Institution

PROTOCOL SYNOPSIS

Sponsor	Eiger BioPharmaceuticals, Inc. (United States)
Product	Pegylated interferon lambda-1a (Lambda, PEG-IFN-λ)
Title	A Phase 2 Study to Eva**l**uate the Safety, Tolerab**i**lity, and Pharmacodynamics of Pegylated Interferon Lambda **M**onotherapy in Patients with Chronic Hepa**t**itis Delta Virus Infection (LIMT-1)
Protocol number	EIG-LMD-001
Study phase	Phase 2
Study center(s)	Approximately 6 centers globally
Indication	Chronic hepatitis D viral infection
Primary objectives	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 2 different doses of Lambda on HDV RNA levels

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 effect of treatment with 2 dose levels of Lambda on the following:
	  • Alanine aminotransferase (ALT) levels
	  • Hepatitis B surface antigen (HbsAg) levels
	  • Gamma-Glutamyl Transferase (GGT) levels

Exploratory objective	The exploratory objectives of the study are to evaluate the effect of treatment with 2 dose levels of Lambda on the following: • Immunologic parameters
Study duration	Approximately 21 months (3 months for enrollment, 12 months of study treatment, 6 months of follow-up)
Study design	Randomized, open-label study of Lambda 120 or 180 μg subcutaneous (SC) injection weekly for 48 weeks in patients with chronic HDV infection. Patients will also take an anti-hepatitis B virus (HBV) nucleos(t)ide analog (NUC) from baseline (Day 1) through the end of the study. Clinic visits at baseline (Day 1), Weeks 1, 2, 4, and every 4 weeks until Week 48. Pharmacodynamics (PD)/efficacy of Lambda will be assessed by measuring HDV and HBV viral loads and viral serologies and Fibroscan results. Safety and tolerability of Lambda will be assessed by adverse event (AE) monitoring, clinical laboratory tests, vital signs and body weight, physical examinations, and concomitant medications. All enrolled patients will be followed for an additional 24 weeks off-treatment. All monthly follow-up visits will include evaluations of viral load (HDV and HBV), quantitative HbsAg (qHBsAg), and all of the safety measures listed above.
Study population and number of patients	Approximately forty patients, 20 in each treatment group (120 or 180 μg weekly) with chronic HDV infection with detectable and quantifiable HDV RNA by quantitative polymerase chain reaction

	(qPCR) will be enrolled. Patients who discontinue the study before Week 12 for reasons other than an AE can be replaced on approval of the sponsor.

Eligibility criteria	**Inclusion Criteria**
	Patients must meet all of the following inclusion criteria before study entry to be eligible for enrollment into the study:
	1. Willing and able to comply with study procedures and provide written informed consent
	2. Male or female, 18 to 65 years of age, inclusive
	3. Chronic HDV infection of at least 6 months' duration documented by a positive HDV antibody (Ab) test; detectable and quantifiable HDV RNA by qPCR at study entry
	4. Serum ALT > upper limit of the normal range (ULN) and <10 × ULN at screening
	5. Electrocardiogram (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
	6. 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
	7. 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
	8. 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 1 year postmenopausal.
	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
	• Surgical sterilization of the partner (vasectomy ≥ 1 month before screening)
	For males
	• Surgical sterilization (vasectomy ≥ 1 month before screening)
	or
	• Both of the following contraceptive methods from screening:
	  • Consistently and correctly use a condom
	  • Partner must use a hormonal contraceptive or a nonhormonal barrier method (IUD or diaphragm with spermicide or cervical cap with spermicide)
	9. Willing and able to provide written informed consent
	10. Willing and able to comply with all study procedures

or other substances	contained in the study medication.	**Exclusion Criteria** Patients meeting any of the following criteria will be excluded from the study: *General Exclusions* 1. Participation in a clinical trial with or use of any investigational 2. 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. 3. History or evidence of any intolerance or hypersensitivity to IFNs 4. 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* 5. Current or previous history of decompensated liver disease (Child-Pugh Class B or C) 6. Co-infected with human immunodeficiency virus (HIV) or hepatitis C virus (HCV). Positive results for HIV or HCV Ab at screening. Patients with a positive HCV Ab at screening are allowed if they have completed a curative antiviral regimen and are documented to be HCV RNA negative (undetectable) at least 3 months before screening and at screening. 7. Past history or current evidence of decompensated liver disease, defined as any of the following at screening: a. Bilirubin level ≥ 2.5 mg/dL unless due to Gilbert's disease b. Serum albumin level <3.5 g/dL c. International normalized ratio (INR) ≥1.5 d. Alpha fetoprotein ≥100 ng/mL 8. Evidence of significant portal hypertension such as hepatic venous pressure gradient (HVPG) ≥10 mmHg; current presence or history of variceal bleeding 9. Current evidence or history of ascites requiring diuretics or paracentesis, or hepatic encephalopathy 10. Any of the following abnormal laboratory test results at screening: a. Platelet count <90,000 cells/mm^3 b. White blood cell (WBC) count <3,000 cells/mm^3 c. Absolute neutrophil count (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× ULN f. Confirmed creatinine clearance (CrCl) < 50 mL/min by Cockroft-Gault 11. Evidence of another form of viral hepatitis or another form of liver disease (eg, autoimmune liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, alcoholic liver disease, nonalcoholic steatohepatitis, hemochromatosis, alpha-1-

	anti-trypsin deficiency) 12. History of hepatocellular carcinoma 13. Patients with any of the following: a. Current eating disorder or alcohol abuse 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: 360 mL of beer, 150 mL of wine, or 45 mL of spirits c. In the opinion of the investigator, an alcohol use pattern that will interfere with study conduct d. Drug abuse within the previous 6 months before screening, with the exception of cannabinoids and their derivatives 14. Prior history or current evidence of any of the following: a. Immunologically mediated disease (eg, rheumatoid arthritis, inflammatory bowel disease, severe psoriasis, systemic lupus erythematosus) that requires more than intermittent nonsteroidal anti-inflammatory medications for management or that requires use of systemic corticosteroids in the 6 months before screening (inhaled asthma medications are allowed) b. Retinal disorder or clinically relevant ophthalmic disorder c. Any malignancy within 5 years before screening. Exceptions are superficial dermatologic malignancies (eg, squamous cell or basal cell skin cancer treated with curative intent). d. Cardiomyopathy or significant ischemic cardiac or cerebrovascular disease (including history of angina, myocardial infarction, or interventional procedure for coronary artery disease) e. Chronic pulmonary disease (eg, chronic obstructive pulmonary disease) associated with functional impairment f. Pancreatitis g. Severe or uncontrolled psychiatric disorder, eg, depression, manic condition, psychosis, acute and/or chronic cognitive dysfunction, suicidal behavior, and relapse of substance abuse h. Active seizure disorder defined by either an untreated seizure disorder or continued seizure activity within the preceding year despite treatment with anti-seizure medication i. Bone marrow or solid organ transplantation 15. Other significant medical condition that may require intervention during the study. Patients with any serious condition that, in the opinion of the investigator, would preclude evaluation of response or make it unlikely that the contemplated course of therapy and follow-up could be completed. Patients for whom participation in the study would increase their risk. *Exclusions Based on Concurrent Medication Use*

	16. 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 17. Use of telbivudine (Tyzeka or Sebivo) within 3 months before screening or during the study 18. Current use of heparin or Coumadin 19. Received blood products within 30 days before study randomization 20. Use of hematologic growth factors within 30 days before study randomization 21. Systemic antibiotics, antifungals, or antivirals for treatment of active infection other than HBV within 14 days before study randomization 22. Any prescription or herbal product that is not approved by the investigator 23. Long-term treatment (> 2 weeks) with agents that have a high risk for nephrotoxicity or hepatotoxicity unless it is approved by the medical monitor 24. Receipt of systemic immunosuppressive therapy within 3 months before screening
Test product, dose, and method of administration	Pegylated interferon lambda-1a (PEG-IFN-λ) (Lambda) Injection, 0.18mg/syringe; 120 or 180 μg; weekly SC administration
Reference therapy, dose, and method of administration	Not applicable
Duration of treatment	48 weeks
Criteria for evaluation	The primary PD/efficacy endpoints are as follows: • Change from baseline in HDV viral load at Week 48 (end of treatment [EOT]) • Change from baseline in HDV viral load at Week 72 (end of follow-up [EOFU]) Additional PD/efficacy endpoints include: • Proportion of patients with sustained viral response: HDV RNA below the lower limit of quantification (LLOQ) 12 weeks after EOT (SVR-12) • Proportion of patients with sustained viral response: HDV RNA below LLOQ 24 weeks after EOT (SVR-24) • Change from baseline in HDV viral load • Change from baseline in HBV viral load • Change from baseline in HBsAg levels • Clearance of HBsAg • Change from baseline in Fibroscan results Safety endpoints include: • 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 • Treatment-emergent changes in clinical laboratory findings • 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
Statistical methods	The sample size of 40 will permit assessment of the safety, tolerability,

	and PD/efficacy of Lambda at 120 vs. 180 µg/week. The primary PD/efficacy endpoints will be assessed in the modified intention-to-treat (MITT) population, which will consist of all patients who receive at least 80% of the total study drug dose throughout the entire 48-week treatment period (ie, no dose interruptions or reductions) and for whom HDV viral load data are available for the Day 1 (baseline) and end-of-treatment (Week 48) study visits.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	antibody
AE	adverse event
Ag	antigen
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANC	absolute neutrophil count
anti-LKM1	liver kidney microsome type 1 antibody
anti-SMA	anti-smooth muscle antibody
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ASV	asunaprevir
AUC	area under the time-concentration curve
AUC_{inf}	area under the time-concentration curve from time 0 extrapolated to infinite time
B2M	beta-2 microglobulin
BMI	body mass index
BP	blood pressure
BSEP	bile salt efflux protein
BUN	blood urea nitrogen
CHB	chronic hepatitis B
CHC	chronic hepatitis C
CHD	chronic hepatitis D (delta)
CD-1	cesarean-derived 1
CFR	Code of Federal Regulations
CK	creatine kinase
C_{max}	maximum observed concentration
CMV	cytomegalovirus
CNS	central nervous system
CrCl	creatinine clearance
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Child-Turcotte-Pugh
CV	coefficient of variation
CYP	cytochrome P450
DAA	direct-acting antiviral
DB	direct bilirubin
DCV	daclatasvir
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DR	dose reduction (DR1=first dose reduction; DR2=second dose reduction)
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOFU	end of follow-up (Week 72)
EOT	end of treatment (Week 48)

Abbreviation	Definition
ESRD	end-stage renal disease
ET	early termination
ETV	entecavir
EU	European Union
FDA	Food and Drug Administration
FU#	follow-up visit #
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transferase
GM-CSF	granulocyte macrophage colony-stimulating factor
GT-x	genotype-x
HBeAb	hepatitis B envelope antibody
HBeAg	hepatitis B envelope antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDV	hepatitis delta virus
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
HSV	herpes simplex virus
HVPG	hepatic venous pressure gradient
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN-α	interferon alpha
IFN-λ	interferon lambda-1a
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
ISG	interferon-stimulated genes
ITT	intention-to-treat
IU	international unit
IUD	intrauterine device
IV	intravenous
IWRS	interactive web response system
Lambda	peg-IFN-λ-1a
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LOD	limit of detection
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility class
MITT	modified intention to treat
MRI	magnetic resonance imaging

Abbreviation	Definition
MRP#	multidrug resistance-associated protein#
NCI	National Cancer Institute
NK	natural killer
NUC	nucleos(t)ide analog
OATP	organic anion-transporting polypeptide
PBL	peripheral blood lymphocyte
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics
PEG	polyethylene glycol
PEG-IFN-λ	pegylated interferon lambda-1a (Lambda)
P-gp	P-glycoprotein
PI	principal investigator
PID	patient identification number
PK	pharmacokinetics
PT	prothrombin time
QA	quality assurance
QC	quality control
qHBsAg	quantitative HBsAg
qPCR	quantitative polymerase chain reaction
QTcF	QT interval corrected using Fridericia formula
QW	once each week
RBV	ribavirin
rIL	recombinant interleukin
RNA	ribonucleic acid
RTU	ready to use
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOP	standard operating procedure
STAT-1	signal transducer and activator of transcription 1
SUSAR	suspected, unexpected serious adverse reaction
SVR-xx	sustained virologic response for xx weeks after EOT
$T_{1/2}$	terminal elimination half-life
T3	triidothyronine
T4	thyroxine
TBILI	total bilirubin
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
TLT	treatment-limiting toxicity
T_{max}	time to peak plasma concentration
TSH	thyroid-stimulating hormone
UGT1A1	uridine diphosphoglucuronosyltransferase 1A1
ULN	upper limit of the normal range
Vss	volume of distribution at steady state
WBC	white blood cell
WHO-DD Enhanced	World Health Organization Drug Dictionary Enhanced

1 INTRODUCTION

1.1 Background

Hepatitis D virus has been identified as the infectious agent causing viral hepatitis in the presence of HBV (Rizzetto et al 1977, Rizzetto et al 1980). While HDV can replicate autonomously inside the hepatocyte, the virus requires coinfection with HBV to complete virion assembly and to facilitate transmission. HDV uses the hepatitis B surface antigen (HBsAg) proteins L, M, and S as its envelope proteins, which are pivotal for HDV exit from host cells and transmission to other hepatocytes (Bonino et al 1986). HDV can be considered a superinfection among patients chronically infected with HBV or as a simultaneous acute coinfection with HBV. The HDV genome is a small circular single-stranded RNA molecule that can be classified into 8 different genotypes (Makuwa et al 2008). HDV genotype 1 is the most prevalent globally and in Europe and North America.

HDV is the most aggressive and virulent of the viral hepatitides. Chronic HDV infection leads to more severe liver disease than HBV monoinfection and is associated with accelerated fibrosis progression and a higher risk of developing hepatocellular carcinoma (Rizzetto 2000, Fattovich et al 1987, Uzunalimoglu et al 2001).

Worldwide, approximately 5% (15–20 million) of HBV-infected individuals are also infected with HDV (Wedemeyer & Manns 2010). The prevalence of HDV is increasing in northern and central Europe due to migration from areas where HDV is endemic.

Chronic HDV infections represent a serious unmet medical need, as currently there is no approved therapy for HDV infection. Multiple direct antiviral agents directed against HBV are available, but these agents have not proven effective against HDV (Wedemeyer et al 1999, Yurdaydin et al 2002, Lau et al 1999, Niro et al 2006).

