CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1 Open-Label, Parallel-Design, Multiple-Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Bulevirtide in Participants with Normal and Impaired Renal Function
Plain Language Short Title:	A Multiple-Dose Study of Bulevirtide in Participants with Normal and Impaired Renal Function
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	125159
EU CT Number:	2022-502054-13-00
ClinicalTrials.gov Identifier:	Not applicable
Indication:	Chronic Hepatitis Delta Infection
Protocol ID:	GS-US-589-6160
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List
Protocol Version/Date:	Original: 22 November 2022 Amendment 1: 02 February 2023
Amendment History:	A high-level summary of the history of amendment is provided in Appendix 11.7
Country-specific Requirements:	Not applicable

This study will be conducted under United States Food and Drug Administration investigational new drug application regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, the United Kingdom, and Switzerland are not included under the investigational new drug application and are not considered to be investigational new drug application sites.

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

A_e	amount of unchanged drug excreted in urine calculated either over a specific interval (A_e (interval)) or cumulatively over all collection intervals, calculated as (concentration of unchanged drug in urine) × (volume of urine collected)
ADA	antidrug antibodies
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BA	bile acids
BMI	body mass index
BLA	biologic license application
BLV	bulevirtide
CCDS	company core data sheet
CDER	Center for Drug Evaluation and Research
CHB	chronic hepatitis B infection
CHD	chronic hepatitis D infection
CHO	Chinese hamster ovary
CI	confidence interval
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent clearance
CL_{cr}	creatinine clearance
CL_{ss}/F	apparent clearance at steady state
CL_r	renal clearance of unchanged drug in a specific interval (CL_r (interval)) or cumulatively over all collection intervals
C_{max}	maximum observed concentration of drug
$C_{max\ ss}$	maximum observed concentration of drug at steady state
COVID-19	Coronavirus disease 2019
CPK	creatine phosphokinase
CSR	clinical study report
C_{trough}	concentration at the end of the dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
CV%	percentage coefficient of variation
CYP	cytochrome
DDI	drug-drug interactions
DNA	deoxyribonucleic acid
ECG	electrocardiogram

eCRF	electronic case report form
EASL	European Association for the Study of the Liver
EDC	electronic data capture
EFD	embryofetal development
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ET	early termination
EU	European Union
FDA	US Food and Drug Administration
F_e	excreted fraction of administered drug
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
Gilead	Gilead Sciences, Inc.
GMP	Good Manufacturing Practices
PS	Patient Safety
GLSM	geometric least-squares mean
GMR	geometric mean ratio
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high density lipoprotein
HDV	hepatitis D virus
HEK293	human embryonic kidney 293 cell line
HIV	human immunodeficiency virus
IB	investigator's brochure
IBW	ideal body weight
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IRB	institutional review board
IUD	intrauterine device
LDL	low density lipoprotein
LLOQ	lower limit of quantitation
MDMA	3,4-methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute

NTCP	sodium-taurocholate cotransporting polypeptide
OATP	organic anion transporting polypeptide
PCR	polymerase chain reaction
PD	pharmacodynamic
PI	principal investigator
PK	pharmacokinetic
PopPK	population pharmacokinetic
PT	preferred term
QD	once-daily
QT (interval)	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
RI	renal impairment
RNA	ribonucleic acid
RSI	reference safety information
SAE	serious adverse event
SC	subcutaneous
SDV	source data verification
SOC	system organ class
SOP	standard operating procedure
SRT	safety review team
SSR	special situations reports
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time (observed time point) of C_{max}
$t_{1/2}$	terminal elimination half-life
ULN	upper limit of normal
US, USA	United States, United States of America
V/F	apparent volume of distribution
V_{ss}/F	apparent volume of distribution at steady state

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Study Title: A Phase 1 Open-Label, Parallel-Design, Multiple-Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Bulevirtide in Participants with Normal and Impaired Renal Function

Plain Language Short Title: A Multiple-Dose Study of Bulevirtide in Participants with Normal and Impaired Renal Function

Regulatory Agency Identifier Number(s):

IND Number: 125159
EU CT Number: 2022-502054-13-00
ClinicalTrials.gov Identifier: Not applicable

Study Sites Planned: Multiple sites globally

Objectives and Endpoints:

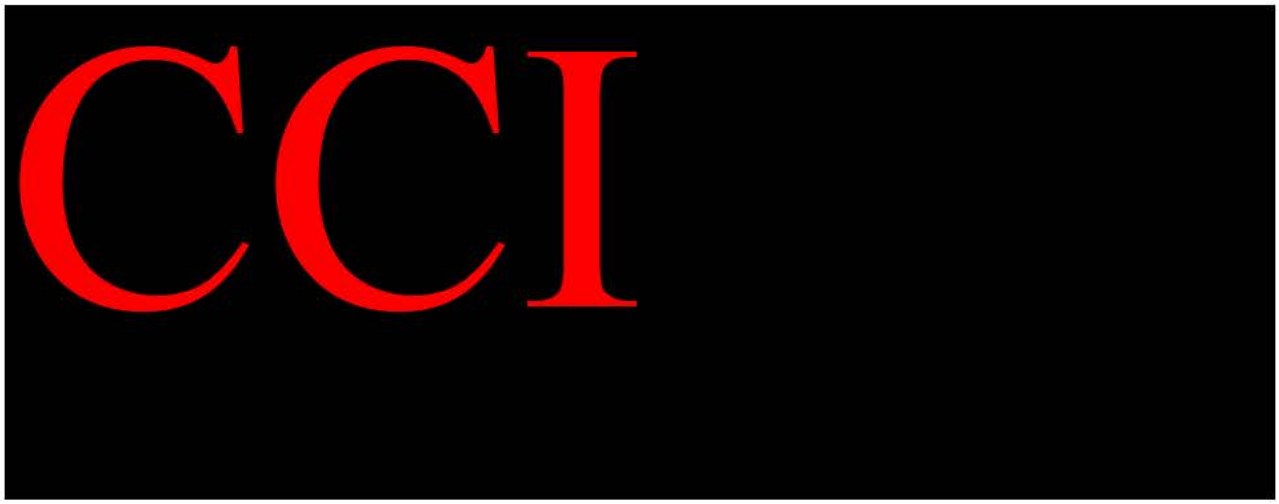
Primary Objective	Primary Endpoint(s)
• To evaluate the steady-state plasma pharmacokinetics (PK) of BLV in non-HDV/HBV-infected participants with renal impairment (RI) and in matched control participants with normal renal function	• BLV steady-state plasma PK parameters: AUC_{tau} and $C_{max\ ss}$
Secondary Objective(s)	**Secondary Endpoint(s)**
• To further characterize the plasma PK of BLV in participants with RI and in matched control participants with normal renal function	• Plasma PK parameters for BLV, as applicable: AUC_{0-24}, C_{max}, T_{max}, $t_{1/2}$, CL_{ss}/F, and V_{ss}/F
• To evaluate the pharmacodynamic (PD) effect of BLV on plasma bile acids (BA) in participants with RI to matched control participants with normal renal function	• Total bile acids concentrations in plasma and exposure parameters for total BA, as applicable: C_{trough}, C_{max}, AUC_{0-24}, T_{max}
• To evaluate the safety and tolerability of BLV following multiple-dose administration in participants with RI and matched control participants with normal renal function	• The incidences of AEs and laboratory abnormalities

ADA = antidrug antibodies; AE = adverse event; BA = bile acids; BLV = bulevirtide; HBV = hepatitis B virus; HDV = hepatitis D virus; PD = pharmacodynamic; PK = pharmacokinetic; RI = renal impairment

CCI

Study Design: Phase 1, open-label, multiple-dose, parallel-group study of bulevirtide (BLV) pharmacokinetic (PK), pharmacodynamic (PD), and safety in participants with renal impairment (RI) and matched control participants with normal renal function. An overview of the study design is described below and in Figure 1-a. The study will begin with Group A and following completion and evaluation of PK and safety data from all participants in Group A, CCI

- **Group A (BLV 2 mg severe RI):** A total of up to 20 participants (10 participants with severe RI and 10 matched control participants) will be enrolled to obtain at least 16 evaluable participants (8 participants with severe RI and 8 matched control participants)



Classification of renal function will be assessed using the estimated glomerular filtration rate (eGFR) based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (expressed for serum creatinine, sex, and age) {Inker 2021} at screening as follows:

- **Group A (BLV 2 mg severe RI):** Participants with severe RI (eGFR ≥15 to ≤ 29 mL/min/1.73 m²) and normal renal function (eGFR ≥ 90 mL/min/1.73 m²) at screening. Participants with severe RI requiring or anticipated to require dialysis within 90 days of study entry will not be eligible.

The matched control group will consist of participants with normal renal function matched for age, sex, and BMI with a participant in the RI group. Within each group, once a participant with RI is enrolled a matched control to that participant will be allowed to enroll. Dosing of matched participant with normal renal function may begin after the corresponding participant with RI in that group has completed the last PK assessment.

A matching control may serve as a matched control only once per study group. A participant with normal renal function may have their PK and BA data reused just once to serve as a match for an another group, if the BLV dose is the same and the matching criteria are met.

Study Population: Male and nonpregnant/nonlactating female participants who have no history of hepatitis D virus (HDV) or hepatitis B virus (HBV) infection. The participants will be classified based on renal function using the eGFR CKD-EPI equation with either severe, moderate, or mild RI, or normal renal function (controls).

Number of Participants Planned: For Group A, a total of up to approximately 20 enrolled (10 non-HDV/HBV participants with severe renal impairment and 10 matched control participants with normal renal function) with a goal of obtaining approximately 16 evaluable participants (8 severe RI and 8 matched controls).

Diagnosis and Main Eligibility Criteria:

Key Inclusion Criteria

All Participants:

- Be aged 18 through 79 years, inclusive, at screening.
- Have a calculated body mass index (BMI) of at least 18.0 kg/m² and no greater than 40.0 kg/m² at screening.
- 12-lead electrocardiogram (ECG) evaluations at screening and admission must be without clinically significant abnormalities as assessed by the investigator.
- Have no known liver disease with hepatic transaminases (aspartate aminotransferase [AST] and ALT) ≤ 3 × upper limit of normal (ULN) at screening.

Participants with RI:

- Have RI classification at screening that has been unchanged (based on medical history, physical examination, and clinical laboratory results with no clinically significant change) during the 90 days prior to study drug dosing, as determined by the investigator.
- eGFR must be the following (using the CKD-EPI equation {Inker 2021}) based on serum creatinine as measured at the screening evaluation:
  - Severe RI (Groups A and B): eGFR ≥ 15 to ≤ 29 mL/min/1.73 m²
  - Moderate RI (Group C): eGFR ≥ 30 to ≤ 59 mL/min/1.73 m²
  - Mild RI (Group D): eGFR ≥ 60 to ≤ 89 mL/min/1.73 m²
- Hemoglobin ≥ 9 g/dL at screening.
- Participants with diseases/conditions associated with RI (eg, cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, etc) and participants with other concomitant diseases not related to RI (eg, hypothyroidism, osteoporosis, and many others) may be included provided that these diseases/conditions are clinically stable (as judged by the investigator, and in consultation with the medical monitor) and without impact on the study outcome.
- For participants with RI who have not been on a stable dose of concomitant medications for at least 4 weeks prior to screening (or 5 half-lives, whichever is longer) and/or for whom dose changes are likely to occur during the study, should have their medications reviewed and approved by the sponsor.

Matched Control Participants:

- Have an eGFR of at least 90 mL/min/1.73 m² (using the CKD-EPI equation) based on serum creatinine as measured at screening evaluation.

- Matched for sex, age (± 10 years), and BMI (± 20%, 18.0 ≤ BMI ≤ 40.0 kg/m²) with the respective participant in the RI group.

Key Exclusion Criteria

All Participants:

- Have a positive test result for the fourth generation HIV antibody/antigen test, HBsAg, or hepatitis C virus (HCV) antibody with detectable HCV viral RNA at screening.

  Note: Any previous treatment for an HCV infection must have been completed at least 12 weeks before screening.

- Have any serious or active medical or psychiatric illness (including depression) that, in the opinion of the investigator, would interfere with participant treatment, assessment, or compliance with the protocol. This would include uncontrolled or unstable cardiovascular, hematologic, hepatic, pulmonary, endocrine, gastrointestinal, metabolic, neurological disease, or active infection.

Participants with RI:

- Recent history of reception of any blood or blood products or history of major bleeding within 4 weeks of dosing.

- Positive test for drugs of abuse, including alcohol at screening or admission, with the exception of opioids and tetrahydrocannabinol (THC, marijuana) under prescription and verified by the investigator as for pain management. Participants who screen positive for benzodiazepines may be allowed if prescribed under the care of a physician and after review by the investigator and sponsor.

- Received treatment with trimethoprim or cimetidine or tenofovir prodrugs (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) (affects elimination of creatinine) or with competitors of renal tubular excretion (eg, probenecid, chronic high-dose nonsteroidal anti-inflammatory drugs) within 28 days of Day –1.

- Received known nephrotoxic drugs (eg, aminoglycosides, amphotericin B, vancomycin, cidofovir, foscarnet, cisplatin, pentamidine, cyclosporine, tacrolimus, herbal remedies [eg, compounds with aristolochic acid]) within 28 days of Day –1.

- Participants requiring or anticipated to require dialysis within 90 days of study entry.

- Serum albumin concentration <25 g/L.

- Uncontrolled treated/untreated hypertension (defined as a mean of 3 repeated measurements for systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg); current or documented history of repeated clinically significant hypotension or severe episodes of orthostatic hypotension (systolic blood pressure <90 mmHg and/or diastolic blood pressure <50 mmHg).

Matched Control Participants:

- Have taken any prescription medications or over-the-counter medications, including herbal products, within 28 days prior to start of study drug dosing, with the exception of vitamins and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications.

Test Product, Dose, and Mode of Administration: For each study group, participants will be administered BLV by SC injection by assigned study staff, once-daily (QD) at approximately the same time (± 30 minutes) each morning on Days 1-6 following an overnight fast (no food or drinks, except water) for at least 8 hours prior to dosing. The study will begin with Group A and additional optional groups (Groups B, C, and D) may be evaluated. The Figure 1-b outlines the PK decision criteria for dose selection and renal population for the subsequent study groups.

- **Group A:** BLV 2 mg in participants with severe RI and matched control participants

- **Optional Group B:** BLV 10 mg in participants with severe RI and matched control participants

- **Optional Group C:** BLV 2 mg or 10 mg (dose to be determined) in participants with moderate RI and matched control participants

- **Optional Group D:** BLV 2 mg or 10 mg (dose to be determined) in participants with mild RI and matched control participants

Reference Therapy, Dose, and Mode of Administration: Not applicable

Duration of Dosing and Duration of Study:

- Duration of Dosing: 6 days for each study group

- Duration of Study: 14 days (± 2 days) for each study group

The study will start with Group A (BLV 2 mg and severe RI with matched controls). Following the completion of screening procedures and study enrollment at admission, eligible participants will remain in the clinic for a period of 9 days, beginning on Day −1 until the completion of assessments on Day 8. Participants will be administered daily SC injection of BLV by assigned study staff, Day 1 through Day 6. A follow-up telephone call to collect adverse event (AE) data will be made on Day 13 (± 2 days).

Once the safety and PK data (refer to PK criteria in Figure 1-b) from all participants in Group A (BLV 2 mg with severe RI) has been reviewed by the safety review team (SRT), CCI [redacted]

Study Procedures/Frequency: Following the completion of screening procedures and study enrollment at admission, eligible participants will be administered study drug and undergo the following PK, PD and safety assessments as outlined in Table 1.

- AE reporting
- Physical examinations
- Vital signs
- 12-lead ECGs
- Safety laboratory
- Other assessments (eg, intensive plasma BLV PK, intensive plasma bile acids [BA] for PD, trough PK and BA PD, protein binding, immunogenicity.CCI [redacted]

Statistical Methods:

Pharmacokinetics and Pharmacodynamics: Plasma concentrations and PK parameters of BLV; and plasma concentrations and PD biomarker parameter of total BA, will be listed and summarized by renal function group and dose level using descriptive statistics. In addition, concentrations of individual BA may be measured and PD parameters may be summarized.

In addition, a one-way analysis of variance (ANOVA) model appropriate for a parallel-design with renal function group as a fixed effect will be fit to the natural logarithmic transformation of PK parameters (AUC_{tau} and $C_{max\ ss}$) for BLV. The 90% CIs will be constructed for the geometric least-squares mean (GLSM) ratio of PK parameters for BLV in the RI group versus the matched control (normal renal function) group. The same analysis will be conducted for PD parameters of total BA, as applicable.

The PK-PD relationship using plasma BLV PK concentrations/parameters and plasma BA concentrations/parameters may be explored using a graphic approach and correlation coefficients as appropriate. Additional PK and PD parameters may be estimated as necessary.

If determined, BLV and BA urine concentrations and parameters will be listed and summarized by renal function group and dose level using descriptive statistics. CCI [redacted]

Urine samples may be analyzed for determining the 6 beta-hydroxycortisol to cortisol ratio as a marker of CYP3A4 metabolic activity at Day 1 predose and at steady state (Day 6).

Plasma will be evaluated for the presence of antidrug antibodies (ADA) to BLV for immunogenicity analysis as applicable. ADA may be further characterized for neutralizing activity.

Safety: The AE data will be listed by participant. The treatment-emergent AEs (TEAEs), serious AEs (SAEs), and AEs leading to permanent study drug discontinuation will be summarized by renal function group, dose, system organ class, and preferred term using the current version of Medical Dictionary for Regulatory Activities (MedDRA).

Listings of individual participant laboratory results will be provided. Laboratory results and changes from baseline values for selected laboratory tests will be summarized by renal function group and dose at scheduled visits. The incidence of treatment-emergent laboratory abnormalities will be summarized by renal function group and dose.

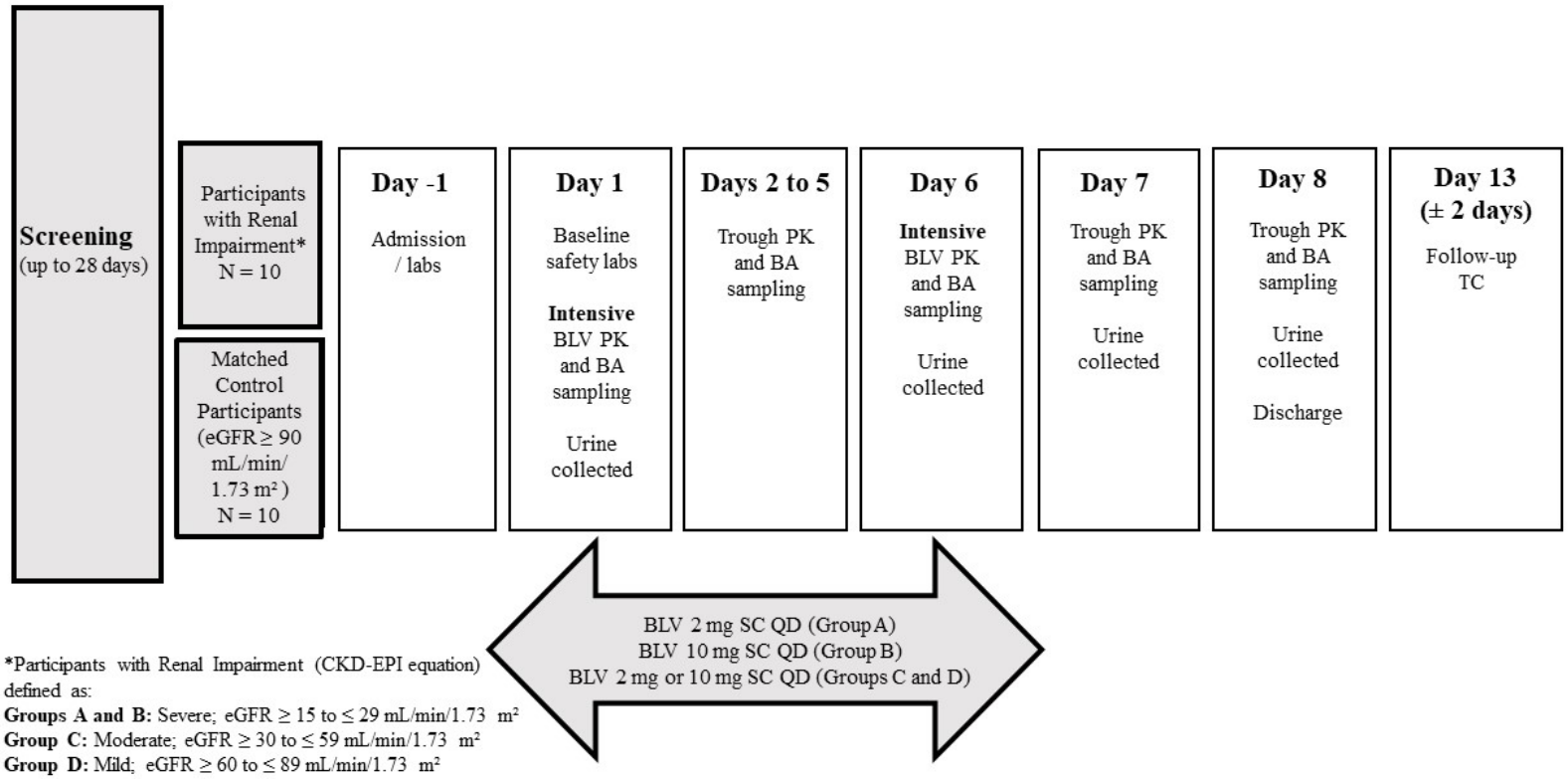
Vital signs and ECG data will be summarized by renal function group and dose.

Sample Size: For study Group A, with 16 (8 RI and 8 matched control [normal renal function]) evaluable participants, the estimated upper limit of the one-sided 95% CIs of the GLSM ratio of RI group versus matched control group with regards to AUC_{tau} and C_{max} of BLV, would be less than 200% with ≥ 80% probability if the expected GLSM ratio is 1.0. This assumes a percentage coefficient of variation (CV%) of no more than 51%, which is supported by previously conducted Study MYR102. Accounting for a 20% dropout rate, a total sample size of 20 participants (10 RI and 10 matched control each) will be required.

Furthermore, given the lower degree of variability in BA concentrations compared to BLV plasma concentrations observed in Study MYR102 {Blank 2018}, this sample size will also provide ≥ 80% probability that the estimated upper limit of the one-sided 95% CIs of the GLSM ratio of RI group versus matched control group with regards to AUC_{tau} and C_{max} of total plasma BA would be less than 200% if the expected GLSM ratio is 1.0. CCI [redacted]

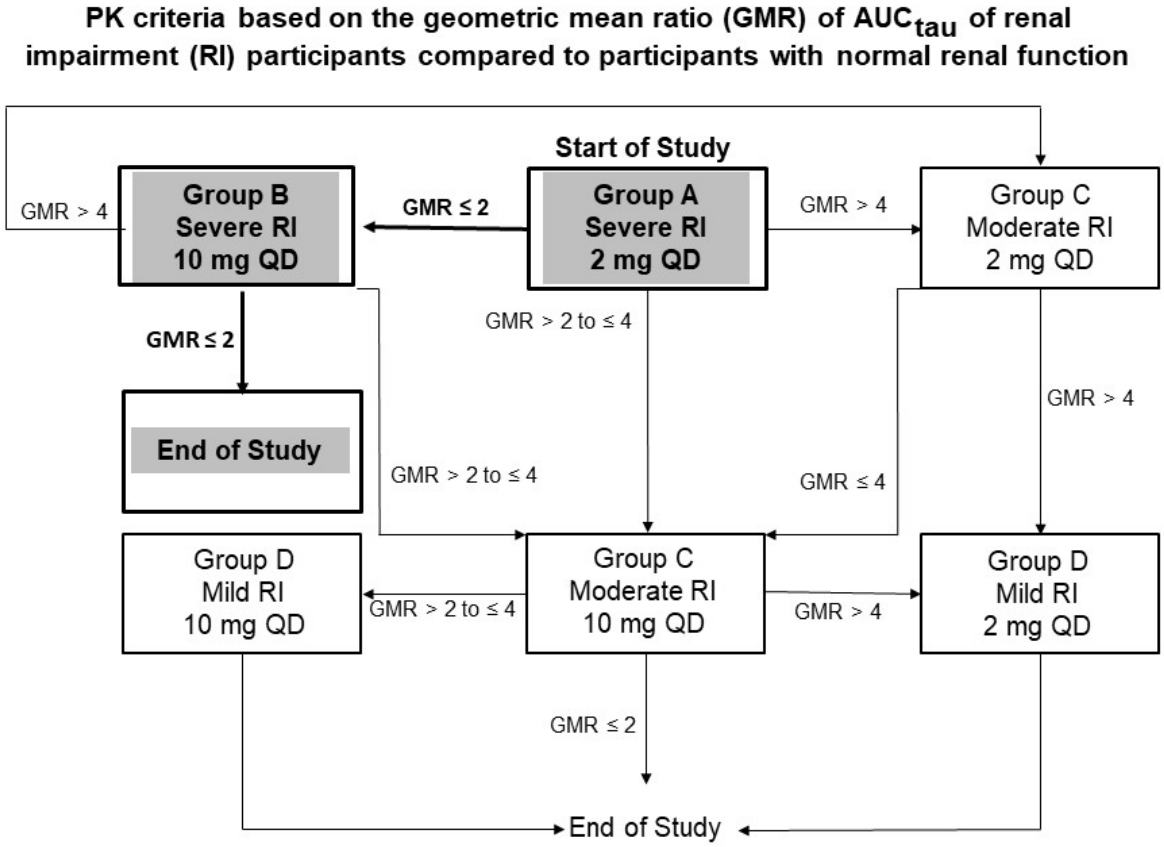
STUDY SCHEMA

Figure 1-a. Study Schema



BA = bile acids; BLV = bulevirtide; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; N = number of participants; PK = pharmacokinetics; QD = once-daily; SC = subcutaneous; TC = telephone call
Note: Refer to Figure 1-b for PK criteria for dose selection and renal population of the subsequent study groups.