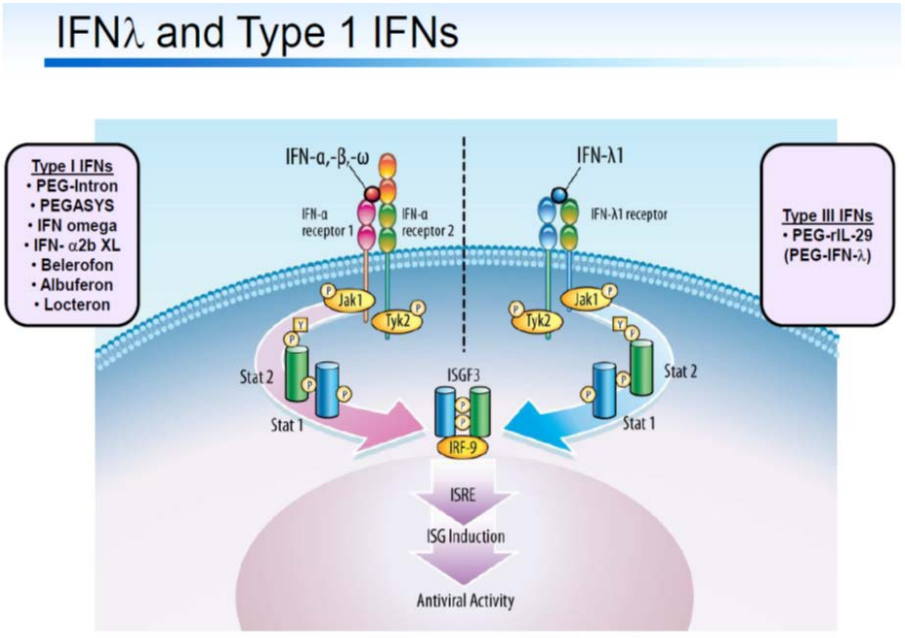
Interferon alpha (IFN-α) or pegylated IFN-α have been tested at different doses and durations in patients with chronic HDV. Up to 25% of patients may achieve suppression of HDV ribonucleic acid (RNA) after 48 to 96 weeks of treatment, but these treatments are associated with a significant relapse rate after discontinuation (Wedemeyer & Manns 2010, Wedemeyer et al 2014). Some patients required premature discontinuation or dose reductions due to adverse effects (AEs), which may have impacted response rates. In the pegIFN-α-2a registration study for the treatment of HBV, 3% to 4% of patients discontinued therapy due to a safety reason and 46% to 47% of patients required dose reductions, most commonly for a laboratory abnormality (Lau et al 2005).

Adverse effects associated with use of currently available IFN-α preparations include a “flu-like” syndrome (manifesting as fever, headache, and myalgia), chronic fatigue, and various significant neuropsychiatric events (in particular, depression, insomnia, and irritability). Another notable risk associated with IFN-α use is cytopenia, with events of leukopenia, neutropenia, and thrombocytopenia most common, and also anemia and pancytopenia. Thyroid dysfunction and various forms of retinitis are additional risks associated with IFN-α therapy.

Finally, hepatic flare (or alanine aminotransferase [ALT] flare, also referred to in the literature as acute exacerbation of hepatitis) is a well described phenomenon during IFN-α therapy for chronic HBV (CHB), reported in 25% to 40% of treated patients. In patients with chronic hepatitis D (CHD), ALT flare is also observed during the natural course of the disease or in response to IFN-α therapy. The pathogenesis of these events is variable; some are host induced, while others are viral induced or of indeterminant etiology. Host-induced hepatic flares appear to be immune mediated, related to reconstitution of virus-specific host effector responses in response to declining viremia. In CHB and in previous studies in CHD, host-induced hepatic flares are generally well tolerated; they rarely lead to hepatic decompensation in patients with compensated liver disease at baseline, and their occurrence has been associated with a favorable outcome, including increased rates of HBsAg seroconversion. Assessment of these events can be complex, given these events may also be spontaneous in nature, related to the underlying viral infection itself as opposed to the immune-stimulant effects of IFN-α, or due to an unrelated event. Drug-induced hepatitis must also be considered.

IFN-λ is a different type of IFN (Type III) with different structural features, receptor characteristics, and biological activities than IFN-α (Type I) (see Figure 1). IFN-λ was first reported in the early 2000s (Kotenko et al 2003, Sheppard et al 2003). Based on IFN-λ's more limited receptor distribution and previous data from studies involving treatment with IFN-λ in patients with HBV or HCV, it is postulated that IFN-λ could induce HDV RNA decline, but with fewer AEs than IFN-α.

Figure 1: Mechanism of Action of Interferons



Lambda is the pegylated form of IFN-λ, a conjugate of recombinant human interleukin 29 (rIL-29) and a linear polyethylene glycol (PEG) chain.

1.2 Rationale for the Study

As shown in Figure 1, IFN-λ and IFN-α share the common ISG (interferon-stimulated gene) induction pathway that leads to broad-spectrum antiviral activities. Since INF-α has demonstrated anti-HDV activity in patients with CHD patients (Wedemeyer & Manns 2010), it is postulated that PEG IFN-λ (Lambda) could also induce HDV RNA decline in patients with CHD.

Based on IFN-λ's more limited receptor distribution and previous data from studies involving treatment with IFN-λ in patients with HBV or HCV, it is postulated that Lambda treatment could be associated with fewer AEs than IFN-α treatment.

EIG-LMD-001 is the first study of Lambda in patients with CHD infection. The primary aims of the study are to define the safety, tolerability, and pharmacodynamics (PD)/efficacy of Lambda monotherapy in patients with CHD.

The Lambda doses chosen for this study were based on the results from studies in healthy volunteers and in patients with CHB or chronic hepatitis C (CHC).

1.3 Preclinical Experience

1.3.1 Antiviral, Immunologic, and Hematologic Effects

Results from in vitro and in vivo studies conducted in CD-1 mice and cynomolgus monkeys that are relevant to the current study are summarized below.

In vitro data on inhibition of HDV by IFN are limited. An in vitro study of HDV-infected primary human hepatocytes demonstrated that simultaneous addition of IFN-α at 600 units/mL, a concentration comparable to that achieved in treated patients, the subsequent HDV RNA accumulation was inhibited by at least 80%. IFN-α produced significant time-dependent increases of host response proteins such as Stat-1, phosphoStat-1, Mx1/2/3 and PKR (Han et al 2011).

In a human hepatoma cell line that consistently secretes HBV, IFN-λ inhibited HBV replication with kinetics and efficiency similar to that of IFN-α/β (Robek et al 2005). This activity was a direct result of the antiviral activity of IFN-λ, not mediated by secondary induction of endogenous IFN-α/β.

Similar results using this HBV-producing hepatoma line and several pegIFN preparations were reported by investigators at the Southern Research Institute (ZymoGenetics Report RES-10556, 2006). The activity of Lambda in this model was similar to that of the currently marketed pegIFN-α preparations (PEGASYS and PEG-INTRON), with no discernible in vitro toxicity (selectivity index > 300).

In in vitro studies using primary human hepatocytes, Lambda induced expression of IFN-stimulated genes (ISGs) to an extent and potency similar to that observed with pegIFN-α-2a. Pharmacology studies conducted in treated cynomolgus monkeys also demonstrated induction of ISGs in hepatocytes, however not in circulating peripheral blood lymphocytes (PBLs). The number of circulating monocytes, granulocytes, lymphocytes, and lymphocyte subsets (B and T lymphocytes and natural killer [NK] cells) did not change following dosing with Lambda in cynomolgus monkeys. Expression of major histocompatibility class (MHC)

Class I molecules on circulating lymphocytes also did not change following administration of a single dose of Lambda to monkeys. However, serum beta-2 microglobulin (B2M) was induced following Lambda administration; B2M levels increased approximately 40% above baseline following a single dose of Lambda. In repeat-dose Lambda studies, doses of at least 0.03 mg/kg were required to induce serum B2M; doses above this level induced B2M to a similar extent.

Consistent with the relatively low level of Lambda receptor expression by bone marrow cells, Lambda did not affect myeloid or erythroid colony formation in human bone marrow cells, while a dose-dependent reduction in colony formation was seen with IFN-α. In addition, no decreases in platelets, erythrocytes, or neutrophils were observed in cynomolgus monkeys or CD-1 mice following repeat Lambda dosing.

Altogether, these findings support the hypothesis that Lambda may be associated with less hematological toxicity than IFN-α.

1.3.2 Toxicology

Lambda has been evaluated in cynomolgus monkeys and CD-1 mice, both of which demonstrate receptor binding and pharmacological response to drug.

In toxicology studies conducted in CD-1 mice, Lambda was well tolerated when administered alone or in combination with ribavirin (RBV) by subcutaneous (SC) injection. Histological examination revealed a generally minimal-to-mild cardiac change consisting of focal myocyte degeneration, increased interstitial cellularity, and interstitial fibrosis in some mice, and the incidence increased with dose. There were no correlative clinical signs or findings associated with these histologic findings. Lambda treatment had no discernible effect on serum troponin-I levels in CD-1 mice. Treatment with RBV alone was not associated with any cardiac pathology.

The safety of Lambda (with or without RBV) was assessed in cynomolgus monkeys in 1-month and 26-week dosing studies. Findings were limited to the transient appearance of skin flaking and reddening generalized to various regions of the body, a dose-dependent decrease in serum fibrinogen levels, and mononuclear cell infiltrates at the SC injection site. The reduction in fibrinogen levels was not considered clinically relevant because concentrations generally remained within the normal range for this species and there were no concurrent abnormalities in other coagulation parameters. On microscopic analysis, the areas of skin change showed an adaptive acanthotic response at the injection sites with or without subepithelial perivascular infiltrates of lymphocytes and/or macrophages. In the monkeys treated for up to 6 months, there was no histologic evidence of cardiomyocyte injury.

A dose-ranging embryo-fetal development study was conducted in pregnant CD-1 mice. The mice were given daily SC injections of Lambda or placebo on gestation Days 6 through 15, then killed on Day 18. Drug-related effects in the fetuses at all doses (≥0.5 mg/kg/day) consisted of increases in embryolethality with associated decreases in litter size (postimplantation losses averaged 62– 91% compared with 32% in the control group; 43%–75% of litters consisted entirely of resorptions or dead fetuses compared with 25% in the control group).

1.3.3 Pharmacokinetics

The pharmacokinetics (PK) of Lambda was evaluated in the mouse, rat, and monkey. Lambda was well absorbed and bioavailable in mice (51%) and monkeys (40%–53%) but less so in rats (13%). The volume of distribution at steady state (Vss) for Lambda in mice, rats, and monkeys after intravenous (IV) administration was less than the reported total body water volumes for these species, indicating limited extravascular distribution. The total plasma clearance in rats with nephrectomy was significantly lower compared with sham-operated rats, suggesting that changes in renal function may affect the elimination of Lambda. In mice, tissue distribution of radioactivity was similar after a single SC dose of 3 mg/kg [^{123}I]Lambda and after 2 weeks of 3-times-weekly dosing. Lambda did not appear to inhibit or induce any of the cytochrome P450 (CYP) isoforms tested in human liver microsomes and hepatocytes and did not alter the total CYP content or the individual enzyme activities in the livers of treated cynomolgus monkeys.

1.4 Clinical Experience

1.4.1 Clinical Efficacy/Pharmacodynamics

Currently there are no clinical data on Lambda for HDV infection.

1.4.2 Clinical Safety

As of 15 September 2014, approximately 3,710 subjects (including 237 healthy subjects; 3,276 subjects with HCV; and 197 subjects with HBV) have received Lambda or comparator in 18 completed, terminated, or ongoing Phase 1, 2, or 3 studies. Study designs for several of the studies mentioned below are shown in Table 1.

Table 1: Key Phase 2 Lambda Studies in HCV or HBV

Study	Study Identifier	Study Population / Phase	Treatments Evaluated	Treatment Duration	Sample Sizes
EMERGE	526F06	HCV Phase 2b	• Lambda 240 µg+RBV • Lambda 180 µg+RBV • Lambda 120 µg+RBV • Alfa-2a 180 µg+RBV	24 weeks (G2/G3) 48 weeks (G1/G4)	• 134 • 131 • 127 • 133
D-LITE	AI452008	HCV Phase 2	• Lambda 180 µg +RBV+ASV • Lambda+RBV+DCV • Alfa-2a+RBV	• 24 or 48 weeks, depending on early response • same as above • 48 weeks	• 44 • 49 • 47
LIRA-B	AI452005	HBV Phase 2	• Lambda 180 µg • Alfa-2a 180 µg	24 weeks	• 93 • 83

ASV, asunaprevir; DCV, daclatasvir; G#, genotype; RBV, ribavarin

Lambda has been generally well tolerated in clinical studies. A lower frequency of musculoskeletal (myalgia, arthralgia, and back pain) and flu-like symptoms (chills, pyrexia, and pain) was observed across Phase 2 studies in subjects receiving IFN regimens containing

Lambda compared with IFN alfa (the drug name of a pharmaceutical product that contains IFN-α).

Hematologic toxicity was notably lacking in the white blood cell (WBC) or platelet lineages in subjects receiving Lambda regimens. Hematologic toxicity was less frequent in the Lambda group compared with the alfa group in the D-LITE and LIRA-B studies (Lambda/RBV/direct-acting antiviral [DAA] vs. alfa/RBV and Lambda vs. alfa, respectively).

In the EMERGE study, expected decreases in hemoglobin levels were observed with concomitant RBV use. However, overall, anemia was less frequent and milder with Lambda/RBV than with IFN alfa/RBV.

In the EMERGE study, laboratory changes associated with autoimmune thyroid disease (elevated thyroid-stimulating hormone [TSH] and reduced free T4) were less common with Lambda/RBV than with alfa/RBV. Serial troponin measurements and electrocardiogram (ECG) findings analyzed at Week 12 of treatment showed no evidence of cardiac toxicity.

In the EMERGE study, hyperbilirubinemia and transaminase elevations leading to dose reduction or discontinuation were observed more frequently with the 240 μg dose than with the other tested doses (80, 120, and 180 μg) or the active comparator (180 μg alfa-2a), while early virologic response was similarly robust with Lambda 180 μg and 240 μg. Based on these findings, further investigation of the Lambda 240 μg dose was discontinued across the HCV and HBV programs. After dose reduction or discontinuation of treatment, the hyperbilirubinemia events resolved with no laboratory evidence of sustained hepatic dysfunction.

Conjugated hyperbilirubinemia was more common in HCV-infected patients treated with Lambda+RBV compared with IFN alfa-2a treatment. Therefore, several in vitro studies were conducted to assess any differences in bilirubin-related metabolic or clearance processes following treatment with Lambda or alfa-2a in sandwich cultures of primary human hepatocytes. Gene expression, inhibition, and confocal microscopy data did not suggest a metabolism- or transporter-related rationale to explain the clinically observed difference in the type and frequency of hyperbilirubinemia following treatment with the 2 IFNs. This ruled out metabolism-related factors of uridine diphospho-glucuronosyltransferase 1A1 (UGT1A1) and transporter-related factors of organic anion-transporting polypeptide (OATP) 1B1, OATP1B3, multidrug resistance-associated proteins MRP3 and MRP2, P-glycoprotein (P-gp), and bile salt efflux protein (BSEP).

When Lambda/RBV was combined with asunaprevir (ASV) in the D-LITE study, a higher frequency of concurrent elevations of ALT and total bilirubin (TBILI) was observed, and 3 cases met the program-defined criteria for potential drug-induced liver injury (DILI). This finding led to the discontinuation of the Lambda/RBV/ASV regimen in future development plans. The combination of Lambda/RBV and daclatasvir (DCV) was well tolerated.

In the LIRA-B study, Grade 3 to 4 ALT/aspartate aminotransferase (AST) elevations in Lambda-treated patients generally occurred early following initiation of study drug (ie, Weeks 1 to 16) and in each case appeared related to an early, on-treatment, host-mediated ALT flare.

Four cases of decompensated cirrhosis have been observed with Lambda. One patient with baseline cirrhosis and Gilbert's disease developed Grade 1 hepatic decompensation and ascites while receiving Lambda 120 μg in the EMERGE study; drug treatment was interrupted, the events resolved, and the patient subsequently resumed therapy at a lower dose. In the Phase 3 study (AI452017) in GT-2 or GT-3 HCV-infected patients, 3 of ~70 randomized patients with preexisting compensated cirrhosis developed decompensated cirrhosis while on treatment. All 3 patients were Child Pugh Class A at entry and had evidence of portal hypertension. Two of these patients subsequently recovered; however, 1 patient died of infectious complications. Based on these data, Lambda appears to be associated with decompensation of cirrhosis especially in the context of portal hypertension. Therefore, in prior studies and the current one, enrollment of cirrhotic patients is restricted to compensated cirrhotic patients (Child Pugh Class A) without evidence of portal hypertension.

In summary, across the clinical development program, laboratory abnormalities with Lambda treatment were generally low grade and self limited. The main safety finding was a higher frequency of transaminase elevations, accompanied in some cases by increases in total and conjugated (direct) bilirubin, but no evidence for impaired liver synthetic function such as decreased albumin or increased international normalized ratio (INR).

1.4.3 Clinical Pharmacokinetics

Lambda PK has been characterized following single- and multiple-dose SC administration of Lambda in healthy subjects and patients with HCV (Table 2). The median time to maximum concentration (T_{max}) ranged from 8.00 to 25.1 hours (range, 1–120 hours). Following single-dose administration of Lambda 180 μg, the geometric mean maximum observed concentration (C_{max}) (coefficient of variation [%CV]) values ranged from 1.06 (102) to 2.41 (177) ng/mL. Following multiple-dose administration, the geometric mean C_{max} (%CV) was 1.54 (86.0) ng/mL, demonstrating modest accumulation. The area under the concentration-time curve from time zero extrapolated to infinite time (AUC_{inf}) (%CV) following single-dose SC administration of Lambda 180 μg to healthy subjects and patients with HCV ranged from 116.9 (73.1) to 221 (59) ng·h/mL. In general, exposure values (area under the concentration-time curve [AUC] and C_{max}) were approximately dose proportional in the 80 to 240 μg dose range. The mean (standard deviation [SD]) terminal elimination half-life (T½) ranged from 50.43 (20.47) to 74.0 (42.7) hours.

Table 2: Lambda Pharmacokinetic Parameters

PK Parameter	Values
T_{max} Median (range)	8.00 to 25.1 h Range (1–120 h)
C_{max} Geometric mean (%CV)	Single-dose: 1.06 (102) to 2.41 (177) ng/mL Multiple-dose: 1.54 (86.0) ng/mL
AUC_{inf} Geometric mean (%CV)	Single-dose 180 μg to healthy subjects or patients with HCV: 116.9 (73.1) to 221 (59) ng·h/mL
T½ Mean (SD)	 50.43 (20.47) to 74.0 (42.7) h

Population PK modeling has demonstrated that body weight affects clearance, consistent with standard allometry; however, while body weight has a significant effect on clearance, the effect is small compared with the overall intersubject variability and, thus, does not warrant weight-based dosing.

Preliminary results have shown that renal impairment increases exposure; C_{max} and AUC were approximately 13% and 20% greater, respectively, in subjects with mild impairment and approximately 2-fold greater across the moderate renal dysfunction, severe renal dysfunction, and end-stage renal disease (ESRD) groups compared with subjects with normal renal function.

Preliminary clinical results suggest that following single, 180-μg dose administration, Lambda is a mild inhibitor of CYP1A2, CYP2C9, and CYP3A4, and a moderate inhibitor of CYP2C19 and CYP2D6.

1.5 Potential Risks and Benefits to Human Patients in This Study

All patients enrolled in this study will receive 48 weeks of treatment with Lambda. Patients with HDV, for which no treatment is approved, may experience benefit from receiving an investigational IFN that may show efficacy in HDV, with a potentially improved safety profile over IFN alfa formulations, based on the available data regarding the biologic effects and different distribution patterns of Lambda vs. IFN alfa receptors, in addition to the available safety data from studies in patients with chronic HCV and HBV infection. See the Peginterferon Lambda-1a investigator brochure (IB) for more information.

The potential benefits to all study patients may include a beneficial impact on their CHD infection, as determined by virologic, serologic, and biochemical responses. An additional potential benefit of Lambda therapy is that after a defined treatment period, responses may be maintained after discontinuation of therapy, presumably reflective of immunologic control of the virus having been attained. Finally, development of viral resistance is not expected based on data from previous studies with IFN-α and IFN-λ in patients with CHB or CHC infection.

For Lambda monotherapy, there are 2 categories of risk: adequacy of the Lambda dose selected for this study and potential drug toxicity. To protect against possible inadequacy of the Lambda dose, 2 doses (120 and 180 μg/week) were selected for this study. Both Lambda and IFN-α have been administered at these doses in studies evaluating efficacy and safety in the treatment of CHB and HCV (Cooksley et al 2003, Chan et al 2015). These biologic treatments are expected to have the same targeted effect across viral hepatitides—expression of the IFN receptors on hepatocytes and other infected cells (Kotenko et al 2003, Sheppard et al 2003)—and so using the same doses seems appropriate in this study in HDV.

Potential drug toxicity risks are based on observations in the nonclinical development program (Section 1.3.2) and safety events noted in clinical trials (Section 1.4.2). In the preclinical program, a minimal-to-mild cardiomyopathy was observed in mice; however, no histologic evidence of cardiomyocyte injury was seen in monkeys treated for up to 6 months. In monkeys, the primary safety findings were a dose-dependent decrease in serum fibrinogen levels, mononuclear infiltrates at SC injection sites, and the transient appearance of skin flaking and reddening. In pregnant mice, Lambda therapy was associated with fetal loss, increased incidence of preterm deliveries, developmental mortality, and fetal dysmorphology.

In completed, Phase 1, single- and multiple-dose studies conducted in healthy volunteers and in HBV- and HCV-infected patients, overall Lambda has been well tolerated, with minimal constitutional symptoms and hematologic events, and no cardiac toxicity. The primary AEs observed included mild, asymptomatic, dose-dependent, primarily isolated, and reversible laboratory abnormalities: (1) elevations in serum transaminases, which were accompanied by increases in conjugated bilirubin in only a small number of patients; (2) changes in coagulation parameters (PT and/or fibrinogen); and (3) increases in serum troponin that were not associated with abnormalities on ECG or cardiac echocardiogram. Most of these abnormalities occurred in the highest dose groups.

Asymptomatic, dose-related, reversible elevations in serum transaminases and/or bilirubin levels have been observed in some patients. Incidences of these events with Lambda 120 or 180 μg/week were similar to those of pegIFN-α, and were higher with Lambda 240 μg/week. Dose-related direct bilirubin (DB) elevations were more frequent with Lambda than with pegIFN-α; the majority of these events were seen with Lambda 240 μg/week. These findings were observed in both noncirrhotic and cirrhotic patients. The current study will not investigate the 240 μg dose.

Resistance development is a risk commonly associated with the use of antiviral agents. However, because Lambda is an immunomodulator, the risk of resistance development is small. Viral resistance has not developed in previous studies with IFNα in CHB, CHC, or CHD, and it is not expected for Lambda therapy.

To mitigate risk in the current study, patients for whom Lambda therapy is considered contraindicated will be excluded from participating. For example, patients with preexisting evidence of hepatic impairment (based on serum bilirubin and measures of liver synthetic function) will be excluded. In addition, intensive laboratory monitoring will be performed throughout the study; detailed requirements for study drug dose interruption, reduction, or discontinuation are described in Section 5.4.3.

2 STUDY OBJECTIVES

2.1 Primary Objectives

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 2 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 effect of treatment with 2 dose levels of Lambda on the following:
  - ALT levels
  - Hepatitis B surface antigen (HbsAg) levels
  - Gamma-Glutamyl Transferase (GGT) levels

2.3 Exploratory Objectives

An exploratory objectives of the study are to evaluate the treatment with 2 dose levels of Lambda on the following:

- Immunologic parameters

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This Phase 2, randomized, open-label, 2 dose level study will assess the safety, tolerability, and pharmacodynamics (PD)/efficacy of Lambda in patients with CHD. Up to forty patients will be enrolled at approximately 6 study sites globally. Patients will be randomized 1:1 to receive 1 of the following treatments with open-label study drug:

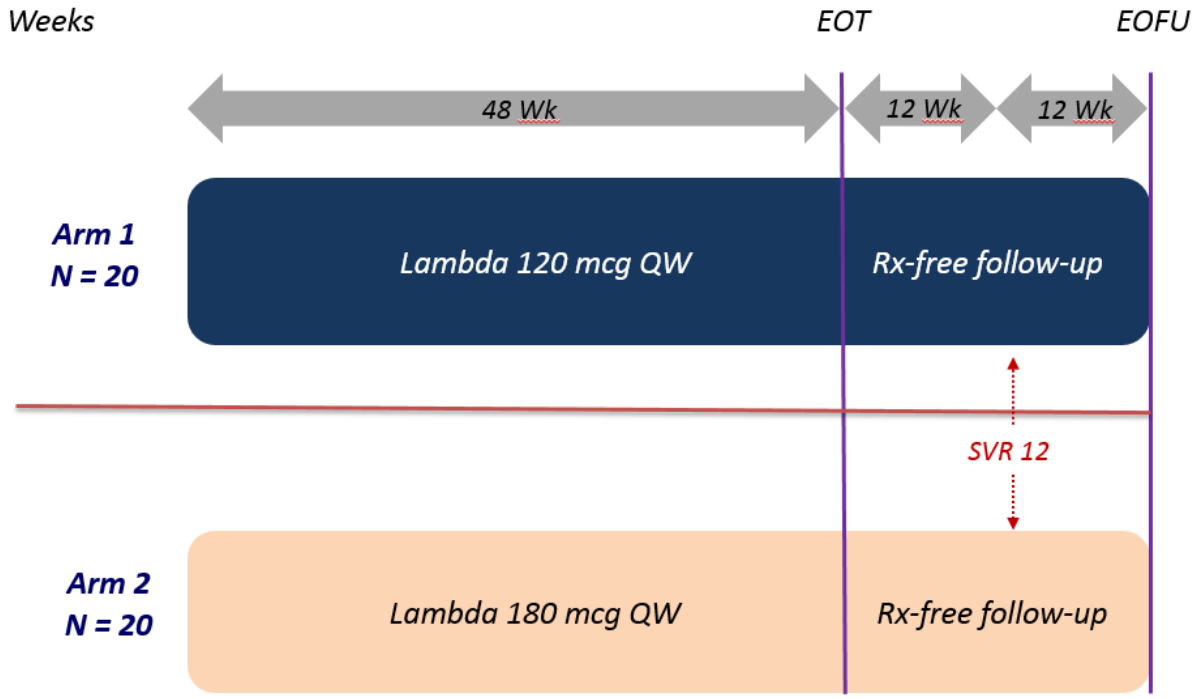
- 120 µg Lambda, weekly SC injection
- 180 µg Lambda, weekly SC injection

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

The study will consist of 3 periods (Figure 2):

- 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 Period: Week 49 though Week 72 (6 months)

Figure 2: 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

All patients, whether they complete the treatment period or not, will be followed for 6 months in the follow-up period. The maximum anticipated time an individual patient will participate in the study will be 19 months (up to 1 month of screening, 12 months of treatment, and 6 months of follow-up).

Patients will be required to take an anti-HBV nucleos(t)ide analog (NUC) 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 (ETV) will be prescribed. This medication will protect patients in the case that HDV suppression may lead to HBV flare.

HDV RNA by qPCR will be measured to assess PD/efficacy. HBV deoxyribonucleic acid (DNA) will also be measured throughout the study. Safety measures include AEs, clinical laboratory values, vital signs, ECG, physical examination findings, and concomitant medication usage. Specific management protocols for several Lambda toxicities documented in the literature and/or the product IB are provided in Section 5.4.3, including recommendations for drug interruption, dose adjustment, and discontinuation.

3.2 Rationale for Study Design

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

3.2.1 Rationale for Dose

The Lambda doses chosen for this study (120 and 180 μg/week) were based on the results from studies in healthy volunteers and patients with CHB or CHC. See Section 1.5 for more information.