Figure 1-b. PK Decision Criteria for Progression to Subsequent Study Groups



BLV = bulevirtide; GMR = geometric mean ratio; PK = pharmacokinetic; QD = once-daily; RI = renal impairment
Boxes in bold and shaded indicate the most likely scenario to be pursued.

STUDY PROCEDURES TABLE

Table 1. Study Procedures Table

Study Procedure	Screening	Admission	Evaluation Period				Discharge[a]	Follow-up[b]	ET[c]	Notes
Study Day:		**−1**	**1**	**2-5**	**6**	**7**	**8**	**13**		
Window:	**≤ 28 days prior to dosing**							**± 2 days**		
Written informed consent	X									
Clinic confinement		X	X	X	X	X	X			
Review study restrictions	X	X					X	X		
Complete medical history	X									
Complete physical examination	X	X					X		X	Symptom-driven physical examination may occur at any other visits if clinically indicated.
Weight, height and BMI	X	X								
COVID-19 testing		X								Must receive a negative PCR result for enrollment. If study site cannot obtain results from the local laboratory in time for Day 1 dosing, then COVID-19 rapid antigen test/rapid PCR is acceptable.
Vital signs	X	X	X	X	X	X	X		X	Vital signs include resting blood pressure, heart rate, and body temperature at: screening, admission (Day –1), Day 1 (predose and approximately 2 hours postdose), Day 6 (predose and approximately 2 hours postdose), then once in the morning of following days/before blood PK sampling: Day 2 through Day 5, Day 7, and discharge (Day 8), and at ET visit (if applicable).

Study Procedure	Screening	Admission	Evaluation Period				Discharge[a]	Follow-up[b]	ET[c]	Notes
Study Day:		**−1**	**1**	**2-5**	**6**	**7**	**8**	**13**		
Window:	**≤ 28 days prior to dosing**							**± 2 days**		
12-Lead ECG	X	X	X	X	X		X		X	12-Lead ECG: screening, admission (Day –1), Day 1 (4 hours postdose), Day 3 (4 hours postdose), Day 6 (4 hours postdose) and discharge (Day 8), and at ET visit (if applicable).
HIV, HBV, and HCV testing	X									Fourth generation HIV antibody/antigen test, HBsAg, HBsAb, HCV antibody, and HCV RNA testing.
eGFR[e]	X	X	X	X	X	X	X		X	eGFR will be estimated at screening, admission (Day –1), predose Day 1 to 6, Day 7, and at discharge (Day 8), and at ET visit if applicable. eGFR will be calculated using the CKD-EPI equation (2021) for allocation to the RI group based on serum creatinine as measured at screening.
Hematology[d,e]	X	X	X	X	X	X	X		X	8 hours fasting required.
Chemistry[d,e]	X	X	X	X	X	X	X		X	8 hours fasting required. Assessment of total BA for safety.
Urinalysis[d,e]	X	X	X	X	X	X	X		X	8 hours fasting required.
Urine drug and alcohol screen	X	X								If study site cannot perform urine alcohol or obtain results from the local laboratory in time for enrollment on Day 1, then an alcohol breathalyzer test is acceptable.
Coagulation[d,e]	X	X	X	X	X		X		X	Prothrombin time, partial thromboplastin time, and international normalized ratio.
Serum pregnancy test	X	X								Required for participants assigned female at birth and of childbearing potential only. Point of care pregnancy test may be used at site if serum test result is not available prior to dosing.

Study Procedure	Screening	Admission	Evaluation Period				Discharge[a]	Follow-up[b]	ET[c]	Notes
Study Day:		**−1**	**1**	**2-5**	**6**	**7**	**8**	**13**		
Window:	**≤ 28 days prior to dosing**							**± 2 days**		
FSH testing	X									FSH testing required for participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure.
Enrollment			X							Participants will be considered enrolled after eligibility is confirmed and a participant number is assigned on Day 1 prior to dosing.
Study drug administration			X	X	X					Day 1 to Day 6, BLV SC injection, QD. See Section 5.3.
Intensive plasma BLV PK and plasma BA for PD			X		X				X	Intensive BLV PK and total plasma BA for PD biomarker sampling will occur relative to the dosing of BLV at the following time points: Day 1 and Day 6 at predose (≤ 30 minutes before dose) at 0.5, 1, 1.5, 2, 3, 4, 6, 9, and 12 hours postdose; and, at ET visit (as applicable).
Trough plasma PK and trough plasma BA for PD				X		X	X		X	Predose (≤ 30 minutes before dose) on Day 2 through Day 5 and at 24 hours post Day 6 dose (Day 7) and 48 hours post Day 6 dose (Day 8), and at ET visit (as applicable). The Day 2 predose trough sample of plasma PK and plasma BA will serve as the 24 hours post Day 1 dose sample for intensive plasma PK and plasma BA, respectively, and would be interpolated programmatically at the time of PK analysis.
Plasma sample for protein binding			X							On Day 1, at predose, and 2 and 12 hours postdose.

Study Procedure	Screening	Admission	Evaluation Period				Discharge[a]	Follow-up[b]	ET[c]	Notes
Study Day:		**−1**	**1**	**2-5**	**6**	**7**	**8**	**13**		
Window:	**≤ 28 days prior to dosing**							**± 2 days**		
[redacted]										
Immunogenicity			X		X					ADA to BLV. Collected predose (≤ 30 minutes before dose).
Meal monitoring		X	X	X	X	X	X			Record the percentage of meal consumed (0-25%, 25-50%, >50%). See Section 5.4 for meal intervals.
Review AEs & concomitant medications	X	X	X	X	X	X	X	X	X	From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any nonserious AEs related to protocol-mandated procedures, on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be captured on the medical history eCRF. See Section 7, Adverse Events and Toxicity Management, for additional details.

ADA = antidrug antibodies; AE = adverse events; BA = bile acids; BLV = bulevirtide; BMI = body mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; ECG = electrocardiogram; eCRF = electronic case report forms; eGFR = estimated glomerular filtration rate; ET = early termination; FSH = follicle-stimulating hormone; HBsAb= hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PCR = polymerase chain reaction; PK = pharmacokinetics; QD = once-daily; RI = renal impairment; SAE = serious adverse event; SC = subcutaneous

a Participants will be discharged from the clinic on Day 8 per investigator's discretion, following all morning assessments.
b Participants will be contacted for evaluation of AEs by telephone on Day 13 ± 2 days ie, 7 days (± 2 days) following last administration of study drug.
c ET assessments will be performed within 24 hours of prematurely discontinuing from the study (prior to Day 8), if possible.
d Performed at screening, admission (Day −1), predose on Days 1 to 6, Day 7, at discharge (Day 8), and at ET visit, if applicable. Predose collections are to be performed ≤ 30 minutes before dose. Coagulation tests will not be performed on Day 7.
e Safety laboratory tests will be collected upon study site admission (Day –1); will be evaluated at the site's local laboratory to obtain results for participant's eligibility prior to dosing on Day 1. Results of the Day –1 safety labs will be maintained with the source documents and will not be entered in the electronic data capture at the site. Day 1 safety labs will be used for baseline values.

1. INTRODUCTION

1.1. Background

Hepatitis delta virus (HDV) infection is the most severe form of viral hepatitis, affecting as many as 10 to 20 million people globally {Stockdale 2020}. Delta hepatitis is caused by the HDV, a defective RNA virus that requires the presence of hepatitis B surface antigen (HBsAg) for its complete replication and transmission {Rizzetto 2009, Sureau 1993, Taylor 2015}, and, as such, this form of hepatitis only occurs in individuals also infected with the hepatitis B virus (HBV). Prevalence rates vary widely; however, HDV infections are mostly concentrated in low- and middle-income countries, with the highest rates reported in Brazil, Mongolia, and parts of Africa {Lempp 2016}. In the United States (US) and European Union (EU), HDV infection is considered an orphan disease, with an estimated prevalence of 100,000 and 130,000 patients, respectively {Rizzetto 2009, Romeo 2018, Wedemeyer 2010b}.

Among patients with chronic hepatitis D (CHD), higher rates of disease progression, including liver-related events, cirrhosis, hepatocellular carcinoma, and death, have been reported than among patients with chronic hepatitis B (CHB) monoinfection {Heidrich 2014}. Several cohort studies have found that this risk may indeed be as much as 9 times higher than in patients with HBV monoinfection {Beguelin 2017}. Collectively, available data support the conclusion that CHD is the most severe form of viral hepatitis in humans {Wedemeyer 2010a}, with a more rapid progression to fibrosis and cirrhosis, earlier onset of hepatic complications, and greater likelihood of liver transplantation than other forms of viral hepatitis {Ni 2014, Yan 2012}.

The therapeutic options for patients with HDV co-infection are very limited. Nucleos(t)ide analogues, while effective in patients with CHB have not been shown to have a meaningful therapeutic effect on HDV RNA levels in patients with CHD {European Association for the Study of the Liver (EASL) 2017}. Currently in the US, there is no approved treatment available for CHD. Based on clinical studies conducted over the past few decades, the current guidelines of the American Association for the Study of Liver Diseases, the Asian Pacific Association for the Study of the Liver, and the European Association for the Study of the Liver (EASL) recommend the off-label use of pegylated interferon alpha (Peg-IFNα) for 12 months {Cornberg 2020, European Association for the Study of the Liver (EASL) 2017, Terrault 2018}. Response rates with Peg-IFNα have been variable, ranging from 17% to 35%, and treatment is frequently associated with adverse effects such as flu-like symptoms, anemia, neutropenia, and thrombocytopenia that result in poor tolerability and subsequent high rates of discontinuation {Alavian 2012, Wranke 2017}. Furthermore, among patients who achieve a response (undetectable HDV RNA posttreatment) when treated with Peg-IFNα, approximately 50% relapse in long-term follow-up {Heidrich 2014}. Overall, Peg-IFNα therapy is estimated to provide a long-lasting benefit for approximately 10% of patients {Heidrich 2014}. Recent advances in the field of HDV drug development include novel antiviral therapies with mechanisms of action such as those that target viral entry or impact assembly and release of viral particles, and treatments that work directly by activating the host immune response {Urban 2021}. Development of therapies that effectively target critical aspects of the HDV replication

cycle and are also well tolerated is needed to improve treatment outcomes and the long-term prognosis of those chronically infected with HDV.

1.2. Background on Study Interventions

A list of study interventions and their authorization status is provided in Appendix 11.2.

1.2.1. Bulevirtide

1.2.1.1. General Information

Bulevirtide (BLV), GS-4438, formerly known as Myrcludex B, is a novel 47-amino acid, N-terminally myristoylated, HBV large envelope protein–derived, synthesized lipopeptide that binds specifically to the sodium-taurocholate cotransporting polypeptide (NTCP) and acts as a potent, highly selective entry inhibitor of HDV (and HBV) into hepatocytes {Ni 2014, Yan 2012}. By blocking the essential entry receptor, the de novo infection of liver cells is decreased, viral spread is inhibited, and the life cycle of HDV is disrupted {Urban 2021}.

Bulevirtide is conditionally approved under the brand name Hepcludex® in the European Economic Area and the United Kingdom and approved as Myrcludex B® in Russia. Bulevirtide as a 2-mg lyophilized powder for injection is to be administered subcutaneously once-daily (QD) for the treatment of CHD in adults with compensated liver disease.

For further information on BLV, refer to the investigator's brochure (IB) for BLV, including information on the company core data sheet (CCDS) and the reference safety information (RSI).

1.2.1.2. Nonclinical Pharmacology, Pharmacokinetics, and Toxicology

Nonclinical Pharmacology

In vitro, BLV specifically binds to NTCP in mouse, rat, rabbit, dog and human hepatocytes and the receptor structure and function are highly conserved between these species. No binding to cynomolgus monkey hepatocytes was observed which is in line with recent studies showing that the cynomolgus monkey expresses an altered form of NTCP. The in vitro functional activity of myristoylated HBVpreS1 peptides (similar to the BLV molecule) to inhibit NTCP transporter function was assessed in a transporter inhibition uptake assay in cells overexpressing human NTCP. The half-maximal inhibitory concentration (IC_{50}) value of 190 nM for bile acids (BA) uptake was obtained in HEK293-NTCP cells and an IC_{50} of 9.7 nM was obtained in primary human hepatocytes. Inhibition of rat NTCP function was assessed using CHO-K1 cells overexpressing the rat NTCP and a dose-dependent inhibition with an IC_{50} value of 0.068 µM was demonstrated. Consistently, an increase in total bile salts was observed in rats treated with 2.5 mg/kg body weight/day BLV for 12 days during pregnancy as part of the embryofetal development (EFD) toxicity study. The increase in total bile salts was also observed in the EFD study in rabbits treated with BLV 2.5 mg/kg body weight/day, thus confirming the functional inhibition of NTCP by BLV. In safety pharmacology studies, no BLV-related influence was observed on pulmonary, neuropharmacological, cardiovascular, renal, hepatic, ophthalmologic or auditory parameters.