4 STUDY POPULATION SELECTION

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

4.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria before study entry to be eligible for enrollment into the study:

1. Willing and able to comply with study procedures and provide written informed consent
2. Male or female, 18 to 65 years of age, inclusive
3. 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
4. Serum ALT > upper limit of the normal range (ULN) and <10 × ULN at screening
5. 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
6. TSH and/or free T4 within 0.8 to 1.2 times the normal limit, or adequately controlled thyroid function as assessed by the investigator
7. 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
8. 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 1 year postmenopausal.
   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
   - Surgical sterilization of the partner (vasectomy ≥ 1 month before screening)

For males

- Surgical sterilization (vasectomy ≥ 1 month before screening)
  or
- Both of the following contraceptive methods from screening:
  - Consistently and correctly use a condom
  - Partner must use a hormonal contraceptive or a nonhormonal barrier method (IUD or diaphragm with spermicide or cervical cap with spermicide)

9. Willing and able to provide written informed consent
10. Willing and able to comply with all study procedures

4.2 Exclusion Criteria

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

General Exclusions

1. 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
2. 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.
3. History or evidence of any intolerance or hypersensitivity to IFNs or other substances contained in the study medication.
4. 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

5. Current or previous history of decompensated liver disease (Child-Pugh Class B or C)
6. Co-infected with human immunodeficiency virus (HIV) or hepatitis C virus (HCV). Positive results for HIV or HCV Ab at screening. Patients with a positive HCV Ab at screening are allowed if they have completed a curative antiviral regimen and are documented to be HCV RNA negative (undetectable) at least 3 months before screening and at screening.
7. Past history or current evidence of decompensated liver disease as defined by the presence of any of the following at screening:
   a. Bilirubin level ≥2.5 mg/dL unless due to Gilbert's disease
   b. Serum albumin level <3.5 g/dL
   c. INR ≥1.5
   d. Alpha fetoprotein ≥100 ng/mL
8. Evidence of significant portal hypertension such as hepatic venous pressure gradient (HVPG) ≥10 mmHg; current presence or history of variceal bleeding

9. Current evidence or history of ascites requiring diuretics or paracentesis, or hepatic encephalopathy
10. Patients with any of the following abnormalities at screening:
    a. Platelet count <90,000 cells/mm^3
    b. WBC count <3,000 cells/mm^3
    c. Absolute neutrophil count (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 × ULN
    f. Confirmed creatinine clearance (CrCl) <50 mL/min by Cockroft-Gault
11. Evidence of another form of viral hepatitis or another form of liver disease (eg, autoimmune liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, alcoholic liver disease, nonalcoholic steatohepatitis, hemochromatosis, alpha-1-anti-trypsin deficiency)
12. History of hepatocellular carcinoma
13. Patients with any of the following:
    a. Current eating disorder or alcohol abuse
    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: 360 mL of beer, 150 mL of wine, or 45 mL of spirits.
    c. In the opinion of the investigator, an alcohol use pattern that will interfere with study conduct
    d. Drug abuse within the previous 6 months before the screening visit with the exception of cannabinoids and their derivatives
14. Prior history or current evidence of any of the following:
    a. Immunologically mediated disease (eg, rheumatoid arthritis, inflammatory bowel disease, severe psoriasis, systemic lupus erythematosus) that requires more than intermittent nonsteroidal anti-inflammatory medications for management or that requires use of systemic corticosteroids in prior 6 months (inhaled asthma medications are allowed)
    b. Retinal disorder or clinically relevant ophthalmic disorder
    c. Any malignancy within 5 years before screening. Exceptions are superficial dermatologic malignancies (eg, squamous cell or basal cell skin cancer treated with curative intent).
    d. Cardiomyopathy or significant ischemic cardiac or cerebrovascular disease (including history of angina, myocardial infarction, or interventional procedure for coronary artery disease)
    e. Chronic pulmonary disease (eg, chronic obstructive pulmonary disease) associated with functional impairment
    f. Pancreatitis
    g. Severe or uncontrolled psychiatric disorder such as depression, manic condition, psychosis, acute and/or chronic cognitive dysfunction, suicidal behavior, and relapse of substance abuse

h. Active seizure disorder defined by either an untreated seizure disorder or continued seizure activity within the preceding year despite treatment with anti-seizure medication
i. Bone marrow or solid organ transplantation

15. Other significant medical condition that may require intervention during the study. Patients with any serious condition that, in the opinion of the investigator, would preclude evaluation of response or make it unlikely that the contemplated course of therapy and follow-up could be completed. Patients for whom participation in the study would increase their risk.

Exclusions Related to Use of Selected Medications

16. Therapy with an immunomodulatory agent; alpha IFN (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
17. Use of telbivudine (Tyzeka or Sebivo) within 3 months before screening or during the study
18. Current use of heparin or Coumadin
19. Received blood products within 30 days prior to study randomization
20. Use of hematologic growth factors within 30 days prior to study randomization
21. Systemic antibiotics, antifungals, or antivirals for treatment of active infection other than HBV within 14 days of study randomization
22. Any prescription or herbal product that is not approved by the investigator
23. Long-term treatment (> 2 weeks) with agents that have a high risk for nephrotoxicity or hepatotoxicity, should be discussed with the medical monitor
24. Receipt of systemic immunosuppressive therapy within the 3 months before start of screening

4.3 Replacement of Patients in Study

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

4.4 Early Withdrawal from Study by Individual Patients

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

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

In addition, specific rules are defined regarding actions to be taken (study drug interruption, study drug discontinuation, and study drug dosage adjustment) in the case of specific toxicities (see Section 5.4.3).

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

When a patient discontinues study drug early, the patient is considered permanently discontinued from the study. The reason for early withdrawal will be noted on the appropriate electronic case report form (eCRF). Every effort should be made to encourage the patient to return to the clinic as soon as possible for early termination (ET) assessments (Section 6.14). Patients who discontinue study medication/withdraw from the study, either during the treatment period or during the follow-up period, will be encouraged to return for all follow-up visits through 24 weeks after drug discontinuation, if possible.

4.5 Early Termination of the Study

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

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

In addition, the regulatory agency or the site's institutional review board (IRB)/independent ethics committee (IEC) has the authority to stop the study.

5 INVESTIGATIONAL PRODUCTS

5.1 Product Description

The study drug, Lambda, is a conjugate of a recombinant version of human IL-29 (rIL-29) and a linear polyethylene glycol (PEG) chain. Other names for Lambda include pegylated interferon lambda (pegIFNλ−1a), PEG-rIL-29, and BMS-914143 (it was licensed from Bristol-Myers Squibb Company).

Lambda has a molecular weight of 41,300 ± 88 Da. The solution appears as colorless to pale yellow , clear to slightly opalescent and essentially free of visible particles.

Lambda will be provided in ready-to-use (RTU) syringes to be administered via SC injection. Each RTU syringe contains a 0.5 mL solution volume at a concentration of 0.4 mg/mL and can deliver up to 180 μg Lambda. The syringes have markings to indicate the appropriate volume to inject for the 180 μg or 120 μg dose, or for a 80 μg dose if needed for dose-reduction.

For additional information on Lambda, please refer to the IB.

5.2 Treatment Groups

5.2.1 Method of Assigning Patients to Treatment Groups

Patients will be randomized equally to receive 1 of the 2 study treatments: 120 μg or 180 μg Lambda as SC weekly injection.

Once protocol eligibility criteria have been confirmed for a particular patient, the site staff will enroll the patient and assign the patient to 1 of the 2 treatment arms. It is important that the investigative staff reconfirm the patient's willingness to continue in the study prior to enrollment and randomization.

5.2.2 Randomization

Patients will be randomly assigned 1:1 to receive either 120 or 180 μg Lambda as SC weekly injection by the interactive web response system (IWRS).

5.3 Blinding

This study is open label, therefore no treatment blinding will be used.

5.4 Treatment Administration

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.

5.4.1 Dosage

The dosage of study drug will be either 120 or 180 μg Lambda, or if a dose reduction was required, 120 or 80 μg Lambda (see Section 5.4.3 and Table 3). Patients will self-administer study drug doses via SC injection once weekly through the entire dosing period. Patients will receive a maximum of 48 doses of study medication, with the final administration of study medication at Week 47 (Day 330).

5.4.2 Dose Titration

No dose titration will be included in this study.

5.4.3 Dose Interruptions, Reductions, and Discontinuations

The following section provides management criteria for laboratory and clinical AEs occurring during the treatment period (Table 4). Additional guidance is provided for occurrences of depression and other neuropsychiatric AEs (Table 5). These recommendations are based on the recognized risks of Lambda therapy in patients with CHB and guidance from the published literature and/or the IB. Specific guidelines for managing events of direct hyperbilirubinemia are included because direct hyperbilirubinemia is a recognized additional potential risk of Lambda therapy.

All assessments regarding a laboratory or clinical AE are to be made by the investigator, using the provided guidance. The tables list the following abnormality categories:

- AEs (Grade 3 at least possibly related and clinically significant, Grade 3 at least possibly related and not clinically significant, depression, and ocular symptoms)
- Hematologic abnormalities (ANC and platelets)
- Hepatobiliary abnormalities (ALT, AST, TBILI, DB, and INR)
- Renal abnormalities (creatinine clearance)

The dose reduction scheme including first and second dose reduction (DR) levels is shown in Table 3. Note that patients who require dose reduction in the 180 μg/week dose group will be given 120 μg/week in the first dose reduction (DR1) and 80 μg/week in the second dose reduction (DR2); patients in the 120 μg/week dose group will be given 80 μg/week in the first dose reduction (DR1) and also in the second dose reduction (DR2; in effect, they cannot be given a dose below 80 μg/week).

All subjects who meet the criteria for <u>treatment interruption, reduction and/or discontinuation</u>, based on hepatobiliary abnormalities should have a clinical work-up that includes the following:

- Autoimmune markers (antinuclear antibody [ANA], anti-smooth muscle antibody [anti-SMA], anti-LC1, anti-SLA liver kidney microsome type 1 and type III antibody [anti-LKM1,3]),
- C3, C4 and CH50,
- Acute viral hepatitis,
    - Serologies for acute hepatitis A and E (IgM);
    - PCR for HCV, hepatitis E (stool and blood),
    - *Cytomegalovirus* (CMV), PCR

  - *Epstein-Barr virus* (EBV), PCR
  - Herpes simplex viruses 1 and 2 (HSV), PCR
- Cholestasis work up with a Doppler US of the liver
- Review of pre-existing hepatic disease (excluding HBV)
- Review of concomitant medication(s), or herbal medications and substances known to be hepatotoxic, tests for alcohol and acetaminophen and drugs of abuse, if indicated
- Ultrasound of the liver should be performed, including doppler, for subjects with a bilirubin level greater than 1.5 times baseline
- If clinically feasible, a liver biopsy should be performed.
  - When a percutaneous biopsy is contraindicated, a transjugular biopsy may be discussed.
- Liver and chemistry labs should be performed weekly (minimally include ALT, AST, bilirubin, INR, alkaline phosphatases and gamma-GT) until the bilirubin returns to baseline value.
- HBV DNA and HDV RNA should be monitored weekly until Bili < 1.5 × ULN
- 5 ml of serum plus 5 ml of plasma should be collected for possible later biomarker analysis

It is preferable that all labs are processed at the designated Central Lab but it is understood that in some instances labs may be drawn at a local lab. Local labs should be used only after consultation with the medical monitor.
Subjects with a 4× increase in baseline GGT, ALT/AST or alkaline phosphatases or > Bili 1.5 mg/dL, direct Bilirubin >0.6 (if Gilbert Syndrome is present), may be prescribed ursodeoxycholic acid for "liver protection".
All confirmed occurrences of potential possible medication related liver injury should be reported as Serious Adverse Events (SAE) and result in immediate patient discontinuation from study drug as defined above. However, in cases where no prior evidence of advanced hepatic fibrosis or alteration of the hepatic synthetic function exist (normal serum albumin, INR, platelet count > 100,000/mm^3) dose continuation or reduction should be discussed with the Sponsor or designated medical monitor. Tenofovir DF or entecavir for treatment of hepatitis B should be maintained.

Table 3: Lambda Dose Reduction Dosages

Assigned Treatment	Starting Dose Dose (μg)	First Dose Reduction (DR1) Dose (μg)	Second Dose Reduction (DR2) Dose (μg)
Lambda	180	120	80
Lambda	120	80	80

Note: For patients in the 120 μg group, the second DR level is the same as the first (80 μg/week).

Table 4: Guidelines for Treatment Interruption or Discontinuation and Dose Modification

Toxicity	Management, Monitoring, and Dose Modification		Discontinuation of Drug
	Immediate Actions/Resolution	**First Recurrence**	
Adverse Events			
AE ≥ Grade 3, considered at least possibly related to study drug and clinically significant, and no specific guidance given below	Interrupt dosing and monitor weekly Resolution: If event resolves to ≤ Grade 1 or baseline value, restart dosing at DR1	If AE recurs at DR1, interrupt dosing and monitor weekly Resolution: If event resolves again to AE ≤ Grade 1 or baseline value, restart dosing at DR2	If event does not resolve in 2 weeks (missed 2 consecutive doses of drug) **or** If event recurs at DR2, discontinue drug
AE ≥ Grade 3, considered at least possibly related to study drug and **not** clinically significant, and no specific guidance given below	Discuss with medical monitor. Not all Grade 3 AEs will require dose modification.		
Depression	See Table 5 and CTCAE neurologic definitions for mild/moderate/severe depression		
New ocular symptoms: New decrease or loss of vision or other clinically significant ocular sign or symptom	Interrupt dosing. Obtain complete eye examination performed by an ophthalmologist. Discuss further management with the medical monitor prior to restarting therapy.		
Hematologic abnormalities			
ANC			
≥750/mm^3	Maintain dose		
≥500/mm^3 and < 750/mm^3	Reduce dose to DR1 and monitor weekly		
< 500/mm^3	Interrupt dosing Resolution: If ANC > 1000/mm^3, restart dosing at DR2		If event does not resolve in 4 weeks (missed 4 consecutive doses) **or** If event recurs (confirmed) at DR2, discontinue drug
Platelets			
< 50,000	Reduce dose to DR2		
< 25,000			If event is confirmed, discontinue drug

Toxicity	Management, Monitoring, and Dose Modification		Discontinuation of Drug
Hepatobiliary abnormalities **For Stage IV liver disease, cirrhosis**			
ALT/AST ≥5 × ULN and < 10 × ULN	Monitor per protocol		
ALT/AST ≥10 × ULN and < 15 × ULN **and** TBILI and/or INR < Grade 2	Continue dosing Monitor ALT, AST, TBILI, DB, albumin, PT/INR weekly If ALT/AST <10×ULN, stop weekly monitoring		
ALT (or AST) ≥15 × ULN **and** TBILI and/or INR < Grade 2	Interrupt dosing Monitor ALT, AST, TBILI, DB, albumin, PT/INR weekly Resolution: If ALT/AST <10×ULN, stop weekly monitoring and restart dosing at DR1	If event recurs at DR1, interrupt dosing and monitor weekly Resolution: If ALT/AST <10×ULN, stop weekly monitoring and restart dosing at DR2	If event does not resolve in 4 weeks (missed 4 consecutive doses) **or** If event recurs (confirmed) at DR2, discontinue drug
ALT (or AST) ≥5×ULN **and** TBILI and/or INR ≥Grade 2			If confirmed, discontinue drug[a]
TBILI > 2.5 × ULN **and** DB > 3 × ULN	Interrupt dosing Monitor ALT, AST, AP, TBILI, DB, albumin, PT/INR weekly Resolution: If TBILI ≤1.5 ×ULN, stop weekly monitoring and restart dosing at DR1	If event recurs at DR1, interrupt dosing and monitor again Resolution: If TBILI ≤1.5 × ULN, restart dosing at DR2	If event does not resolve in 2 weeks (missed 2 consecutive doses) **or** If event recurs (confirmed) at DR2, discontinue drug

Toxicity	Management, Monitoring, and Dose Modification		Discontinuation of Drug
A potential treatment related liver event as defined below that would result in the labeling of this as a "serious medication related liver event" would have to satisfy all 5 of the conditions below: 1. ALT > 10× ULN 2. ALT > 5× baseline or nadir, whichever is lower 3. Total bilirubin > 5 × ULN 4. INR > 1.5 × ULN confirmed with local confirmation 5. No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to, acute viral hepatitis, obstructive jaundice, preexisting hepatic disease excluding HBV, or the administration of other drug(s), or herbal medications and substances known to be hepatotoxic.			If confirmed, and no other immediately apparent possible causes[a], discontinue drug and report as potential SAE (Section 9.3.4.1)
Renal function abnormalities			
Creatinine clearance < 50 mL/min			Discontinue drug

Note:
Stage IV disease: keep current stopping rules if kPa≥ 11.5 at Baseline as above
For patients with:
Stage 0-III disease: ≤ 11.4 kPa at Baseline, new dose interruptions, then reductions then discontinuations is sequence as provided;

- In patients with
  - Alb >3.5 g/dL AND
  - INR <1.5 AND
  - Total Bilirubin <3 mg/dL
- Then
  - Dose interruption 1 at ALT >20× ULN (>1000 IU/mL)
  - Restart at next lower lambda dose when ALT < 10x ULN (<500 IU/mL)
  - Next dose interruption 2 at ALT 20× ULN (>1000 IU/mL)
  - Restart at next lower lambda dose when ALT < 10× ULN (<500 IU/mL) or stop if at 80 ugm dose if bilirubin 3.0 mg/dL or greater

All dosing discontinuations are permanent. Laboratory abnormalities that result in discontinuation must be reported to the medical monitor.
AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; DB, direct bilirubin; DILI, drug-induced liver injury; PT, prothrombin time; SAE, serious adverse event; TBILI, total bilirubin; ULN, upper limit of the normal range
a Including, but not limited to, acute viral hepatitis, cholestasis, preexisting hepatic disease excluding HBV, or the administration of other drug(s), or herbal medications and substances known to be hepatotoxic

Table 5 lists the guidelines to be used for patients who experience depression or other neuropsychiatric disorders during the study. In addition to these recommendations, additional drug therapies such as antidepressants can be provided at the discretion of the investigator.

Table 5: Depression or Other Neuropsychiatric Disorders: Guidelines for Treatment Interruption or Discontinuation or Dose Modifications

	Initial Management (4–8 weeks)		Subsequent Symptoms on Regular Evaluation		
Severity	**Dose Modification**	**Visit Schedule**	**Symptoms Remain Stable**	**Symptoms Improve**	**Symptoms Worsen**
Mild	No change	Evaluate weekly (visit and/or phone)	Continue weekly visit schedule	Resume normal visit schedule	Go to moderate or severe row of this table.
Moderate	Decrease dose to 1st dose reduction level (or if necessary, to 2nd dose reduction level)	Evaluate weekly (visit at least every 2 weeks)	Consider psychiatric consultation. Continue reduced dosing.	If symptoms stable for 4 weeks, resume normal visit schedule. Continue reduced dosing.	Go to severe row of this table.
Severe	Discontinue dosing.	Obtain immediate psychiatric consultation.	Initiate/continue psychiatric therapy.		

Note: Severity based on definitions in the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 (CTCAE 2010)

Additional requirements regarding dose interruption, reduction, or discontinuation are listed below.

For all events, at the investigator's discretion, patients should be evaluated for other non-drug-related causes of the event.

Dose interruption

- Doses of study drug that are withheld during dose interruption are not to be replaced (ie, maximum duration of the treatment period is 48 weeks for all patients).
- The laboratory abnormality or AE that led to dosing interruption will be monitored weekly until resolution or discontinuation of study drug.
- During dose interruption, the patient will maintain the same visit and assessment schedule.
  - If HDV RNA testing was not done while study drug was interrupted, an unscheduled HDV RNA should be done prior to restarting study drug.

Dose reductions

- Following a dose reduction, the dose should NOT be re-escalated.
- Up to 2 dose reductions will be allowed; events that do not resolve despite 2 dose reductions will result in the patient discontinuing study drug.

Discontinuations

- If a laboratory abnormality requires drug discontinuation, the laboratory value must be confirmed within 72 hours, and the medical monitor must be informed.
- If study drug is discontinued based on the above recommendations, the patient will be classified as having a treatment-limiting toxicity (TLT). Events meeting this criterion must be reported to the sponsor within 2 business days; these events will be reviewed and validated by the sponsor for a final determination.

5.4.4 Missed Doses

Patients will be instructed to self-administer Lambda once a week in the evening. If a dosing window (±1 day) is missed, the patient should skip the dose completely.

If a patient misses 4 consecutive Lambda doses, the patient will be discontinued from the study.

5.5 Treatment Compliance

At the initial study visit on Day 1, patients will be given a patient diary in which to record study drug dosing administrations (dates and times of both Lambda and NUC doses) and patient-reported outcomes. A sample diary is included in Appendix 3. Patients will be instructed to bring their patient diary when they return to the clinic for their next study visit during the treatment period. Adherence with the prescribed regimen for each study drug (Lambda and NUC) will be measured using diary information.

Patients will be reminded to record all drug administrations in the patient diary at each applicable study visit (from Day 1 through the Week 44 visit for study drug, and from Day 1 through the Week 68 penultimate follow-up visit for NUC).

5.6 Treatment Packaging and Labeling

Lambda will be supplied in RTU syringes. Each box of syringes will be labeled for use in an open-label study; label information will include protocol, sponsor, contents, storage conditions, investigational caution statement, and other information as needed. Each box will contain syringes for a 4-week supply of study drug. The number of syringes provided will depend on the interval to the next study visit.

5.7 Treatment Storage and Retention at Study Site

Lambda needs to be stored at 2°C to 8°C (35.6°F to 46.4°F). Patients will be provided with cooler bags and cool packs at baseline, which should be brought back for each study visit. RTU syringes containing Lambda must not be frozen or shaken; they should be protected from light. The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and the sponsor should be contacted immediately.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study patients. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

Dispensing instruction will be provided in a study manual.

5.8 Prior and Concomitant Therapies

All prior medications taken within 28 days before screening and all concomitant medications taken during the study (from Day 1 after the first dose of study drug is administered until the last study follow-up visit at Week 72) will be recorded in the eCRF. All prior treatments administered for HDV and HBV infections will be recorded on the eCRF.

5.8.1 Prior Therapies

Patients will not be enrolled in the study if they have taken any of the following medications within the time frames specified below:

- Any investigational product within 1 month before screening
- Systemic immunosuppressive therapy within 3 months before screening
- An immunomodulatory agent; alpha IFN (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
- Telbivudine (Tyzeka or Sebivo) within 3 months before screening
- Blood products within 1 month before study randomization (Day 1)
- Hematologic growth factors within 1 month before study randomization (Day 1)
- Systemic antibiotics, antifungals, or antivirals for treatment of active infection other than HBV within 14 days of study randomization (Day 1)

In addition, patients with the following drug therapy history must be approved by the medical monitor before enrollment:

- Long-term treatment (>2 weeks) with agents that have a high risk for nephrotoxicity or hepatotoxicity

5.8.2 Concomitant Therapies

All prescription and over-the counter medications including herbal products taken during the study conduct must be approved by the study investigator.

5.8.2.1 Nucleos(t)ide Analog Medication

Patients will be required to take a NUC from baseline (Day 1) until the end of the study to protect them in the case that HDV suppression may lead to HBV flare. NUC therapy will continue through the final follow-up visit, regardless of any Lambda dose interruptions, reductions, or discontinuation.

A NUC will be chosen for each patient at the baseline visit using the scheme shown in Table 6. For patients not currently taking a NUC at screening, TDF 300 mg/day will be prescribed. Patients taking telbivudine (Tyzeka or Sebivo) will not be permitted to enroll. If the patient is already taking ETV (Baraclude) 0.5 mg/day, that treatment will be continued. If the patient is already taking any other NUC (not ETV, TDF, or telbivudine) and has a documented history of at least 6 months of undetectable HBV DNA, the patient will continue that medication at the same dose.

Table 6: Choice of NUC Therapy to Be Taken During Study Conduct

NUC at Screening	Action Taken at Baseline Visit
None	Start TDF (start ETV if TDF is contraindicated)
Telbivudine	Screen failure
ETV	Continue ETV
Any other NUC	HBV undetectable ≥6 months? Yes: Continue the NUC No: Switch to TDF (switch to ETV if TDF is contraindicated)

During the study, the investigator can change the NUC medication or dosage if medically warranted in a particular patient. The investigator will use clinical judgment and follow the applicable NUC prescribing label. The TDF prescribing information can be obtained at http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/viread/viread_pi.pdf. The ETV prescribing information can be found at http://www.hivandhepatitis.com/hep_b/treatment/Baraclude%20PI.pdf.

5.8.2.2 Prohibited Medications

The following concomitant medications are prohibited while the patient is receiving study drug:

- Any hematopoietic growth factor including granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF), pegylated G-CSF, erythropoietin, darbepoetin, eltrombopag, romiplostim, or oprelvekin
- Except the prescribed concomitant NUC, any other medications with known or potential anti-HBV activity, including any other IFNs or other HBV NUCs
- Heparin or Coumadin
- Drugs known to prolong the PR or QT interval

In addition, patients taking the following concomitant drug therapies must be approved by the medical monitor:

- Long-term treatment (> 2 weeks) with agents that have a high risk for nephrotoxicity or hepatotoxicity

5.8.2.3 Other Restrictions and Precautions

Patients who enter the study taking concomitant medications with safety profiles that include risks commonly seen with IFN therapy (eg, hematologic, liver, central nervous system [CNS]) should be on stable doses of those medications for at least 4 weeks prior to the first

dose of study drug. If the patient is on chronic medication, a consistent dosing schedule is recommended for the duration of this study, if medically possible.

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

6 STUDY PROCEDURES AND ASSESSMENTS

All study procedures and assessments are shown by visit in Appendix 1.

6.1 Informed Consent

Written informed consent must be obtained at screening before initiating any study-mandated procedures. See Section 11.4 for additional information regarding informed consent.

6.2 Demographics

At screening, patient demographic (eg, age, sex, race, and ethnicity) and baseline characteristics data will be collected.

6.3 Medical History

Medical history, including details regarding illnesses and allergies, date(s) of onset, and whether conditions are currently ongoing, and medication history will be collected on all patients during screening.

6.4 Retinal Examination

Retinal examinations will be performed at screening unless the patient has a document record of a retinal examination within 1 year before screening, and at Week 48.

For the screening evaluation only, if the patient has diabetes, hypertension, or other risk factors for retinal disease, the retinal examination has to be performed by a licensed ocular specialist; for all other patients, the study investigator or a licensed ocular specialist can perform the retinal examination. The Week 48 retinal examination can be performed by the study investigator in all cases.

6.5 Baseline Virology Tests

Blood samples will be collected at baseline (Day 1) for serum HDV genotypic analysis to determine HDV subtypes (1–8) and to understand the natural polymorphisms of HDV.

6.6 Inclusion/Exclusion Criteria

At the screening visit, patients will be interviewed to determine if they meet all of the inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2). Prior to randomization at baseline (Day 1), patients will be rechecked to be sure that they meet study entry criteria.

6.6.1 Drug and Alcohol Testing

At screening, a blood sample will be collected for blood ethanol testing and a urine sample will be collected for drugs of abuse testing.

6.6.2 Alpha Fetoprotein Screening Test

In addition to the standard screening blood samples (Section 6.11.2), a blood sample will be collected to measure alpha fetoprotein.

6.6.3 Abdominal Imaging

Abdominal imaging (ultrasound, magnetic resonance imaging [MRI], or computed tomography [CT]) will be performed at screening if the patient does not have abdominal imaging documentation obtained ≤6 months before screening.

6.7 Pregnancy Testing

For women of childbearing potential (see Section 4.1, Inclusion Criterion 8), a blood sample will be collected for a serum hCG test at screening.

Urine samples will be collected for a urine hCG test at all subsequent visits from baseline through follow-up (except the Week 1 visit) in women of childbearing potential. If a urine pregnancy test is found to be positive, it will be confirmed immediately with a serum pregnancy test.

6.8 Study Enrollment

Patients who meet all of the inclusion criteria and none of the exclusion criteria during the screening period and at baseline (Day 1) will be enrolled in the study. Refer to Section 5.2.1 for the method of assigning patients to treatment groups.

A screen failure is defined as a patient who has signed the ICF, does not meet all the entry criteria as outlined in this protocol, and has not been randomized or received study drug. A screening log will be maintained by the investigator or designee, indicating the reason for the screen failure.

6.9 Study Treatment Dispensing

A designated member of the study staff will dispense study drug to the patient at each visit from baseline (Day 1) through the Week 44 visit based on the treatment assignment and any required dose reductions as described in Section 5.4.3.

6.9.1 Anti-HBV Nucleos(t)ide Analog Dispensing

At baseline, the choice of NUC is made for a given patient using the rules specified in Section 5.8.2.1.

If the patient will start a NUC or will change the NUC medication at baseline, the appropriate NUC will be dispensed to patients at each study visit from baseline (Day 1) through the penultimate follow-up visit at Week 68. Otherwise, the patient will continue his or her existing NUC prescription over the same time period.

6.10 Pharmacodynamics/Efficacy Assessments

6.10.1 Molecular and Serologic Tests

6.10.1.1 Hepatitis D Virus

A blood sample will be collected at screening for the HDV serology test.

Blood samples will be collected for HDV RNA analysis at all visits from screening though the follow-up period. HDV RNA viral load will be quantified using the RoboGene® HDV RNA Quantification Kit, which uses real-time qPCR of HDV RNA in human serum samples. The assay is designed to detect HDV GT-1, -2, -5, -6, -7, and -8, applying probes and primers specific for a subsequence of the hepatitis delta antigen. The assay has a lower limit of quantitation (LLOQ) of 14 IU/mL based on calibrated standards using a reference HDV GT-1 positive serum.

6.10.1.2 Hepatitis B Virus

HBV DNA

Blood samples will be collected for HBV DNA analysis at screening, baseline (Day 1), and all visits starting with Week 4 including all follow-up visits.