Nonclinical Pharmacokinetics

An extensive program of nonclinical absorption and distribution studies with BLV was conducted in animals. Bulevirtide is a highly target-specific drug that was found exclusively distributed to the liver in all tested animals besides the cynomolgus monkey. It is rapidly absorbed after subcutaneous (SC) administration with maximum plasma concentrations (C_{max}) being reached within 4 to 6 hours. Area under the curve (AUC) generally increased in approximate proportion to dose in rats and dogs (0.25-2.5 mg/kg dose). After a single SC dose, the bioavailability of BLV was 81% in rats. Bulevirtide is highly plasma protein bound. In dogs, binding to plasma proteins was investigated by size exclusion chromatography. The radioactivity peak of BLV-y-123I overlapped with the main plasma protein peak showing BLV binding. In vitro, the plasma protein binding of BLV has been additionally evaluated using rat, dog, rabbit and human plasma by cross filtration demonstrating that the bound fraction percentage ranges from >99.90% to >99.92%. Given that BLV is a 47-amino acid peptide, it is likely eliminated via peptide catabolism by peptidases in systemic circulation and tissues, and no active metabolite is to be expected. Finally, the potential of drug-drug interactions (DDI) for BLV were evaluated in vitro and overall a low DDI risk was predicted. The renal excretion of BLV is likely very low as indicated by an observed lack of renal excretion of radiolabeled peptides in nonclinical species.

Nonclinical Toxicology

A comprehensive toxicology program was conducted in accordance with the regulatory guidelines. Toxicology studies included a single-dose study in rats, and repeated-dose studies up to 13 weeks in dogs and 6 months in rats, as well as antigenicity studies in rats. No BLV-related toxicity was noted. Developmental and reproductive toxicology studies conducted in rats and rabbits showed no embryofetal and reproductive toxicity in either species. Within the rabbit embryofetal toxicity study, a maternal toxicity in the form of minimal reduction in body weight and food intake in dams administered BLV 2.5 mg/kg/day was observed. There were no effects on the male and female fertility parameters in fertility and early embryonic development studies and no effects on pre- or post-natal development in rats up to 2.5 mg/kg/day, the highest dose tested.

1.2.1.3. Additional Clinical Experience with Bulevirtide

The pharmacokinetic (PK) profile of BLV has been evaluated in a total of 7 clinical studies, of which 2 were Phase 1 studies (MYR101 and MYR102), 1 was a Phase 1/2 study (MYR201 [HBV]), 3 were Phase 2 studies (MYR202, MYR203, and MYR204), and 1 was a Phase 3 study (MYR301). Bulevirtide exhibited dose-dependent, nonlinear PK following IV and SC administration. Following single and multiple-dose SC administration, absorption was rapid and T_{max} occurred between 0.5 to 3 hours postdose across all doses tested. After reaching peak concentrations, plasma levels declined with a $t_{1/2}$ of 3 to 7 hours. With increasing doses greater than 2 mg daily, BLV exposure was greater than dose proportional with an estimated increase in $AUC_{0\text{-}24h}$ of 3.9-fold and 10.9-fold, respectively, for 5 mg and 10 mg doses compared with the 2 mg reference dose. There was also a corresponding reduction in apparent clearance (CL/F) and volume of distribution (V/F), suggesting saturation of binding of BLV to its target receptor, NTCP, in the liver with the excess BLV within the circulation resulting in higher than dose proportional plasma concentrations.

Following single and multiple doses in Study MYR102 {Blank 2018, Blank 2016}, no full-length peptide was detected in urine samples of healthy participants, demonstrating that renal elimination of BLV is unlikely. Considering that BLV is a linear peptide, it is also not expected that hepatic metabolism would contribute to BLV elimination. In an integrated population PK (PopPK) modeling analysis, participants (N = 154) with cirrhosis (Child-Pugh A mild hepatic impairment) were found to have slightly lower CL (14% decrease), higher AUC_{0-24h} (16.6%), and higher C_{max} (13.3%) than participants without cirrhosis, resulting in no clinically relevant impact on BLV exposure (BLV PopPK report CTRA-2021-1057). Therefore, no dose adjustment is recommended for participants with mild hepatic impairment. The PK of BLV has not been evaluated in participants with moderate and severely hepatic impairment (Child-Pugh B and C, respectively).

The molecular target of BLV is the NTCP receptor in the liver, which is inhibited by BLV as a direct result of its mechanism of action against HDV. Dose-dependent asymptomatic BA elevations were consistently observed across studies, as an expected consequence of the blockage of NTCP by BLV in accordance with its mechanism of action. Importantly, the BA elevations resolved upon discontinuation of BLV treatment and were asymptomatic.

Population PK modeling (n=60) found no impact of mild renal impairment (RI) (creatinine clearance [CL_{cr}] ≥ 60 and < 90 mL/min) on BLV PK. The safety and PK of BLV has not been evaluated in patients with moderate and severe RI (CL_{cr} < 60 mL/min), or in patients with end-stage renal disease, including those on dialysis. As BLV is > 99.9% protein bound, dialysis is not expected to alter exposures of BLV. No dosage adjustment of BLV is required in patients with mild RI. This Phase 1 study is being conducted to determine whether study drug PK parameters are altered in participants with impaired renal function as compared to participants with normal renal function to an extent that dose adjustments of study drug in participants with RI may be warranted.

In a clinical PK DDI study in healthy volunteers, there was no significant effect of BLV on the PK of tenofovir disoproxil fumarate (TDF), a potential concomitant medication for the treatment of HBV infection. No CYP or transporter inhibition or induction by BLV was observed in vitro at clinically relevant concentrations.

The safety of BLV was assessed in participants with CHD without cirrhosis or with compensated cirrhosis from three Phase 2 studies and one Phase 3 study. BLV was generally safe and well tolerated when assessed in the combined and the separated dose analyses, with a low frequency of Grade 3 or 4 adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation of BLV; no SAEs were assessed as related to BLV while on treatment. The AE profile was generally similar between the BLV monotherapy groups and the control group, with the exception of higher rates of total BA increased, injection site reactions, headache, and pruritus that were very commonly reported with BLV treatment but not reported in the control group.

Bulevirtide has the potential to induce antidrug antibodies (ADA), as detected in clinical studies using an enzyme-linked immunosorbent assay (ELISA). In Studies MYR203 and MYR301, a total of 64 patients who were treated with BLV 2 mg monotherapy for 48 weeks were eligible for

assessment of ADA prevalence; 18 of these patients (28.1%) were positive for ADA prevalence, of which 3 patients (4.7%) were positive for ADA at baseline. Similar ADA findings were observed at the BLV 10 mg dose level. There is no evidence that the pharmacokinetics, safety, or effectiveness of BLV were altered in these patients.

1.2.2. Information About Comparator

This is a match-controlled, open-label study. No comparator drug is provided.

1.2.3. Information About Auxiliary Medicinal Products

Auxiliary medicinal products are not planned for this study.

1.3. Rationale for This Study

Renal impairment has been associated with changes in drug absorption, plasma protein binding, transport, and tissue distribution. These changes are prominent in patients with severely impaired renal function. In healthy participants the lack of full-length peptide was detected in urine PK with 24-hour urine collection after single doses and at steady state with BLV 10 mg QD therapy. Therefore, RI is not expected to substantially affect the exposure of BLV. Accordingly, a reduced study design at the "extremes" of renal function will be used, in accordance with regulatory guidance from the Food and Drug Administration (FDA) "Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling" {U.S. Department of Health and Human Services 2020}. The results from this study (Groups A and B) will inform the decision to evaluate the PK of BLV in participants with moderate and/or mild RI in additional optional groups of this study (Groups C and D).

The RI categorization for entry criteria in this study will be based on the CKD-EPI (2021) equation to estimate GFR, as this is recommended by the National Kidney Foundation and the American Society of Nephrology {Delgado 2022}. This study will evaluate the multiple-dose PK of BLV in participants with severe RI, not requiring dialysis (eGFR $\geq$ 15 to $\leq$ 29 mL/min/1.73 m^2) as compared to matched control participants with normal renal function (eGFR $\geq$ 90 mL/min/1.73 m^2) with a goal to provide appropriate dosing recommendations in patients with RI. The matched control group will be composed of participants with normal renal function and matched for age, body weight, and sex.

Bulevirtide has a dose-dependent effect of elevating plasma BA concentrations, as a consequence of its mechanism of action (inhibition of the NTCP receptor responsible for uptake of BA into hepatocytes). Bile acids are eliminated in the urine, with increases in urine BA observed in a previous healthy participant study (MYR102) following BLV treatment. Given this, there is the potential that BA concentrations may be further elevated in patients with RI, thus this study will evaluate plasma BA concentrations and may explore urine BA concentrations.

Administration of BLV with multiple dosing (QD) will be utilized in this study as BLV has demonstrated dose- and time-dependent PK, with approximately a 2-fold accumulation after QD multiple dosing despite a short apparent terminal half-life (3-7 hours). A previous study, MYR102 {Blank 2016}, demonstrated that steady-state accumulation can be achieved within 6 days of dosing and that effects on elevations of plasma and urine BA appeared to plateau within this time frame. Renal impairment may also be associated with changes in protein binding, and thus plasma protein binding of BLV may also be evaluated in this study.

Intensive PK and BA assessments will be conducted to ensure sufficient characterization of terminal elimination phase of BLV. To ensure participant safety, a minimum confinement until Day 8 will be required.

Non-HDV/HBV-infected participants (participants with RI and matched control participants with normal renal function) are selected for this study to remove potential confounding effects of the target disease and/or therapies in participants with hepatitis D infection. In addition, this study design, conducted at Phase 1 units will provide comparisons of PK and PD data and generate safety data to provide appropriate dosing recommendations in patients with RI.

1.4. Rationale for the Dose Selection of Bulevirtide

The 2 doses for this study were chosen based on the following factors: 1) the 2 mg in Group A is the conditionally approved dose in some regions such as the EU, administered as a SC QD dose for the treatment of CHD in adults with compensated liver disease and a dose that has resulted in efficacy for the treatment of CHD in Phase 2 and 3 studies. 2) CCI [redacted]

1.5. Risk/Benefit Assessment for the Study

In addition to the established risks associated with SC injection of BLV, potential risks of a participant's study involvement include unknown AEs, laboratory abnormalities, and general risks associated with frequent clinic visits and laboratory blood draws. Strategies to mitigate these risks include close monitoring of participants' clinical status, laboratory values, and AEs. Parameters for discontinuation of the study drug due to AEs will be well defined and closely followed.

Dose-dependent elevations of serum bile salts has been very commonly observed with BLV which are typically asymptomatic. It is possible that BA concentrations may be further elevated in participants with RI.

There is no direct benefit to participants in this study; however, data from this study will support the development of BLV for the treatment of CHD in adults with compensated liver disease.

An infectious disease pandemic may pose additional risks to study drug availability, study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 11.3 for further details on the risks and risk mitigation strategy.

Considering the above, the benefit-risk balance for this study is considered positive.

1.6. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are presented in Table 2.

Table 2. Study Objectives and Endpoints

Primary Objective	Primary Endpoint(s)
• To evaluate the steady-state plasma PK of BLV in non-HDV/HBV-infected participants with RI and in matched control participants with normal renal function	• BLV steady-state plasma PK parameters AUC_{tau} and $C_{max\ ss}$
Secondary Objective(s)	**Secondary Endpoint(s)**
• To further characterize the plasma PK of BLV in participants with RI and in matched control participants with normal renal function • To evaluate the PD effect of BLV on plasma BA in participants with RI to matched control participants with normal renal function • To evaluate the safety and tolerability of BLV following multiple-dose administration in participants with RI and matched control participants with normal renal function	• Plasma PK parameters for BLV, as applicable: AUC_{0-24}, C_{max}, T_{max}, $t_{1/2}$, CL_{ss}/F, and V_{ss}/F • Total BA concentrations in plasma and exposure parameters for total BA, as applicable: C_{trough}, C_{max}, AUC_{0-24}, T_{max} • The incidences of AEs and laboratory abnormalities
CCI	

ADA = antidrug antibodies; AE = adverse event; BA = bile acids; BLV = bulevirtide; HBV = hepatitis B virus; HDV = hepatitis D virus; PD = pharmacodynamic; PK = pharmacokinetic; RI = renal impairment
CCI

3. STUDY DESIGN

3.1. Study Design

The study adheres to the guidelines for studies with renally impaired participants according to the recommendations given by the FDA {U.S. Department of Health and Human Services 2020}.

This protocol describes a Phase 1, open-label, multiple-dose, parallel-group study to evaluate multiple-dose PK, PD, and safety of BLV in participants with severe RI and matched control participants with normal renal function. Additional groups of participants with mild and/or moderate RI (and with matched control participants) may be included pending evaluation of safety and PK results in severe RI participants.

Non-HDV/HBV-infected participants assigned male at birth and nonpregnant, nonlactating participants assigned female at birth, aged 18 through 79 years inclusive with a body mass index (BMI) from 18.0 kg/m² to 40.0 kg/m² will be enrolled in the study.

The matched control group will consist of matched participants with normal renal function. Each match participant (normal renal function ie, eGFR ≥ 90 mL/min/1.73 m²) will be matched for age (± 10 years), sex (assigned at birth), and BMI (± 20%, 18.0 ≤ BMI ≤ 40.0 kg/m²) with a participant in the RI group.

An overview of the study design is described below and shown in Figure 1-a. In accordance with the objectives, a reduced study design starting in participants with severe RI was selected. The study will begin with Group A. Following completion and evaluation of PK and safety data from all participants in Group A, additional optional groups (Groups B, C, and D) may be evaluated as per the criteria detailed in Section 3.1.1.1 and Figure 1-b.

- **Group A (BLV 2 mg severe RI):** A total of up to 20 participants (10 participants with severe RI and 10 matched control participants) will be enrolled to obtain at least 16 evaluable participants (8 participants with severe RI and 8 matched control participants)
- **Optional Group B (BLV 10 mg severe RI):** A total of up to 20 participants (10 participants with severe RI and 10 matched control participants) will be enrolled to obtain at least 16 evaluable participants (8 participants with severe RI and 8 matched control participants)
- **Optional Group C (BLV 2 mg or 10 mg moderate RI):** A total of up to 20 participants (10 participants with moderate RI and 10 matched control participants) will be enrolled to obtain at least 16 evaluable participants (8 participants with moderate RI and 8 matched control participants)
- **Optional Group D (BLV 2 mg or 10 mg mild RI):** A total of up to 20 participants (10 participants with mild RI and 10 matched control participants) will be enrolled to obtain at least 16 evaluable participants (8 participants with mild RI and 8 matched control participants)

Classification of renal function will be assessed using the eGFR based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (expressed for serum creatinine, sex, and age) {Inker 2021} at screening (Refer to Section 4.1 for equation) as follows:

- **Group A (BLV 2 mg severe RI):** Participants with severe RI (eGFR ≥15 to ≤ 29 mL/min/1.73 m²) and normal renal function (eGFR ≥ 90 mL/min/1.73 m²) at screening. Participants with severe RI requiring or anticipated to require dialysis within 90 days of study entry will not be eligible.

- **Optional Group B (BLV 10 mg severe RI):** Same target participant population as Group A.

- **Optional Group C (BLV 2 mg or 10 mg moderate RI):** Participants with moderate RI (eGFR ≥ 30 to ≤ 59 mL/min/1.73 m²) and normal renal function (eGFR ≥ 90 mL/min/1.73 m²) at screening.

- **Optional Group D (BLV 2 mg or 10 mg mild RI):** Participants with mild RI (eGFR ≥ 60 to ≤ 89 mL/min/1.73 m²) and normal renal function (eGFR ≥ 90 mL/min/1.73 m²) at screening.

Study procedures will include safety, PK, and PD assessments for all participants. Clinical procedures in all groups will be identical to those described for Group A.

3.1.1. Dose Selection

Participants will be administered BLV by SC injection by assigned study staff, QD for 6 days:

- **Group A:** BLV 2 mg in participants with severe RI and matched control participants

- **Optional Group B**: BLV 10 mg in participants with severe RI and matched control participants

- **Optional Group C**: BLV 2 mg or 10 mg (dose to be determined) in participants with moderate RI and matched control participants

- **Optional Group D**: BLV 2 mg or 10 mg (dose to be determined) in participants with mild RI and matched control participants

Additional optional groups (Groups B, C, and D) may be evaluated as per the safety and PK criteria for dose selection and renal population outlined in Figure 1-b and Section 3.1.1.1. Once the safety and PK data from all participants in Group A (2 mg severe RI) has been reviewed, Group B (10 mg severe RI) or Group C (2 or 10 mg moderate RI) may be opened. Once the data from all participants in Group B has been reviewed, Group C may be opened. Once the data from all participants in Group C has been reviewed, Group D (2 or 10 mg mild RI) may be opened.

Within each group, once a participant with RI is enrolled, a matched control to that participant will be allowed to enroll. Dosing of matched participant with normal renal function may begin after the corresponding participant with RI in that group has completed the last PK assessment.

A matching control may serve as a matched control participant only once per study group. A participant with normal renal function may have their PK and BA data reused just once to serve as a matched control for an another group, if the BLV dose is the same and the matching criteria are met.

3.1.1.1. Criteria for Proceeding to Optional Groups (Groups B, C, and D)

The decision to proceed to enrollment for optional groups will be based on review of safety and PK data from Day 1 through Day 8 from all participants enrolled in any previously conducted groups as detailed below. Available BA data will be reviewed from the safety perspective. Based on the PK properties of BLV, a significant increase in exposure in renal impaired participants is not expected. Thus, a reduced study design starting in participants with severe RI was selected. The study design also includes the option of two dose levels of 2 mg and 10 mg for characterization in this population.

The individual group will be discontinued if 2 or more participants in that group experience the same or similar SAE following administration of the study drug. The severity of treatment-emergent adverse events (TEAEs) will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. NOTE: conditions that exist before enrollment (eg, alanine aminotransferase [ALT] elevation before study drug administration) are not to be reported as TEAEs unless a notable deterioration occurs, or SAE occurs after BLV dosing. The investigator will assess all results of laboratory tests that deviate from normal ranges and decide whether or not these deviations qualify as AEs. Dose-dependent asymptomatic BA elevations were consistently observed across studies, as an expected consequence of the blockage of NTCP by BLV in accordance with its mechanism of action. Given this, asymptomatic elevation of BA with BLV dosing in this study should not be documented as AEs. Furthermore, the decision to conduct Group B will consider safety data including any AEs as reviewed at an internal safety review meeting held by the sponsor. The decision to conduct Group C and/or Group D and the selection of the dose in each group will consider safety data from all previously completed groups, including any AEs as reviewed at an internal safety review meeting held by the sponsor.

In addition to safety and tolerability assessment, PK criteria will be used to select the dose and population of the remainder of the study. The flowchart in Figure 1-b outlines the PK decision criteria for progression to subsequent study groups. The area under the concentration versus time curve (AUC) over the dosing interval (AUC_{tau}) was selected to represent the exposure metric for decision making. In general, a nominal increase (ie, $\leq$ 2-fold) in PK exposure, as measured by the geometric mean ratio (GMR) of AUC_{tau} in participants with RI compared to participants with normal renal function, would allow escalation of the dose to 10 mg QD in the severe RI population. Similarly a GMR of $>$ 2 to $\leq$ 4 will also allow dose escalation to 10 mg for the subsequent study groups. In contrast, while not anticipated, a large increase in PK exposure (ie, GMR $>$ 4) in participants with RI would trigger further investigation in additional groups of

participants with moderate (Group C) and/or mild (Group D) impaired renal function. This follows the FDA RI guidance - Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling {U.S. Department of Health and Human Services 2020}.

3.1.1.2. Safety Review Team and Charter

A safety review team (SRT) will review all PK and safety data from completed Group A before opening Group B or Group C; and from completed Group B before opening Group C; and from completed Group C before opening Group D (refer to PK criteria in Figure 1-b).

A SRT charter defining the team membership, meeting conduct, and decision making process will be agreed upon by all team members before the first SRT meeting. The data reviewed at the team meetings to make decisions to allow proceeding to subsequent optional groups will be defined in the charter. The quality control checks performed on the data reviewed and used for making dose selection and/or modification decisions will also be described in the charter.

Source data verification may not be performed before SRT meetings. Alternative data quality control checks that are performed on data used to make dose escalation decisions will be described in the SRT and/or dose escalation team charter (or similar document).

3.2. Duration of Dosing

The study will be conducted in 5 parts for each group: screening, admission, evaluation, discharge, and follow-up. Study participation for each group will be approximately 16 days, excluding the screening period, and dosing with BLV will occur QD for 6 days from Day 1 through Day 6.

3.3. Protocol-Specific Discontinuation Criteria

3.3.1. Criteria for Early Discontinuation for the Individual Participant

3.3.1.1. Criteria for Early Discontinuation for the Individual Participant from the Study Intervention

Study interventions will be discontinued in the following instances:

- Adverse event that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in Section 7.7, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the participant's best interest
- Any treatment-emergent study drug-related Grade 3 or higher AE

- Any treatment-emergent Grade 3 or higher confirmed laboratory abnormality suspected to be related to study drug by the investigator (with the exception of asymptomatic BA elevations and clinically insignificant Grade 3 or 4 cholesterol, triglyceride, glucose, creatine kinase [CK] elevations) (Refer to Section 7.7 for toxicity management)

  Note: As per the mechanism of action of BLV, asymptomatic elevation of BA with BLV dosing in this study will not be documented as AEs.

- Participant request to discontinue for any reason
- Participant noncompliance
- Pregnancy during the study (refer to Appendix 11.4)
- Lost to follow-up
- Discontinuation of the study at the request of Gilead, regulatory agency, or an institutional review board (IRB)/independent ethics committee (IEC)

3.3.1.2. Criteria for Early Discontinuation for the Individual Participant from the Study

The participant will be discontinued from the study early in the following instances:

- Participant noncompliance
- Investigator discretion
- Lost to follow-up
- Discontinuation of the study at the request of Gilead or an IRB/IEC
- Withdrawal of consent
- Death

CCI [redacted]

3.3.3. Criteria for Early Discontinuation of the Study

The study will be discontinued in the following instances:

- The number and/or severity of AEs justifies discontinuation of the study
- Discontinuation of the study at the request of Gilead or an IRB/IEC

3.3.4. Loss to Follow-Up

Should the participant fail to return to the study site for a scheduled protocol-specified visit (eg, repeat laboratory assessments if the participant was discontinued early) or the participant fails to respond to the safety follow-up telephone call (7 days [± 2 days] following last administration of study drug), the site will need to make at least 3 attempts by telephone or email to contact the participant. After the third unsuccessful contact attempt, the site will send a letter to the participant via registered courier/mail and the participant must sign for the letter. The site must document all attempts to contact the participant. If a participant does not respond within 10 days after the letter is received, the participant will be considered lost to follow-up and no additional contact will be required.

3.3.5. Early Termination

Early termination (ET) assessments will be performed within 24 hours of prematurely discontinuing the study, if possible as outlined in Table 1 and in Section 6.6.1.

3.4. Clinic Confinement

Following the completion of screening procedures and study enrollment at admission, eligible participants will remain in the clinic for a period of 9 days, beginning on Day –1 until the completion of assessments on Day 8. Safety laboratory tests will be collected upon study site admission (Day –1); will be evaluated at the site's local laboratory to obtain results for participant's eligibility prior to dosing on Day 1. Baseline safety laboratory assessments will be performed on Day 1 and then participants will be administered daily injections of BLV and will undergo blood sampling for plasma PK and plasma BA PD assessments from Day 1 through Day 6. Additional sampling will be performed on Day 7 and Day 8 and participants will be discharged on Day 8. A follow-up telephone call to collect safety data will be made at 7 days (± 2 days) following last administration of study drug.

3.5. Definitions for Time of Primary Endpoint and End of Study

3.5.1. Primary Endpoint

The date for the last participant last visit for the primary endpoint is the date of the last visit to perform assessments for the primary analysis.

3.5.2. End of Study

The end of this study will be the last participant's last observation (or visit/telephone call).

3.6. Source Data

The source data for this study will be obtained from medical records, local laboratory, and/or specialty laboratory (for PK data).

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

For each group, up to approximately 20 non-HDV/HBV-infected male and nonpregnant/nonlactating female participants (10 participants with RI and a maximum of 10 matched control participants with normal renal function), aged 18 through 79 years inclusive, will be enrolled. Each participant with RI will have a matched control participant with a goal of obtaining approximately 16 evaluable participants (8 renal impaired and 8 matched controls) in each group.

The study will begin with the enrollment of Group A (10 severe renal impaired and 10 matched control participants). Following completion and evaluation of PK and safety data from Group A, additional optional groups (Groups B, C, and D) may or may not be initiated.

At screening, participants will have their eGFR measured and classified based on the CKD-EPI equation for renal function (expressed for serum creatinine, sex, and age) {Inker 2021}.

The CKD-EPI Creatinine equation (2021) is:

$$\mathbf{eGFR = 142 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012\ [if\ female]}$$

where:
eGFR (estimated glomerular filtration rate) expressed in mL/min/1.73 m²
S_{cr} (standardized serum creatinine) in mg/dL
κ is 0.7 for females and 0.9 for males
α is -0.241 for females and -0.302 for males
min indicates the minimum of S_{cr}/κ or 1.0
max indicates the maximum of S_{cr}/κ or 1.0
age is expressed in years

4.1.1. Participant Replacement

If necessary, replacement participants may be enrolled after discussion and approval from Gilead if participants do not complete all intensive PK procedures or the participant is considered nonevaluable. Replacement participants will not be enrolled for participants who discontinue the study due to study drug-related AEs.