HBV DNA will be analysed using the Aptima HBV Quant DX assay via the fully automated Hologic Panther system. Hologic have determined the limit of detection for the Aptima HBV assay to be 5.58 IU/ml in plasma and 4.29 IU/ml in serum. This was determined using the 3rd WHO international standard and the quantification limit to be 10 IU/ml across HBV genotypes A, B, C, D, E, F, G and H. The upper limit of quantification is 10^9 IU/ml. The assay is reported as Not detected, detected <10 IU/ml, or a quantitative result between 10 and 10^9 IU/ml, for samples over the upper limit, repeat testing will be done at a 1:100 dilution to find the actual value.

If HBV DNA is detectable in the screening sample, a viral genotype analysis will be performed.

HBsAg, HBsAb, HBeAg, HBeAb

Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B envelope antigen (HBeAg), and hepatitis B envelope antibody (HBeAb) levels may be important to indicate seroconversion or disease course.

HBsAg: Blood samples will be obtained for quantitative measurement of HBsAg (qHBsAg) at screening, baseline (Day 1), and all visits starting with Week 4 including all follow-up visits.

HBsAb: A blood sample will be obtained for measurement of HBsAb at screening, baseline (Day 1), and at the Week 48 and 72 visits.

HBeAg and HBeAb: Blood samples will be obtained for measurement of HBeAg and HBeAb at screening, baseline (Day 1), at the Week 24 and 48 visits, and at the Week 60 and 72 visits in the follow-up period.

6.10.1.3 Hepatitis C

A blood sample will be obtaining for HCV serology testing at screening.

6.10.1.4 HIV

A blood sample will be obtaining for HIV serology testing at screening.

6.10.2 Fibroscan

A Fibroscan will be performed at screening, at the end of treatment (Week 48 visit), and at the end of the study (Week 72 visit) to measure liver stiffness. Patients must fast for at least 3 hours before the Fibroscan is performed. Ten stiffness measurements will be obtained, each by pressing the probe in between the ribs; a pressure value (in kPa) is read off the instrument and recorded on the eCFR. A standard M probe will be used for patients with BMI $\leq$30 kg/m^2, and an XL probe will be used for patients with BMI >30 kg/m^2.

6.11 Safety Assessments

6.11.1 Adverse Events

Information on adverse events (AEs) will be collected at any time in the study from the baseline visit (Day 1) through the follow-up visit. In addition, patients will be asked to complete a patient-reported outcomes diary every morning starting on Day 2 through the EOFU specifically to record any flu-like symptoms (headache, chills, fever, joint pains, or muscle pains) and injection-site reaction symptoms (pain, itching, tenderness, redness, and swelling). See Section 9 for a complete description of AE reporting.

6.11.2 Clinical Laboratory Tests

Blood samples will be collected for clinical laboratory tests (hematology, coagulation, thyroid panel, and clinical chemistry) at screening, baseline (Day 1) and every subsequent visit during the treatment and follow-up periods. Urine samples will be collected for urinalysis at screening, baseline (Day 1), and at the Week 8, 16, 24, 32, 40, and 48 visits in the treatment period and the Week 60 and 72 visits in the follow-up period. Safety laboratory analytes are listed in Table 7. All samples will be sent to the central laboratory for analysis. Additional information on sample collection and processing can be found in the study laboratory manual.

If any test returns an abnormal result, the test will be repeated at the subsequent visit.

Table 7: Serum and Blood Chemistry Laboratory Tests

Test Category	
Hematology	**Clinical Chemistry**
Hemoglobin	Alanine aminotransferase (ALT)
Hematocrit	Albumin
Erythrocyte count (red blood cell)	Alkaline phosphatase (ALP)
Mean corpuscular volume (MCV)	Amylase
Mean corpuscular hemoglobin (MCH)	Aspartate aminotransferase (AST)
Mean corpuscular hemoglobin concentration (MCHC)	Bicarbonate
Leukocytes (WBCs)	Bilirubin (direct, indirect, and total)
Neutrophils, segmented	Blood urea nitrogen (BUN)
Lymphocytes	Calcium
Monocytes	Chloride
Eosinophils	Cholesterol
Basophils	Creatine kinase (CK)
Platelets	Creatinine; calculate creatinine clearance
	Gamma-glutamyl transferase (GGT)
Coagulation	Globulin
Prothrombin time (PT)	Glucose, nonfasting
Fibrinogen (if > Grade 2, do activated partial thromboplastin time [APTT])	Lactate dehydrogenase (LDH)
INR	Magnesium
Thyroid Panel	Phosphorus
TSH	Potassium
Free thyroxine (free T4)	Sodium
Total or free triiodothyronine (total or free T3)	Triglycerides
Urinalysis	Total protein
Specific gravity	Uric acid
Bilirubin	**Additional Screening Tests**
Glucose	Alpha fetoprotein
pH	
Blood	
Ketones	
Protein	
Urobilinogen	
Nitrite	
Microscopic examination of sediment	

6.11.3 Vital Signs

Vital signs (blood pressure [BP], heart rate, respiratory rate, and body temperature) will be measured at screening, baseline (Day 1), and all subsequent visits in the treatment and follow-up periods. BP and heart rate should be measured after the patient has been sitting for 5 minutes.

Body weight will also be measured at all visits (without shoes and heavy outerwear such as jackets and coats).

Height will be measured at screening. Body mass index (BMI) will be calculated at screening.

6.11.4 Physical Examination

A comprehensive physical examination including all body systems pertinent to the patient will be performed at screening. Child-Turcotte-Pugh (CTP) scoring and an encephalopathy assessment will be included (see Appendix 2).

Brief, directed physical examinations will be performed at every subsequent visit in the treatment and follow-up periods; these will include the head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, and lower extremity.

Any clinically significant abnormalities observed before Day 1 will be reported in the patient's medical history. Any new clinically significant abnormality observed on or after Day 1 will be reported as an AE.

6.11.5 Electrocardiograms

Twelve-lead serial ECGs will be performed at screening, baseline (Day 1), Week 4, 12, and 48 after the patient has rested in a supine position for ≥5 minutes. All ECGs will be performed in triplicate (×3) 2 to 3 minutes apart, and 3 interpretable ECGS recordings (ie, without artifacts) should be obtained. (Single ECG recordings can be obtained at unscheduled time points if needed.)

ECGs must be read by the investigator or a qualified designee, and the results recorded in the eCRF. On-treatment ECG results should be compared with the patient's baseline ECG values as part of routine safety monitoring. All clinically relevant abnormalities will be reported as AEs. ECG printouts will be maintained with the study records.

6.11.6 Concomitant Medications

Information about the usage of concomitant medications will be recorded at each visit from screening through the end of the follow-up period.

6.12 Exploratory Assessments

6.12.1 Immunologic Assessments

6.12.1.1 Genetic Biomarker Testing

A blood sample will be collected at baseline (Day 1) for future exploratory polymorphism analysis, ie, to explore the relationship of host genotype (for Il28A, IL28B, IL29, IFNAR2, IL10RB genes) and response to Lambda (New Zealand and US only).

6.12.1.2 Immunogenicity Testing

A blood sample will be collected for serum immunogenicity testing at baseline (Day 1), at the Week 1, 2, 4, 12, 24, 36, and 48 visits, and at the Week 60 and 72 visits in the follow-up period. This test will quantitate formation of Lambda antibodies over time.

6.12.1.3 Host Immune Response Biomarker Testing

Blood samples will be collected at baseline (Day 1), at the Week 4, 12, 24, and 48 visits, and at the final follow-up visit at Week 72 for biomarker analysis. These tests will explore the

effect of Lambda on host immune responses to HDV (cell surface markers, cytokines, and chemokines) over time (New Zealand and US only).

6.12.1.4 Future Exploratory Assessments

Blood samples will be collected for peripheral blood mononuclear cells (PBMCs) at baseline (Day 1) and at the Week 12, 24, and 48 visits and at the Week 72 follow-up visit for future analysis (New Zealand and US only).

6.13 Viral Resistance Analysis

If a patient experiences virologic failure, a blood sample will be collected for genotypic analysis of HDV.

Virologic failure is defined as any of the following:

- Serum HDV RNA increases at least 1.0 log above the nadir value on 2 consecutive visits in patients who are on Lambda treatment
- Serum HDV RNA detectable by qPCR in patients who had undetectable HDV RNA during therapy (breakthrough) or during the follow-up period (relapse).
- Serum HDV RNA less than 1 log reduced from the baseline value to the EOT value

6.14 Early Termination

Patients who discontinue from the study in the treatment period will be asked to return for an ET visit (Section 7.16) within 5 days of stopping study drug, and will continue in the follow-up period with 6 monthly visits. Patients who discontinue from the study in the follow-up period will be encouraged to complete the 6 follow-up visits if possible.

If a patient withdraws, all efforts should be made to complete and report the observations, particularly the follow-up examinations, as thoroughly as possible. The investigator should contact the patient either by telephone or through a personal visit, or a responsible relative should be contacted to determine as completely as possible the reason for the withdrawal. If the reason for removal of a patient from the study is an AE or an abnormal laboratory result, the principal scientific event or test will be recorded on the appropriate eCRF. If the patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the AE outcome.

7 STUDY ACTIVITIES

The study comprises 3 periods: the screening period, treatment period, and follow-up period. Patients will return to the clinic for enrollment, randomization, and dosing on Day 1 (baseline), and again at Week 1, Week 4, and then every 4 weeks until the final end-of-treatment (EOT) visit at Week 48. After patients complete (or discontinue) treatment, they will be encouraged to return for monthly follow-up visits for 6 months.

Visit windows are ±5 days.

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

7.1 Screening Assessments (Day -27 to 0)

At the start of the screening period, the site staff will register the patient and obtain a patient identification number (PID) using the EDC system and IWRS.

Screening evaluations can occur at ≥1 visit within 4 weeks before Day 1, when the patient will be enrolled, randomized, and started on study drug. Patients may be rescreened a single time (for a total of 2 screens), 2 weeks after the initial screening, if it can be reasonably expected that study criteria will be met. However, beyond this, patients should be re-evaluated only after consultation with the study team.

One of the screening assessments, Fibroscan, is conducted when the patient is in a fasted state (no solid food for 3 hours).

Following screening, the IWRS will be used to enroll and randomize a patient who meets all of the eligibility criteria. The EDC system will be used to register patients who do not meet the eligibility criteria as screen failures.

The screening assessments are as follows:

- Obtain informed consent
- Review inclusion/exclusion criteria
- Obtain medical history
- Obtain demographics and baseline characteristics
- Review prior and concomitant medications
- Conduct retinal examination for patients without documentation of retinal exam ≤ 1 year before screening. Must be performed by a licensed ocular specialist if patient has diabetes, hypertension, or other risk factors for retinal disease; otherwise, can be performed by study investigator or licensed ocular specialist.
- Conduct Fibroscan after 3-hour fast
- Conduct a complete physical examination
- Measure vital signs
- Obtain height and body weight; calculate BMI

- Perform 12-lead ECGs
- Collect blood samples for viral loads (HDV RNA, HBV DNA), serology tests (HDV, HCV, HIV, HBV including qHBsAg, HBsAb, HBeAg, and HBeAb), clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel), alpha-fetoprotein, drug test, alcohol test, serum pregnancy test (for female patients of childbearing potential)
- Collect urine samples for clinical laboratory tests (urinalysis)
- Abdominal imaging (ultrasound, MRI, or CT) if patient does not have prior documentation ≤6 months before screening.

7.2 Baseline Assessments (Day 1)

- Review inclusion/exclusion criteria
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Perform 12-lead ECGs
- Collect blood samples for HDV genotype, viral loads (HDV RNA, HBV DNA), qHBsAg, HBsAb, HBeAg, HBeAb, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel), immunogenicity testing; for New Zealand and US sites the following should also be collected: immune biomarker testing, PBMCs, and polymorphism analysis
- Collect urine samples for clinical laboratory tests (urinalysis), pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Enroll eligible patients and randomize to dose group
- Administer first dose of study drug
- Dispense sufficient study drug to last until the next visit
- Dispense anti-HBV NUC medication (for patients not continuing the same NUC therapy from before the study)
- Distribute patient diary

7.3 Week 1 Assessments (Day 7 ±5)

- Collect and review patient diary, assess compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight

- Collect blood samples for viral load (HDV RNA), clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel), immunogenicity testing
- Record any AEs
- Record concomitant medications
- Dispense sufficient study drug to last until the next visit
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.4 Week 2 Assessments (Day 14 ±5)

- Collect and review patient diary, assess compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral load (HDV RNA), clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel), immunogenicity testing
- Record any AEs
- Record concomitant medications
- Dispense sufficient study drug to last until the next visit
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.5 Week 4 Assessments (Day 28 ±5)

- Collect and review patient diary, assess compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Perform 12-lead ECGs
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel), immunogenicity testing; for New Zealand and US sites the following should also be collected: immune biomarker testing
- Collect urine sample for pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications

- Dispense sufficient study drug to last until the next visit
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.6 Week 8 Assessments (Day 56 ±5)

- Collect and review patient diary, assess compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel)
- Collect urine samples for clinical laboratory tests (urinalysis) and pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Dispense sufficient study drug to last until the next visit
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.7 Week 12 Assessments (Day 84 ±5)

- Collect and review patient diary, assess compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel), immunogenicity testing; for New Zealand and US sites the following should also be collected: immune biomarker testing and PBMCs
- Collect urine sample for pregnancy test (for female patients of childbearing potential)
- Perform 12-lead ECGs
- Record any AEs
- Record concomitant medications
- Dispense sufficient study drug to last until the next visit
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.8 Week 16 Assessments (Day 112 ±5)

- Collect and review patient diary, assess compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel)
- Collect urine samples for clinical laboratory tests (urinalysis) and pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Dispense sufficient study drug to last until the next visit
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.9 Week 20 Assessments (Day 140 ±5)

- Collect and review patient diary, assess compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel)
- Collect urine sample for pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Dispense sufficient study drug to last until the next visit
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.10 Week 24 Assessments (Day 168 ±5)

- Collect and review patient diary, assess compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight

- Collect blood samples for viral load (HDV RNA, HBV DNA), qHBsAg, HBeAg, HBeAb, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel), immunogenicity testing; for New Zealand and US sites the following should also be collected: immune biomarker testing and PBMCs
- Collect urine samples for clinical laboratory tests (urinalysis) and pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Dispense sufficient study drug to last until the next visit
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.11 Week 28 Assessments (Day 196 ±5)

- Collect and review patient diary, assess compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel)
- Collect urine sample for pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Dispense sufficient study drug to last until the next visit
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.12 Week 32 Assessments (Day 224 ±5)