4.2. Inclusion Criteria

Participants must meet all of the following inclusion criteria to be eligible for participation in this study:

All Participants:

1) Have the ability to understand and sign a written informed consent form (ICF), which must be obtained prior to initiation of study procedures.

2) Be aged 18 through 79 years, inclusive, at screening.

3) Have a calculated BMI of at least 18.0 kg/m² and no greater than 40.0 kg/m² at screening.

4) Participants assigned male at birth and participants assigned female at birth and of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 11.4.

5) Participants have not donated blood within 56 days of study entry or plasma within 7 days of study entry and must refrain from blood donation from clinic admission, throughout the study period, and continuing for at least 30 days following the last dose of study drug.

6) 12-lead electrocardiogram (ECG) evaluations at screening and admission must be without clinically significant abnormalities as assessed by the investigator.

7) Have no known liver disease with hepatic transaminases (aspartate aminotransferase [AST] and ALT) ≤ 3 × upper limit of normal (ULN) at screening.

8) Must be willing and able to comply with all study requirements.

Participants with RI:

Participants with RI must also meet the following additional inclusion criteria to be eligible for participation in this study:

9) Have RI classification at screening that has been unchanged (based on medical history, physical examination and clinical laboratory results with no clinically significant change) during the 90 days prior to study drug dosing, as determined by the investigator.

10) eGFR must be the following (using the CKD-EPI equation {Inker 2021}) based on serum creatinine as measured at the screening evaluation:

    a) Severe RI (Groups A and B): eGFR ≥ 15 to ≤ 29 mL/min/1.73 m²

    b) Moderate RI (Group C): eGFR ≥ 30 to ≤ 59 mL/min/1.73 m²

    c) Mild RI (Group D): eGFR ≥ 60 to ≤ 89 mL/min/1.73 m²

11) Hemoglobin ≥ 9 g/dL at screening.

12) Participants with diseases/conditions associated with RI (eg, cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, etc) and participants with other concomitant diseases not related to RI (eg, hypothyroidism, osteoporosis and many others) may be included provided that these diseases/conditions are clinically stable (as judged by the investigator, and in consultation with the medical monitor) and without impact on the study outcome.

13) For participants with RI who have not been on a stable dose of concomitant medications for at least 4 weeks prior to screening (or 5 half-lives, whichever is longer) and/or for whom dose changes are likely to occur during the study, should have their medications reviewed and approved by the sponsor.

Matched Control Participants:

In addition to the criteria listed for all participants, matched control participants must also meet the following additional inclusion criteria to be eligible for participation in this study:

14) Have an eGFR of at least 90 mL/min/1.73 m² (using the CKD-EPI equation) based on serum creatinine as measured at screening evaluation.

15) Matched for sex, age (± 10 years), and BMI (± 20%, 18.0 ≤ BMI ≤ 40.0 kg/m²) with the respective participant in the RI group.

16) Must, in the opinion of the investigator, be in good health based upon medical history, physical examination, vital signs, and screening laboratory evaluations.

4.3. Exclusion Criteria

Participants who meet *any* of the following exclusion criteria will not be enrolled in this study:

All Participants:

1) Positive serum pregnancy test at screening and upon admission in participants assigned female at birth. (Appendix 11.4).

2) Lactating/breastfeeding participant.

3) Participants assigned female at birth and of childbearing potential who plan egg donation and in vitro fertilization during study drug dosing and until end of contraception requirement.

4) Have received any study drug within 30 days (or 5 half-lives whichever is longer) prior to study dosing.

5) Have current alcohol or substance abuse judged by the investigator to potentially interfere with participant compliance or participant safety, or a positive drug or alcohol test at screening or admission.

6) Have a positive test result for the fourth generation HIV antibody/antigen test, HBsAg, or hepatitis C virus (HCV) antibody with detectable HCV viral RNA at screening.

   Note: Any previous treatment for a HCV infection must have been completed at least 12 weeks before screening.

7) Have poor venous access that limits phlebotomy.

8) Have been treated with systemic steroids, immunosuppressant therapies, or chemotherapeutic agents within 3 months prior to screening or is expected to receive these agents during the study (eg, corticosteroids, immunoglobulins, other immune- or cytokine-based therapies).

9) Have previous diagnosis of malignancy with the exception of basal cell carcinoma or squamous cell carcinoma localized to the skin.

10) Acute illness within 14 days prior to study drug administration unless mild in severity and approved by the investigator and sponsor's medical representative.

11) Have a history of any of the following:

    a) Significant serious skin disease, such as but not limited to rash, food allergy, eczema, psoriasis, or urticaria.

    b) Significant drug sensitivity or drug allergy (such as anaphylaxis or hepatoxicity or nephrotoxicity).

    c) Known hypersensitivity to the study drugs, their metabolites, or to formulation excipients (see Section 5.2).

    d) Significant cardiac disease in the past 2 years (including history of myocardial infarction based on ECG and/or clinical history, any history of ventricular tachycardia, congestive heart failure [New York Heart Association Class III or IV], or dilated cardiomyopathy with left ventricular ejection fraction ≤ 40%); or a family history of long QT syndrome, or unexplained death in the family, in an otherwise healthy individual between the ages of 1 and 30 years that in the clinical judgment of the investigator, may not be an appropriate candidate to participate in the study.

    e) Syncope, palpitations, or unexplained dizziness.

    f) Implanted defibrillator or pacemaker.

    g) Liver disease, including Gilbert syndrome.

12) Have any serious or active medical or psychiatric illness (including depression) that, in the opinion of the investigator, would interfere with participant treatment, assessment, or compliance with the protocol. This would include uncontrolled or unstable cardiovascular, hematologic, hepatic, pulmonary, endocrine, gastrointestinal, metabolic, neurological disease, or active infection.

13) Are unable to comply with study requirements or are otherwise believed, by the study investigator, to be inappropriate for study participation for any reason.

14) Requirement for ongoing therapy with or prior use of any prohibited medications listed in Section 5.6.

Participants with RI:

15) Recent history of reception of any blood or blood products or history of major bleeding within 4 weeks of dosing.

16) Positive test for drugs of abuse, including alcohol at screening or admission, with the exception of opioids and tetrahydrocannabinol (THC, marijuana) under prescription and verified by the investigator as for pain management. Participants who screen positive for benzodiazepines may be allowed if prescribed under the care of a physician and after review by the investigator and sponsor.

17) Received treatment with trimethoprim or cimetidine or tenofovir prodrugs (TDF or tenofovir alafenamide or [TAF]) (affects elimination of creatinine) or with competitors of renal tubular excretion (eg, probenecid, chronic high-dose nonsteroidal anti-inflammatory drugs) within 28 days of Day –1.

18) Received known nephrotoxic drugs (eg, aminoglycosides, amphotericin B, vancomycin, cidofovir, foscarnet, cisplatin, pentamidine, cyclosporine, tacrolimus, herbal remedies [eg, compounds with aristolochic acid]) within 28 days of Day –1.

19) Participants requiring or anticipated to require dialysis within 90 days of study entry.

20) Anticipated changes in concomitant medications or dosage used to treat symptoms of RI or associated comorbid conditions that could lead to clinically significant changes in medical conditions during the course of the study.

21) Acute renal failure (as judged by the investigator).

22) History of transplant (eg, kidney, liver) regardless of functionality.

23) History of nephrectomy.

24) Serum albumin concentration <25 g/L.

25) Uncontrolled treated/untreated hypertension (defined as a mean of 3 repeated measurements for systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg); current or documented history of repeated clinically significant hypotension or severe episodes of orthostatic hypotension (systolic blood pressure <90 mmHg and/or diastolic blood pressure <50 mmHg).

Matched Control Participants:

26) Have taken any prescription medications or over-the-counter medications, including herbal products, within 28 days prior to start of study drug dosing, with the exception of vitamins and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications.

5. STUDY INTERVENTIONS AND CONCOMITANT MEDICATIONS

5.1. Enrollment and Blinding

5.1.1. Enrollment

It is the responsibility of the investigator to ensure that the participant is eligible for the study prior to enrollment.

The study will begin with Group A (severe RI and with matched control participants). Additional groups of participants with severe, moderate and/or mild RI (and with matched control participants) may be included pending evaluation of PK and safety results in participants with severe RI (Group A).

At screening, study participants will be assigned a screening number at the time of consent. The renal function of all participants will be assessed, and the participants will be allocated into the respective renal function group.

Once eligibility has been confirmed following completion of the admission procedures on Day –1, eligible participants will be enrolled and assigned a participant number.

All screening and admission (Day –1) tests and procedures must be completed and reviewed by the investigator prior to the administration of the first dose of study drug on Day 1. Once a participant number has been assigned to a participant, it will not be reassigned to another participant. If necessary, replacement participants may be enrolled after discussion and approval by the sponsor. A new unique participant number will be assigned to the replacement participant.

5.1.2. Blinding

Blinding to treatment assignments or data will not be performed in this study.

Study drug will be dispensed by the study pharmacist, or designee, in an open-label fashion to participants.

5.2. Description and Handling of Bulevirtide

5.2.1. Formulation

Bulevirtide for injection, 2 mg, is a preservative-free, white to off-white lyophilized powder containing 2 mg BLV that is to be reconstituted with 1 mL of sterile water for injection prior to SC injection. In addition to the active ingredient, BLV for injection, 2 mg, contains the following inactive ingredients: mannitol, sodium carbonate, sodium bicarbonate, water for injection, sodium hydroxide, and hydrochloric acid.

Bulevirtide for injection, 10 mg, is a preservative-free, white to off-white to yellow lyophilized solid containing 10 mg BLV that is to be reconstituted with 1 mL of sterile water for injection prior to SC injection. In addition to the active ingredient, BLV for injection, 10 mg, contains the following inactive ingredients: mannitol, histidine, sucrose, water for injection, sodium hydroxide, and hydrochloric acid.

5.2.2. Packaging and Labeling

Bulevirtide for injection, 2 mg, is supplied as a sterile product in a single use, 2R Type I clear glass vial. Each vial is sealed with an elastomeric stopper and an aluminum overseal with a blue, plastic flip-off cap.

Bulevirtide for injection, 10 mg, is supplied as a sterile product in a single use, 2R Type I clear glass vial. Each vial is sealed with an elastomeric stopper and an aluminum overseal with a green, plastic flip-off cap.

Study drug(s) to be distributed to study sites in the US shall be labeled to meet applicable requirements of the US FDA, and/or other local regulations.

Gilead or designated distribution depots will distribute study drug to sites according to Good Manufacturing Practices (GMP) requirements.

5.2.3. Storage and Handling

Bulevirtide for injection, 2 and 10 mg, will be provided by Gilead. Bulevirtide for injection vials (2 mg and 10 mg) should be stored in a refrigerator between 2°C to 8°C (36°F to 46°F) prior to use. Bulevirtide for injection vials (2 mg and 10 mg) should be kept in the original carton to protect from light. Storage conditions are specified on the label. Until dispensed to the participants, all vials of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the sterility, stability, and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied. Keep the vials tightly closed to protect from moisture.

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.

Bulevirtide for injection must be reconstituted with sterile water for injection prior to use. Reconstituted BLV for injection must be used right away and should not be saved for later use. The total storage time of reconstituted solution containing BLV for injection should not exceed 2 hours at room temperature.

Refer to the pharmacy manual for detailed instructions.

5.3. Dosage and Administration

The study will begin with the dosing of Group A and proceed to optional groups (Groups B, C, or D) if applicable. For each group, following completion of screening and admission assessments, eligible participants will be administered BLV by SC injection QD for 6 days starting on Day 1 by assigned study staff, at the doses described in Section 3.1.1. During each study treatment, each dose will be administered by assigned study staff at approximately the same time (± 30 minutes) each morning on Days 1 to 6 following an overnight fast (no food or drinks, except water) for at least 8 hours prior to dosing.

Refer to Pharmacy manual for BLV injection and administration instructions.

To prepare study drug for injection, the contents of each BLV vial assigned for administration on the day of dosing will be reconstituted with 1 mL of the supplied diluent and administered with the supplied syringe. Study drug should be reconstituted on the day of dosing immediately before dosing. The total storage time of reconstituted solution containing BLV for injection should not exceed 2 hours at room temperature.

5.3.1. Administration Site Reactions

Bulevirtide is intended for SC injection, and has been associated with the risk for injection site reactions such as swelling, redness, irritation, itchiness, infection, hematoma and local pain. Any instances of injection site reactions are to be reported as AEs and graded using the CTCAE toxicity grading scale, Version 5.0.

5.4. Fasting and Meals

Each dose will be administered via SC injection at approximately the same time (± 30 minutes) each morning on Days 1 through 6, following an overnight fast (no food or drinks, except water) for at least 8 hours prior to dosing.

The extent of food consumption during in-clinic days will be monitored.