- Collect and review patient diary, assess compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel)
- Collect urine samples for clinical laboratory tests (urinalysis) and pregnancy test (for female patients of childbearing potential)
- Record any AEs

- Record concomitant medications
- Dispense sufficient study drug to last until the next visit
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.13 Week 36 Assessments (Day 252 ±5)

- Collect and review patient diary, assess compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel), immunogenicity testing
- Collect urine sample for pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Dispense sufficient study drug to last until the next visit
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.14 Week 40 Assessments (Day 280 ±5)

- Collect and review patient diary, assess compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel)
- Collect urine samples for clinical laboratory tests (urinalysis) and pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Dispense sufficient study drug to last until the next visit
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.15 Week 44 Assessments (Day 308 ±5)

- Collect and review patient diary, assess compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel)
- Collect urine sample for pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Dispense sufficient study drug to last until the next visit
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.16 Week 48 Assessments (EOT; Day 336 ±5) or Early Termination

- Collect and review patient diary, assess compliance, record patient-reported outcomes
- Conduct Fibroscan after 3-hour fast
- Conduct retinal examination (unless patient discontinues early from the study before Week 12); this exam can be performed by the study investigator
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Perform 12-lead ECGs
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, HBsAb, HBeAg, HBeAb, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel), immunogenicity testing; for New Zealand and US sites the following should also be collected: immune biomarker testing and PBMCs
- Collect urine samples for clinical laboratory tests (urinalysis), pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.17 Follow-up Week 52 (FU1; Day 364 ±5)

- Collect and review patient diary, assess NUC compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel)
- Collect urine sample for pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Dispense anti-HBV NUC medication (if applicable)
- Distribute patient diary

7.18 Follow-up Week 56 (FU2; Day 392 ±5)

- Collect and review patient diary, assess NUC compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel)
- Collect urine sample for pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Dispense anti-HBV NUC medication
- Distribute patient diary

7.19 Follow-up Week 60 (FU3; Day 420 ±5)

- Collect and review patient diary, assess NUC compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, HBeAg, HBeAb, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel), immunogenicity testing

- Collect urine samples for clinical laboratory tests (urinalysis), pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Dispense anti-HBV NUC medication
- Distribute patient diary

7.20 Follow-up Week 64 (FU4; Day 448 ±5)

- Collect and review patient diary, assess NUC compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel)
- Collect urine sample for pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Dispense anti-HBV NUC medication
- Distribute patient diary

7.21 Follow-up Week 68 (FU5; Day 476 ±5)

- Collect and review patient diary, assess NUC compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel)
- Collect urine sample for pregnancy test (for female patients of childbearing potential)
- Record any AEs
- Record concomitant medications
- Dispense anti-HBV NUC medication
- Distribute patient diary

7.22 Follow-up Week 72 (FU6; Day 504 ±5) (EOS)

- Collect and review patient diary, assess NUC compliance, record patient-reported outcomes
- Conduct a brief, directed physical examination
- Measure vital signs
- Measure body weight
- Collect blood samples for viral loads (HDV RNA, HBV DNA), qHBsAg, HBsAb, HBeAg, HBeAb, clinical laboratory tests (hematology, clinical chemistry, coagulation, thyroid panel), immunogenicity testing; for New Zealand and US sites the following should also be collected: immune biomarker testing and PBMCs
- Collect urine samples for clinical laboratory tests (urinalysis), pregnancy test (for female patients of childbearing potential)
- Conduct Fibroscan after 3-hour fast
- Record any AEs
- Record concomitant medications

7.23 Unscheduled Visits

Study visits not specified in the protocol may be scheduled at the discretion of the investigator.

8 STATISTICAL ANALYSIS

The objectives of this study are to evaluate the safety, tolerability, and PD/efficacy of Lambda treatment (120 or 180 μg/week SC) over the 48-week treatment period and 24-week follow-up period in patients with CHD infection.

8.1 Randomization and Treatment Assignment

In this randomized, open-label, uncontrolled study, 40 patients will be randomized to receive either Lambda 120 or 180 μg/week in a 1:1 ratio. A block randomization will be used.

8.2 Determination of 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 μg/week. The sample size was not formally calculated using power analysis.

8.3 Analysis Populations

The modified intention-to-treat (MITT) population will consist of all patients who receive at least 80% of the total study drug dose throughout the entire 48-week treatment period and for whom HDV viral load data are available for the Day 1 (baseline) and end-of-treatment (Week 48) study visits. Patients who receive less than 80% of the dose on any given treatment day (eg, dose missed, interrupted, or reduced to DR1 or DR2) would be excluded. This population will be used for analysis of the primary PD/efficacy endpoints.

The intention-to-treat (ITT) population will consist of all patients who receive at least 1 postbaseline HDV RNA measurement. This population will be used for analysis of the secondary PD/efficacy endpoints.

The safety population will consist of all patients who receive at least 1 dose of study drug. This population will be used for analysis of all safety endpoints.

In each study population, patients will be analyzed according to the dose group to which they are randomized.

8.4 Hypothesis Testing

No formal hypothesis testing will be performed in this study.

8.5 Study Endpoints

The primary PD/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 (end of follow-up [EOFU])

Additional PD/efficacy endpoints include:

- Proportion of patients with sustained viral response: HDV RNA below the lower limit of quantification (LLOQ) 12 weeks after EOT (SVR-12)
- Proportion of patients with sustained viral response: HDV RNA below the LLOQ 24 weeks after EOT (SVR-24)
- Change from baseline in HDV viral load
- Change from baseline in HBV viral load
- Change from baseline in HBsAg levels
- Clearance of HBsAg
- Change from baseline in Fibroscan results

The safety endpoints are as follows:

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

The exploratory endpoints will be provided in the statistical analysis report (SAP).

8.6 Analysis Plan

8.6.1 Demographic and Baseline Data

Descriptive statistics will be used to summarize demographic and baseline patient characteristics. Continuous-scale variables (eg, age) will be summarized with mean, median, SD, quartiles, and minimum and maximum values. Categorical variables (eg, sex) will be summarized using patient counts and percentages.

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

8.6.2 Pharmacodynamics/Efficacy

8.6.2.1 Viral Loads and Serology

Viral load and serology concentration data will be presented by dose group and time point in summary tabulations and by-patient listings. These data will also be presented graphically. Mean and median levels and change from baseline of the viral load will be calculated at each time point. For analysis of HDV change from baseline, baseline will be defined as the geometric mean of the HDV RNA titer obtained at the screening and pretreatment baseline (Day 1) visits. The numbers and percentages of patients with 1 log reduction from baseline in viral load (HDV, HBV) will be summarized at each time point. The numbers and percentages of patients with reductions in viral load below the LLOQ and below the LOD will be summarized by dose group and time point. HBsAg clearance will be summarized as number and percentage of patients who are HBsAg reactive/nonreactive at each time point.

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

8.6.2.2 Fibroscan

Fibroscan results in kPa will be summarized by dose group at each time point using summary statistics for absolute and change-from-baseline values and listed by patient.

8.6.3 Safety Analyses

No inferential statistics are planned for safety data.

8.6.3.1 Adverse Events

AEs will be mapped to system organ classes and preferred terms in MedDRA. Treatment-emergent AEs (TEAEs) are defined as those that start or worsen after the start of study treatment and up to 28 days after the last dose of study treatment; any AEs that occur after that time will be considered posttreatment AEs.

Summaries by dose group, system organ class, and preferred term will be provided for TEAEs (overall, by event severity and by the event’s relationship to Lambda treatment), treatment-emergent SAEs (overall and by the event's relationship to Lambda treatment), AEs that lead to early discontinuation, and AEs that lead to Lambda dose reduction.

At each level of summation, patients will be counted only once for a given event, under the greatest severity and strongest study-drug relationship (as reported by the investigator). Events with missing severity will be classified as Grade 3; events with missing attribution will be classified as related to study drug.

AEs will be listed by patient, along with information regarding onset, duration, severity, and relationship to study drug. SAEs and AEs that lead to early discontinuation will also be listed by patient.

Posttreatment AEs will also be summarized and listed by patient.

Patient-reported Outcomes

Patient-reported outcomes from the patient diaries (flu-like symptoms and injection-site reactions) will be summarized by event for each dose group and listed by patient.

8.6.3.2 Clinical Laboratory Test Results

Clinical laboratory data will be summarized using descriptive statistics (mean, SD, median, and range) for actual and change-from-baseline values at each time point. Shift tables will be presented for baseline and highest postbaseline clinical laboratory values by Common Terminology Criteria for Adverse Events (CTCAE) grade for each dose group. All clinical laboratory values collected during the study will be listed, with values outside the normal ranges flagged for clinical evaluation. Grade 3 and 4 laboratory results will be summarized and listed by patient. In addition, ALT, AST, total bilirubin, and AP values will be summarized by CTCAE grade for each dose group.

8.6.3.3 Vital Signs

Vital sign data (actual values and change-from-baseline values) will be summarized by dose group at each time point and listed by patient. Body weight will be summarized by dose group at each time point and listed by patient.

8.6.3.4 Physical Examination Findings

Full physical examination findings will be summarized by body system and listed by patient at screening. The subsequent limited examinations will not be summarized, but any clinically significant finding will be reported as an AE.

8.6.3.5 ECG Results

ECG interval results will be calculated by averaging results from the 3 recordings at each time point. QT interval data will be corrected using Fridericia correction (ICH 2005). ECG interval data (actual values and change-from-baseline values) will be summarized by dose group for each time point using descriptive statistics and listed by patient. Clinical interpretations of ECG results will also be listed by patient.

8.6.3.6 Concomitant Medications

A medication that was started or increased in dose after the first dose of study drug until 28 days after the final dose of study drug will be considered a concomitant medication. Concomitant medications will be mapped to drug classes and generic terms in the World Health Organization Drug Dictionary Enhanced (WHO-DD Enhanced), then summarized by dose group for each time point. All medications will be listed by patient.

Medications that are used within 28 days before screening will be considered prior medications; these will be summarized separately using WHO-DD Enhanced and listed by patient.

8.6.4 Exploratory Analyses

The exploratory analyses will be described in the SAP.

8.6.4.1 Immunologic Analyses

Polymorphism Analysis

IL-28B polymorphisms have been associated with response to therapy in patients infected with HCV and possibly in patients with HBV as well. Host DNA samples (peripheral blood cells) will be collected from consenting patients to assess IL-28B polymorphisms and their correlation with HDV RNA responses (New Zealand and US only).

Immunogenicity Analysis

Serum samples will be stored for later analysis. The immunogenicity testing strategy will use a tiered approach that is designed to screen for binding antibodies, confirm antibody specificity, determine antibody titer, and assess the neutralizing potential of antibodies to Lambda in patient serum samples.

Immune Biomarker Analysis

Serum samples from select sites will be stored for later analysis.

PBMC Analysis

PBMC samples from select sites will be stored for later analysis.

8.6.5 Viral Resistance Analysis

For resistance surveillance, genotypic analysis and sequencing of HDV from patients with virologic failure will be conducted. Virologic failure is defined in Section 6.13.

9 SAFETY EVENTS DOCUMENTATION AND REPORTING

9.1 Investigator's Responsibilities

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

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

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

9.2 Monitoring Safety Data During Study

Safety results collected during the study (eg, AEs, laboratory test results, physical examination findings, ECGs) will be monitored on an ongoing basis by the medical monitor and the investigator.

9.3 Definitions of Types of Adverse Events

9.3.1 Adverse Events

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

9.3.2 Suspected Adverse Reactions

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

9.3.3 Life-Threatening Adverse Events

An AE or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of either the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

9.3.4 Serious Adverse Events

An AE or suspected adverse reaction is considered ‘‘serious’’ if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE (see Section 9.3.3)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.3.4.1 Potential Treatment Related Liver Event

A potential treatment related liver event as defined below that would result in the labeling of this as a “serious medication related liver event” would have to satisfy all 5 of the conditions below:

- ALT > 10 × ULN
- ALT > 5 × baseline or nadir, whichever is lower
- Total bilirubin > 5 × ULN
- INR > 1.5 × ULN confirmed with local confirmation
- No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to, acute viral hepatitis, obstructive jaundice, preexisting hepatic disease excluding HBV, or the administration of other drug(s), or herbal medications and substances known to be hepatotoxic.

9.3.4.2 Clinical Jaundice

Any occurrence of clinical jaundice must be reported as an SAE in this study.

9.3.5 Unexpected Adverse Events

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

- It is not listed in the IB or is not listed at the specificity or severity that has been observed.
- If an IB is not required or available, it is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

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

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

9.4 Adverse Event Classification

9.4.1 Severity Grades of Adverse Events and Serious Adverse Events

The seriousness of an AE should not be confused with its intensity (severity). To describe the maximum intensity of the AE on the AE eCRF, the investigator will use the National Cancer Institute (NCI) CTCAE, Version 4.03 (CTCAE 2010). For events not listed in the CTCAE, the definitions from the CTCAE provided in Table 8 should be used to evaluate the grade of severity for the AE.

Table 8: Adverse Event Grades Based on the Common Terminology Criteria for Adverse Events

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

Source: NCI CTCAE, Version 4.03 (CTCAE 2010)

9.4.2 Relationship of Adverse Event to Investigational Products

The investigator’s assessment of causality must be provided for all AEs (serious and nonserious). An investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. To describe the relationship of the AE to study drug on the AE eCRF, the investigator will use the terms and definitions provided in Table 9. For a particular AE, the investigator will assess the relationship to study drug (Lambda).

Table 9: Categories for Assessing Relationship of Adverse Events to Investigational Products

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

9.5 Documentation of Adverse Events

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

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

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

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

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

For SAEs, an SAE Form must also be completed with as much information as possible and submitted in the time frame described in Section 9.6.1. When new significant information is obtained as well as when the outcome of an event is known, the investigator should record the information on a new SAE Form. If the patient was hospitalized, then a copy of the discharge summary and any other relevant hospital records (eg, admission report, laboratory test results) must be included as part of the patient medical file.

All AEs considered to be related (definitely or probably related, see Section 9.4.2) to study drug and all SAEs will be followed until resolved or until a stable status has been achieved.

9.5.1 Study Drug Action Taken

The action taken for each study drug should be classified according to the categories shown in Table 10.

Table 10: Classifications for Study Drug Action Taken with Regard to an Adverse Event

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

9.5.2 Outcome of Adverse Event

The outcome should be classified according to the categories shown in Table 11. All AEs considered to be related (definitely or probably related, see Section 9.4.2) to study drug and all SAEs will be followed until resolved or until a stable status has been achieved.