On the days of intensive PK and BA PD sampling, and urine collection (Day 1 and Day 6), participants will continue to fast until after collection of the 4-hour PK sample, relative to study drug dosing. Additionally, participants will be restricted from water consumption from 1 hour before until 2 hours after dose administration.

A standardized lunch (meal calories and fat content will be prespecified) will be provided to participants after the 4-hour postdose blood draw (when relevant), and a standardized dinner (meal calories and fat content will be prespecified) will be provided at approximately 10 hours postdose on each day that the participants are in the clinic. Water may be consumed ad libitum.

A standardized breakfast will be provided after dosing on Days 2 to 5 and after collection of trough PK and BA samples on Day 7 and Day 8. Water may be consumed ad libitum, however participants with RI should observe the restriction on fluid consumption related to their underlying disease.

Participants with RI having comorbidities can take their concomitant medications with the first meal of the day if the medication is to be administered with food or fasting if needed as guided by the prescribing physician and approved by the medical monitor.

As BA are being monitored in this study, the caloric count of meals associated with bile acids collection will be standardized and the timing and consumption of meals will be monitored.

All meals and/or snacks given to participants during their stay in the clinical study facility will be standardized for all matched control participants and should be similar in calorie and fat content and taken at approximately the same time each day. All meals and/or snacks given to participants with RI will follow local recommendations regarding fasting and diet. All meals provided must be approved by the sponsor. Components of meals (eg, margarine, jelly, bread) should be given to participants in individual portions (eg, 1 tablespoon) per the approved meal schedule. The provision of meal components in bulk (eg, a jar of jelly for participants to share) should not be practiced. All meals should be given at approximately the same time each day.

5.5. Dispensing, Accountability, and Disposal or Return of Study Drug

The investigator (or designee, eg, study site pharmacist) will acknowledge receipt of the study drug (after reviewing the shipment's content and condition) from Gilead (or designee). The investigator will maintain an accurate inventory of all study drug. Each dose of the study drug administered at the study site will be administered by qualified study site staff. The dose of study drug administered to participants in the clinic under the supervision of staff will be accurately recorded on the Study Drug Accountability form provided by Gilead (or on equivalent documentation maintained by the study site), which indicates the date and quantity of each dosage formulation dispensed to individual participants.

Gilead recommends that used study drug should be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for the electronic Trial Master File (eTMF). If study drug is destroyed onsite, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

For both disposal options listed above, the study monitor must first perform drug accountability during an onsite monitoring visit. The study monitor will review study drug supplies and associated records at periodic intervals.

Unused study drug should be stored at the site, pending further instructions from Gilead.

5.6. Concomitant Medications and Other Protocol Restrictions

5.6.1. Concomitant Medications

Participants with RI:

Concomitant use of certain medications or herbal/natural supplements with study drug may result in PK or PD interactions resulting in increases or decreases in exposure of study drug or these medications or alterations in PD effects of study drug or these medications. Concomitant medications taken within 30 days of screening through the follow-up visits must be recorded in the source documents and case report form (CRF)/electronic case report forms (eCRFs).

All prior medication(s) with long-lasting biologic effect even after discontinuation, such as systemic corticosteroid, immunosuppressant therapies, or chemotherapeutic agents must be reviewed by the medical monitor to determine the participant's eligibility.

Participants with RI who have not been on a stable dose of concomitant medications for at least 4 weeks prior to screening (or 5 half-lives, whichever is longer) and/or for whom dose changes are likely to occur during the study should have their medications reviewed and approved by the sponsor.

All concomitant medications, including over-the-counter and herbal products, must be approved by the investigator and medical monitor prior to study enrollment and study drug administration. Any changes in concomitant medications during the study should be reviewed and approved by the medical monitor. The following medications are excluded during the study (from screening until discharge) for participants with RI:

- Any and all illegal or illicit drug use, including use of prescription drugs outside the care of the prescribing physician (excluding prescribed benzodiazepines, opioids, and tetrahydrocannabinol [THC, marijuana] verified by the investigator, and with the investigator and sponsor review and approval)

- Chronic systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (eg, infliximab) or other immune or cytokine based therapies within 3 months prior to screening

- Investigational agents or devices for any indication

- Drugs that are reported to be clinical inhibitors of OATP1B1/3 {Food and Drug Administration (FDA) 2022, University of Washington School of Pharmacy 2022}:

  — Atazanavir, clarithromycin, cyclosporin, elbasvir, enasidenib, fostemsavir, gemfibrozil, grazoprevir, lopinavir, ritonavir, rifampin, roxadustat, sofosbuvir, velpatasvir, voxilaprevir

- Drugs that have been reported in vitro to be inhibitors of NTCP function (IC_{50} or K_i < 20 µM from NTCP transfected cells) {University of Washington School of Pharmacy 2022}

  — aprocitentan, bosentan, cyclosporine, fluvastatin, furosemide, glyburide (glibenclamide), itraconazole, irbesartan, macitentan, piroxicam, propranolol rifamycin, ritonavir, rosiglitazone, saquinavir, simeprevir, simvastatin, sulindac, sulfasalazine, tolvaptan, zafirlukast

  Note: Fluvastatin and simvastatin are not allowed due to being both NTCP substrates and weak inhibitors)

  — In scenarios where potential participants are receiving these medications, exploration by the medical monitor and investigator into alternative medications of the same therapeutic class and/or for the same indication is encouraged

- Use of any of the following medications:

  — Drugs that affect elimination of creatinine (trimethoprim, cimetidine, tenofovir prodrugs [TDF or TAF])

  — Competitors of renal tubular excretion (probenecid, chronic high-dose nonsteroidal anti-inflammatory drugs)

  — Known nephrotoxic drugs (eg, aminoglycosides, amphotericin B, vancomycin, cidofovir, foscarnet, cisplatin, pentamidine, cyclosporine, tacrolimus, herbal remedies [eg, compounds with aristolochic acid]).

- In scenarios where potential participants are receiving these medications, exploration by the medical monitor and investigator into alternative medications of the same therapeutic class and/or for the same indication is encouraged.

- Medications to treat disease conditions that are excluded from the protocol are not listed under this concomitant medication section and are disallowed in the study.

Should participants have the need to initiate treatment with any excluded concomitant medication, the investigator should make every effort to consult the medical monitor and seek approval prior to initiation of the new medication. In an instance where an excluded medication must be initiated prior to discussion with the medical monitor (eg, a medical emergency), the investigator must notify Gilead as soon as he/she is aware of the use of the medication.

Matched Control Participants:

The following medications are excluded from screening until discharge for participants with normal renal function:

- Any prescription medications and over-the-counter medications, including herbal products and antacids, with the exception of vitamins, and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications. However, the short-term use of topical hydrocortisone cream or A&D ointment to treat minor skin irritation due to ECG leads will be allowed. If a participant requires use of a disallowed medication, a request for such use must be reviewed by the sponsor and if approved, participants may continue to participate in the study.

- Any and all illegal or illicit drug use, including use of prescription drugs outside the care of the prescribing physician.

- Recreational or medical cannabinoids or derivatives.

Should participants have the need to initiate treatment with any excluded concomitant medication, the investigator should make every effort to consult the medical monitor and seek approval prior to initiation of the new medication. In an instance where an excluded medication must be initiated prior to discussion with the medical monitor (eg, a medical emergency), the investigator must notify Gilead as soon as he/she is aware of the use of the medication.

5.6.2. Other Protocol Restrictions

- Participants will be required to refrain from the consumption of beverages containing alcohol products 72 hours prior to the first dose of study drug and during the course of the study through the follow-up visit.

- Participants will be required to refrain from the use of nicotine or nicotine-containing products while confined in the clinic to ≤ 5 cigarettes per day, or its nicotine equivalent.

- While confined at the study site, tea, coffee, chocolate, and other foods and beverages containing caffeine and other methyl xanthines will be prohibited on each dosing day. At all other times, caffeine-containing beverages and foodstuffs may be served or withheld in accordance with normal practice at the site. Caffeine-containing beverages and foodstuffs will not be restricted while participants are outside of the clinic.

- Participants will be required to refrain from consumption of grapefruit juice, grapefruits, and Seville orange and juice from 72 hours prior to the first dose of study drug and during the course of the study through the end of study drug administration period.

- Participants will be encouraged to avoid strenuous or prolonged exercise, as well as saunas, steambaths, and sunbathing or other prolonged ultraviolet exposure (eg, in a tanning salon) from the screening evaluation until completion of the follow-up visit, as these activities are known to affect certain clinical laboratory test parameters (eg, CK) and will provide false indicators of a potentially treatment-related toxicity.

- There are no substantial safety data regarding the concomitant administration of the coronavirus disease 2019 (COVID-19) vaccines and BLV. Participants are allowed to receive the COVID-19 vaccine, and study visits should continue as planned if vaccination occurs while the participant is on the study. Investigators should follow local guidelines for concomitant administration of the COVID-19 vaccines with the study drug.

Upon admission to the clinic, each participant will be questioned as to their compliance with the above protocol restrictions. If a participant is unable to comply with any of the restrictions described above, the participant's continued participation in the study will be reevaluated by the investigator in consultation with the sponsor.

6. STUDY ASSESSMENTS

The study procedures to be conducted for each participant enrolled in the study are detailed in Table 1.

Any deviation from protocol procedures should be noted in the participant's clinical chart and appropriate eCRFs. In addition, the sponsor should be promptly notified of any protocol deviations.

The study site will not initiate dosing until the following have all been met:

- The IRB/IEC/other applicable regulatory agencies have reviewed and approved the study and the informed consent document.
- All requested regulatory documents have been submitted to and approved by Gilead.
- A master services agreement and/or study agreement is executed.
- The study initiation meeting has been conducted by Gilead (or designee).

The initiation meeting will include but is not limited to a review of the protocol, the IB, study drug(s), and investigator responsibilities.

Documentation of the personally signed and dated ICF for each participant, using the study-specific, IRB/IEC-approved ICF, is required before initiating the screening process.

6.1. Informed Consent

Written informed consent must be obtained from each participant before initiation of any screening procedure. After a participant has provided informed consent, the investigator and other study personnel will determine if the participant is eligible for participation in the study (Section 6.3.2).

6.2. Participant Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

It is the responsibility of the investigator to ensure that participants are eligible to participate in the study prior to enrollment and continue to remain eligible throughout the study.

Once the ICF has been obtained, all screening and admission tests and assessments have been assessed, and study eligibility has been confirmed, participants will be enrolled to receive study drug on Day 1.

Participants will be administered the study treatments as described in Section 5.3.

6.3. Instructions for Study Procedures

6.3.1. Adverse Events

From the time informed consent is obtained through the first administration of study drug, all SAEs, as well as any AEs related to protocol-required procedures will be recorded on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history.

After study drug administration, all AEs and SAEs will be reported. Evaluation of AEs will occur at the visits shown in Table 1. See Section 7 for additional details.

6.3.2. Screening Assessments

Prospective participants should be screened no more than 28 days prior to administration of the first dose of study drug. If a participant does not begin the treatment phase within this 28-day window, all screening evaluation procedures must be repeated. Screening laboratory assessments may be repeated once within 28 days prior to administration of study drug for exclusionary laboratory values if, in the investigator's opinion, one of the following are met: there is reason to believe the retest value will be within accepted parameters, if the initial value was deemed to be inaccurate or inconsistent with the participant's previous result(s), if the initial value was generated in error (eg, mishandled sample), or there is another relevant extenuating circumstance. In any instance, the site should obtain approval from Gilead prior to repeating the laboratory assessment.

A sufficient number of participants will be screened to identify planned number of participants for enrollment.

Participants should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the screening visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

Written informed consent must be obtained from each participant before initiation of any screening procedure. After a participant has provided informed consent, the investigator and other study personnel will determine if the participant is eligible for participation in the study. The screening assessment will include a review of the inclusion/exclusion criteria and completion of all screening procedures as outlined in Table 1 and described in the following text.

Eligible participants meeting all of the inclusion criteria and none of the exclusion criteria will be instructed on all protocol requirements, including the restrictions on concomitant medication usage and other substances as well as consumption of food or beverages containing alcohol, caffeine, or xanthine. Participants will be asked to arrive at the study site on Day –1 for admission assessments.

6.3.3. Admission Assessments

Participants should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the admission visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection.

Participants meeting all eligibility criteria following the screening evaluation will return to the site for admission assessments on Day –1. The admission evaluations and/or procedures are outlined in Table 1.

Prior to dosing on Day 1, the results of the clinical and laboratory evaluations (as described in Table 1) must be reviewed by the investigator to confirm the continued eligibility of each participant to participate in the study, including have received a negative COVID-19 polymerase chain reaction (PCR) test at Day –1 admission. If study site cannot obtain results from the local laboratory in time for Day 1 dosing, then COVID-19 rapid antigen test/rapid PCR is acceptable.

At the time of enrollment, participants will be assigned a participant number as described in Section 5.1.1. Participants will remain confined to the study clinic for the duration as described in Section 3.4 and Table 1.