Table 11: Classifications for Outcome of an Adverse Event

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

9.6 Reporting Serious Adverse Events

9.6.1 Reporting to Sponsor

The SAE form must be completed within 1 day of the investigator becoming aware of the SAE. The completed SAE form should be emailed or faxed to Novella Clinical within 1 day (pvgsafety@novellaclinical.com) as follows:

Country Name	Telephone Number	Fax Number
United States	1.866.758.2798	1.866.761.1274
Israel	1.809.42.4626	1.919.313.1412
New Zealand	0800.447.176	0800.446.957
Pakistan	1.919.313.7111	1.919.313.1412

In addition, all SAEs that occur up to and including 1 month (28 days) after administration of the last dose of study drug must be reported to the sponsor within 1 working day of the investigator becoming aware of the SAE. Any SAEs reported more than 1 month (28 days) after the last dose of study drug will be considered posttreatment SAEs.

Investigators must report to the sponsor any SAE, whether or not considered drug related, including those listed in the protocol or the IB. The report must include an assessment of causality (see Section 9.4.2).

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

9.6.2 Reporting to Regulatory Agencies and Independent Ethics Committee

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

It is the responsibility of the investigator to promptly notify the IRB/IEC of all SUSARs involving risk to patients.

9.6.3 Emergency Sponsor Contact

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

Hervé Mommeja Marin, MD
Consultant Medical Monitor
Eiger BioPharmaceuticals, Inc.
350 Cambridge Avenue, Suite 350
Palo Alto, CA 94306 USA
Telephone: +1 919.886.1398
Alternate Phone: + 1 919-597-9381
Email address: hmommeja-marin@spriclinicaltrials.com

9.7 Pregnancy

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

9.8 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE. If a higher dose is taken, it is recommended that supportive measures be given until the drug clears.

10 DATA QUALITY CONTROL AND ASSURANCE

10.1 Overview

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

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

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

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

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

10.2 Study Monitoring

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

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

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

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

Monitoring visits will be conducted according to the US Code of Federal Regulations (CFR) Title 21, Parts 50, 56, and 312; EU Directive 2005/28/EC; and the ICH GCP guideline. The monitor will submit written reports to the sponsor following each contact with the investigator or a designee, regardless of whether it is by phone or in person.

10.3 Data Management

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

10.4 Quality Assurance Audit

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

10.5 Data Handling and Recordkeeping

10.5.1 Case Report Form Completion

eCRFs will be completed for each patient enrolled in the study.

Only data for the procedures and assessments specified in this protocol should be submitted to Eiger on a eCRF. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the patient's medical record and should not be provided to Eiger, unless specifically requested from the sponsor.

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

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

Data will be entered into the eCRF by site personnel using a secure, validated web-based EDC application. Any data not entered by the site will be entered into an eCRF by trained data entry staff using a secure, validated, web-based EDC application. The sponsor will have access to all data on entry in the EDC application.

10.5.2 Data Handling

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

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

10.5.3 Study Files and Retention of Study Records

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

Biological samples at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years. Samples may be retained for future determination of active metabolite concentrations, HDV and HBV analyses, and host DNA (at select sites only) analyses of polymorphisms that may impact drug response.

10.6 Drug Accountability

It is the responsibility of the investigator to maintain drug accountability at the study site and ensure that a current record of investigational product disposition is maintained. It is the responsibility of the investigator to ensure that the investigational product is used only in accordance with the approved protocol. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from Eiger BioPharmaceuticals and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the drug.

At the end of the study, after final drug inventory reconciliation confirmed by the monitor, the study site will dispose of and/or destroy all unused investigational product supplies, including empty containers, according to standard procedures.

11 ETHICAL AND LEGAL CONSIDERATIONS

11.1 Ethical Conduct and Good Clinical Practice

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

Since this is a "covered" clinical trial, the investigator will ensure adherence to 21 CFR, Part 54 "Financial Disclosure by Clinical Investigators". A "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all subinvestigators must provide documentation of their financial interest or arrangements with Eiger BioPharmaceuticals, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any subinvestigator. The investigator and subinvestigator agree to notify Eiger BioPharmaceuticals of any change reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date that the last patient has completed the protocol-defined activities.

11.2 Institutional Review Board/Independent Ethics Committee

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

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

Other investigator responsibilities relative to the IRB/IEC requirements include the following:

- Submit to the IRB/IEC and to the sponsor or its designee for review any advertisements that will be used to recruit patients or any other relevant materials intended or directed to patients
- During the conduct of the study, submit timely and accurate progress reports to the IRB/IEC, if required, and request re-review of the study at least once a year
- Report, in writing, to the IRB/IEC any SAEs that occur during the study or SAEs reported in other studies using Lambda, per local IRB/IEC regulations
- Inform the IRB/IEC of any changes in the protocol and obtain documented IRB/IEC approval of the changes
- Provide the IRB/IEC with any other information it requests before or during the conduct of the study
- Maintain a file of study-related information, including all correspondence with the IRB/IEC

11.3 Patient and Data Confidentiality

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

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

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

11.4 Informed Consent

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

The ICF will be used to explain the risks and benefits of study participation in simple terms before the patient will be entered into the study. The ICF will contain a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time.

The ICF must include information about the possible retention of biological samples at the conclusion of this study. The samples will retain only the patient's randomization number so that they cannot be linked back to an individual patient. Because these tests are investigational and not yet validated, the patients will not receive their results. The samples will be kept for a minimum of 10 years or until the testing can be completed, whichever is longer.

New Zealand only: samples will be obtained for future determination of active metabolite concentrations and host DNA analyses of polymorphisms that may impact the course of the disease and/or drug response. Genetic polymorphisms have been demonstrated to alter the development and clinical course of a number of different diseases. The purpose of assessing genetic polymorphisms in this study is to understand their potential role in the pathogenesis of HDV and in clinical outcomes. Some countries, municipalities, institutions, or local IRBs/IECs do not allow the study of genetic polymorphisms or RNA testing. Therefore, these assessments will only be conducted at institutions in which such research is in accordance with local law and institutional regulations. Patient participation in these assessments is voluntary, and declining participation will in no way influence eligibility for this study. This information will be outlined either in the ICF or in some cases in a separate genetic consent, depending on the local IRB requirements.

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

The ICF must be written in a language understandable to the patient or to his or her representative. The investigator is responsible for keeping the original signed and dated ICF in a secure place. A signed and dated copy of the ICF must be given to the person signing the

document. This document should not be displayed or made accessible to any third party except for Eiger BioPharmaceuticals or regulatory agency representative.

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

11.5 Protocol Amendments

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

11.6 Delegation of Responsibilities of the Principal Investigator

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

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

11.7 Principal Investigator

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

11.8 Compensation, Insurance, and Indemnity

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

11.9 Publication Policy

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

11.10 Direct Access to Source Data

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

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

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13 APPENDICES

APPENDIX 1 SCHEDULE OF ASSESSMENTS AND PROCEDURES

		Treatment Period															Follow-Up Period					
Visit	**SCR**	**BL**	**W1**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48 (EOT/ ET[a])**	**FU1**	**FU2**	**FU3**	**FU4**	**FU5**	**FU6/ EOS**
Week			**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**
Day	**–27 to 0**	**1**	**7±5**	**14±5**	**28±5**	**56±5**	**84±5**	**112±5**	**140±5**	**168±5**	**196±5**	**224±5**	**252±5**	**280±5**	**308±5**	**336±5**	**364±5**	**392±5**	**420±5**	**448±5**	**476±5**	**504±5**
Event/Procedure																						
Informed consent	X																					
Inclusion/exclusion criteria	X	X																				
Height	X																					
Demographics, baseline characteristics	X																					
Medical history	X																					
Abdominal imaging[b]	X																					
Retinal exam[c]	X															X[d]						
Blood sample: HDV genotype		X																				
Blood sample: HBV genotype	X[e]																					
Blood sample: alpha fetoprotein	X																					
Blood samples: Serology tests HDV, HCV, HIV	X																					
qHBsAg	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBsAb	X	X														X						X
HBeAg and HBeAb	X	X								X						X			X			X
Blood samples: Exploratory																						
Polymorphism analysis (New Zealand and US only)		X																				
Immunogenicity testing		X	X	X	X		X			X			X			X			X			X
Immune biomarker testing (New Zealand and US only)		X			X		X			X						X						X
PBMC collection (New Zealand and US only)		X					X			X						X						X
12-lead ECG[f]	X	X			X		X									X						
Drug/alcohol lab tests	X																					
Pregnancy test[g]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy measures:																						
Blood sample: HDV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

		Treatment Period															Follow-Up Period					
Visit	**SCR**	**BL**	**W1**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48 (EOT/ ET[a])**	**FU1**	**FU2**	**FU3**	**FU4**	**FU5**	**FU6/ EOS**
Week			**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**
Day	**–27 to 0**	**1**	**7±5**	**14±5**	**28±5**	**56±5**	**84±5**	**112±5**	**140±5**	**168±5**	**196±5**	**224±5**	**252±5**	**280±5**	**308±5**	**336±5**	**364±5**	**392±5**	**420±5**	**448±5**	**476±5**	**504±5**
(qPCR)																						
Blood sample: HBV DNA (COBAS)	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fibroscan[h]	X															X						X
Safety measures:																						
Physical examination[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[k]	X[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample: clinical laboratory tests[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample: urinalysis	X	X				X		X		X		X		X		X			X			X
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral resistance analysis																						
Blood sample: viral resistance[n]																						
Study conduct:																						
Enrollment, randomization		X																				
Dispense/administer study drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Dispense anti-HBV NUC[o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Distribute/review patient diary[p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BL, baseline; EOS, end of study; EOT, end of treatment; ET, early termination; SCR, screening

a All patients who discontinue the study early are asked to return within 5 days for an ET visit. All assessments done at the Week 48 visit will be done at the ET visit. Patients will be asked to return for 6 follow-up visits after the ET visit.

b Abdominal imaging (ultrasound, MRI, or CT) performed only if patient does not have abdominal imaging documentation ≤6 months before screening.

c In patients without documented record of retinal exam within 1 year

d Unless patient discontinued study before Week 12

e HBV genotype test done only if HBV DNA is detectable at screening.

f 12-lead ECGs performed after patient has rested in a supine position for ≥5 minutes. Triplicate ECGs obtained, each 2-3 minutes apart, and each interpretable (ie, without artifacts).

g In female patients of childbearing potential: Human chorionic gonadotropin (hCG) pregnancy tests at screening (serum); all subsequent tests are in urine. If urine pregnancy test result is positive, confirm immediately with serum pregnancy test.

h Patient must fast for 3 hours before Fibroscan.

i Complete physical exam at screening including all body systems pertinent to the patient, including CTP scoring and encephalopathy assessment. Brief, directed physical exam at all other visits, including HEENT, heart, lungs, abdomen, and lower extremity.

j Vital signs include heart rate, BP, respiratory rate, and body temperature. Measure BP and heart rate after the patient has been sitting for 5 minutes.

k Measure body weight without shoes or heavy outerwear.

l BMI will be calculated at screening.

m Safety clinical laboratory tests include hematology, coagulation, thyroid panel, and clinical chemistry
n Blood sample collected only if a patient experiences virologic failure or virologic rebound (see Section 6.13 for more information)
o The appropriate NUC will be dispensed to all patients who are not already on the appropriate NUC at baseline.
p Patient will document dosing of both study drug and NUC in the diary; compliance will be assessed for both drugs through EOT and also for NUCs in the follow-up period.

APPENDIX 2 HEPATIC SCREENING ASSESSMENTS

The Child-Turcotte-Pugh (CTP) Score

The score employs five clinical measures of liver disease. Each measure is scored 1–3, with 3 indicating most severe derangement. Patients with a total CTP score of 7 or higher are *not* eligible to participate in this study.

Measure	1 point	2 points	3 points	Units
Bilirubin (total)	<34 (<2)	34-50 (2–3)	>50 (>3)	µmol/L (mg/dL)
Serum albumin	>35	28–35	<28	mg/L
INR	<1.7	1.72–20	>2.20	No unit
Ascites	None	Suppressed with medication	Refractory	No unit
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory)	No unit

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

Assessment for Hepatic Encephalopathy

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

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

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

APPENDIX 3 SAMPLE PATIENT DOSING DIARY AND PATIENT-REPORTED OUTCOMES DIARY

Please complete this diary every time you take a dose of Lambda or NUC.
Lambda study medication (injection) should be taken once a week on the same evening.
NUC medication should be taken according to its prescribing information.

Day	Week	Date of Dose (YYYY/MM/DD)	Time of dosing (24-hour clock) (HH:MM)		Study Medication	Check if Taken
1	1	|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
			Evening	|__|__|:|__|__|	LAMBDA	☐
2		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
3		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
4		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
5		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
6		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
7		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐

Day	Week	Date of Dose (YYYY/MM/DD)	Time of dosing (24-hour clock) (HH:MM)		Study Medication	Check if Taken
8	2	|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
			Evening	|__|__|:|__|__|	LAMBDA	☐
9		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
10		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
11		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
12		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
13		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
14		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐

Day	Week	Date of Dose (YYYY/MM/DD)	Time of dosing (24-hour clock) (HH:MM)		Study Medication	Check if Taken
15	3	|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
			Evening	|__|__|:|__|__|	LAMBDA	☐
16		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
17		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
18		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
19		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
20		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
21		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐

Day	Week	Date of Dose (YYYY/MM/DD)	Time of dosing (24-hour clock) (HH:MM)		Study Medication	Check if Taken
22	4	|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
			Evening	|__|__|:|__|__|	LAMBDA	☐
23		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
24		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
25		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
26		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
27		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐
28		|__|__|__|__|/|__|__|/|__|__|	Morning	|__|__|:|__|__|	NUC	☐

Please complete this diary every morning to record your symptoms, if you happen to have any of the symptoms listed below. You should also record any reactions you may have at the site of the last injection.

PATIENT REPORTED OUTCOMES

Have you experienced headache, chills, fever, joint pains, or muscle pains today? ○0 No ○1 Yes

If **Yes**, select each Flu Like Symptom:

☐1 Headache
☐1 Chills
☐1 Fever
☐1 Joint Pain
☐1 Muscle Pain

Each symptom caused:
○0 No effect on daily activities
○1 Some effect on daily activities
○2 Significant effect with daily activities

Have you experienced pain, itching, tenderness, redness, or swelling at an injection site today?

If Yes, select each Injection Reaction Symptom: ○0 No ○1 Yes

☐1 Pain
☐1 Itching
☐1 Tenderness
☐1 Redness
☐1 Swelling

Each symptom caused:
○0 No effect on daily activities
○1 Some effect on daily activities
○2 Significant effect with daily activities