The study will be initiated with dosing of participants in Group A. Following completion of all participants and evaluation of all safety and PK data from Group A, an internal safety review meeting will be held by the sponsor to determine if the study should proceed to any optional groups (Groups B, C, and D).

6.3.4. Treatment Assessments

Study procedures and assessments are outlined in Table 1.

6.3.5. Pharmacokinetic and Pharmacodynamic Assessments

6.3.5.1. Plasma Sample Collection for Pharmacokinetics and Pharmacodynamics

Intensive plasma PK and total plasma BA sampling for PD will occur relative to the dosing of BLV at the following time points:

Day 1 at predose (≤ 30 minutes before dose), 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 hours postdose, and at the ET visit, as applicable.

Day 6 at predose (≤ 30 minutes before dose), 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 hours postdose, and at the ET visit, as applicable.

A trough (predose) PK and PD biomarker BA sample (≤ 30 minutes before dose) will be collected on Day 2 through Day 5 and at 24 hours post Day 6 dose (Day 7) and 48 hours post Day 6 dose (Day 8), and the ET visit (as applicable).

A time window of ± 10% will be allowed for samples collected through 4 hours postdose. All other samples collected beyond 4 hours postdose will have a ± 30 minute window.

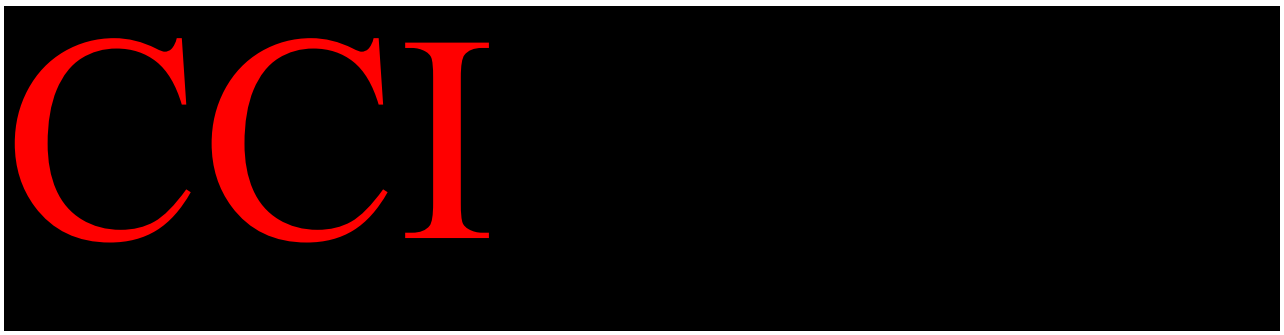
Clinical staff should make every effort to ensure that sampling time is as close as possible to nominal time. The exact time and date of the blood draw must be recorded. For all plasma BA and plasma PK samples, a primary and backup sample will be collected and the backup sample will be stored for potential further analysis or reanalysis.

Plasma concentrations of BLV and plasma concentrations of total BA will be determined, and BLV PK and bile acids PD parameters will be estimated.

Plasma Protein Binding Evaluation: On Day 1, additional blood samples will be collected predose (≤ 30 minutes prior to BLV dosing); and at 2 hours and 12 hours postdose. These samples in addition to other predose and postdose PK samples may be utilized for plasma protein binding evaluation and percent plasma protein binding may be determined. A single blood sample for PK analysis will also be collected at the ET visit (if applicable) and may be analyzed.


CCI


CCI


CCI

6.3.6. Plasma Collection for Immunogenicity Evaluation

Immunogenicity sampling will occur on Days 1 and 6 at predose (≤ 30 minutes before dose). Plasma will be evaluated for the presence of ADA to BLV. ADA may be further characterized for neutralizing activity.

6.4. Safety Assessments

Safety assessments will include physical examination (complete or symptom-driven), vital signs, height, weight, clinical laboratory tests, urine drug and alcohol assessments, 12-lead ECG, pregnancy testing, fourth generation HIV antibody/antigen test, HBsAb, HBsAg, HCV antibody, and HCV RNA testing, and assessment of AEs.

All safety assessments will be completed predose unless otherwise specified. The Day 1 safety labs will be used for baseline values. Safety will be evaluated throughout the study. Refer to Table 1 for a schedule of assessments.

6.4.1. Electrocardiogram Assessment

Participants should rest quietly in the supine position for a minimum of 10 minutes prior to each scheduled ECG acquisition and should remain in that position until the recording is complete.

There should be no environmental distractions (including TV, radio, video games, and conversation) while the participants are resting prior to and during the recordings. Electrocardiograms will be recorded using the site's standard ECG equipment. All ECGs will be obtained using instruments that analyze data using the same algorithms and produce the same data for interpretation. Electrode placement will be performed according to the method of Wilson, Goldberger, and Einthoven with a check to confirm that the aVR lead is not inverted.

The investigator or other qualified individuals at the study site will review ECGs to assess for changes in ECG intervals and morphology as compared with pretreatment ECGs.

Collection of additional ECGs for routine safety monitoring at additional time points or days is at the discretion of the investigator based on GCP.

6.4.2. Physical Examination

Physical examinations conducted throughout the study will be a complete physical examination or a symptom-driven physical examination, as outlined in Table 1. The complete physical examination conducted at screening will also include the following assessments:

- Review medical history, including history of allergies, prior and current use of nicotine or nicotine-containing products, alcohol and illegal drug use, and prior (within 30 days) and current medication use.

6.4.3. Vital Signs

Vital sign measurements include resting blood pressure, heart rate, and body temperature and should be taken once participants are seated or in the supine position. Participant position for measurement should be kept consistent throughout the study. Refer to Table 1 for vital signs collection time points.

6.4.4. Body Mass Index

Height and weight will be collected at screening for calculation of BMI for inclusion criteria.

6.4.5. Clinical Laboratory Tests/Assessments

Blood and urine samples for safety evaluations will be collected throughout the study as outlined in Table 1 and Table 3.

Table 3. Laboratory Analytes

Safety Laboratory Measurements				Virological Measurements	Other Laboratory Measurements
Chemistry (Serum or Plasma)	**Hematology**	**Urinalysis**	**Coagulation**		
• AST • ALT • Albumin • Total protein • Alkaline phosphatase • Triglycerides • Total cholesterol • High density lipoprotein • Low density lipoprotein • Creatine kinase • Serum creatinine • eGFR[a] • Lactic acid dehydrogenase • BUN • Total bilirubin • Direct bilirubin • Indirect bilirubin • GGT • Glucose • Lipase[b] • Calcium • Inorganic phosphate • Bicarbonate • Sodium • Potassium • Chloride • Uric acid (serum) • Total BA	• RBC (count and morphology) • Hemoglobin • Hematocrit • MCH • MCHC • MCV • RDW • Platelets • WBC total • WBC differential • ANC • Eosinophils • Basophils • Lymphocytes • Monocytes • Neutrophils • Reticulocytes	• pH • Specific gravity • Color • Protein • Glucose • Ketones • Hemoglobin (erythrocytes) • Leukocytes • Microscopic analysis, if urine is positive for protein, leukocytes, or hemoglobin	• Prothrombin time • Partial thromboplastin time • INR	• HIV antibody/antigen test • HBsAb • HBsAg • HCV antibody (reflex to HCV RNA if positive)	• Serum/urine pregnancy test • FSH • Urine drug and alcohol testing

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BA = bile acids; BLV = bulevirtide; BUN = blood urea nitrogen; CK = creatine kinase; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FSH = follicular stimulating hormone; GGT = gamma glutamyl transferase; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RDW = red blood cell distribution width; RNA = ribonucleic acid; ULN = upper limit of normal; WBC = white blood cell
Refer to Table 1 for collection time points.
a eGFR will be calculated using the CKD-EPI equation (expressed for serum creatinine, sex. and age)
b Reflex lipase testing will be performed in participants with total amylase greater than 1.5 × ULN

6.4.5.1. Blood Samples

Blood samples will be collected for the following laboratory analyses:

- Hematology: hematocrit, hemoglobin, platelet count, red blood cell count, red blood cell morphology, mean corpuscular hemoglobin; mean corpuscular hemoglobin concentration, mean corpuscular volume, red blood cell distribution width, white blood cell count with differential (absolute and percentage), including reticulocytes, lymphocytes, monocytes, absolute neutrophil count, neutrophils, eosinophils, and basophils

- Coagulation panel: prothrombin time, partial thromboplastin time, and international normalized ratio

- Chemistry (fasting): alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total BA (for safety assessments; total BA for PD assessments will be drawn separately), gamma glutamyl transferase (GGT), total protein, albumin, triglycerides, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), lactic acid dehydrogenase, CK, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine (see below Section 6.4.6 for eGFR), glucose, inorganic phosphate, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in participants with total amylase greater than 1.5 × ULN)

- Serum pregnancy test (females of childbearing potential only) at screening and admission Day –1

- Follicle-stimulating hormone testing (screening only): participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure

- Fourth generation HIV antibody/antigen test, HBsAb, HBsAg, HCV antibody, and HCV RNA testing (screening only)

Upon study site admission (Day –1), safety laboratory tests will be collected and will be sent to the site's local laboratory to obtain results in time for enrollment on Day 1. Eligibility will be determined based on local laboratory results. The Day 1 safety labs will be used for baseline values.

6.4.5.2. Urine Samples

Urine samples will be collected for urinalysis and alcohol and drug screen assessments which include: amphetamines/3,4-methylenedioxymethamphetamine (MDMA), tricyclic antidepressants, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, methadone, and phencyclidine.

- If study site cannot perform urine alcohol or obtain results from the local laboratory in time for enrollment on Day 1, then an alcohol breathalyzer test is acceptable.

- Point of care pregnancy test may be used at site if serum pregnancy test result is not available prior to dosing.

6.4.6. Estimated Glomerular Filtration Rate

Serum creatinine will be collected at screening to calculate eGFR for inclusion criteria. The eGFR will be calculated using the CKD-EPI creatinine equation (expressed for sex and age) for allocation to the RI group based on serum creatinine as measured at screening (refer to Section 4.1 for CKD-EPI creatinine equation).

In addition, eGFR values will be estimated at admission (Day –1), predose Day 1 to 6, Day 7, and at discharge (Day 8), and at ET visit if applicable.

6.4.7. Concomitant Medications/Protocol Restrictions

Review of concomitant medications, and review of protocol restrictions will occur at the times shown in Table 1. See Sections 4.3 and 5.6 for more information about concomitant medications.

6.5. Posttreatment Assessments

Participants will be discharged from the clinic on Day 8, following all morning assessments as outlined in Table 1.

All participants will be contacted for evaluation of AEs, by follow-up telephone call at Day 13 (± 2 days) ie, 7 days (± 2 days) following last administration of study drug.

6.6. Assessments for Early Discontinuation from Study Intervention and from the Study

6.6.1. Assessments for Early Discontinuation from Study Intervention

If a participant discontinues study treatment dosing (see Section 3.3), for example as a result of an AE, every attempt should be made to keep the participant and continue to perform procedures for stabilization per the investigator.

If the participant withdraws consent from the study, the ET evaluations and/or procedures outlined in Table 1 should be performed within 24 hours of permanently discontinuing the study if possible.

Evaluations indicating abnormal results believed to be possibly or probably related to study treatment at the ET visit should be repeated weekly or as often as deemed appropriate by the investigator until the abnormality resolves, returns to baseline visit levels, or is otherwise explained.

6.6.2. Assessments for End of Study

A participant who completes the study will undergo assessments and procedures for discharge on Day 8 as specified in Table 1. Additionally, as described in Section 6.5, a safety follow-up at end of study will be conducted by telephone on Day 13 ± 2 days.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a study drug that does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures, or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations in which an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, or social and/or convenience admissions).
- Overdose without clinical sequelae (see Section 7.1.3).
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented medical history.

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

A SAE is defined as an event that, at any dose, results in the following:

- Death.
- A life-threatening situation (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Inpatient hospitalization or prolongation of existing hospitalization.

- Persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- A medically important event or reaction; such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.3. Study Drugs and Gilead Concomitant Therapy Special Situation Reports

Special situations reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit or falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a participant.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively that is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the participant has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one’s professional or nonprofessional occupation.

Drug interaction is defined as any drug-drug, drug-food, or drug-alcohol interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine is defined as any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drug and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship for each study drug using clinical judgment and the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).
- **Yes:** There is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture, SC injection or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the CTCAE, Version 5.0. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 11.5).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study medication, the following types of events must be reported on the applicable eCRFs: all SAEs and any AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study treatment, all AEs will be collected, regardless of cause or relationship, throughout the duration of the study until the end of study including the protocol-defined posttreatment follow-up period and will be reported on the eCRFs as instructed.

All AEs and clinically significant laboratory abnormalities will be followed until resolution or stability of the abnormality has been demonstrated, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the participant first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and Patient Safety (PS) as instructed below in this section. This also includes any SAEs resulting from protocol associated procedures performed after informed consent is signed.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if an investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of the study drug, the investigator should promptly document and report the event to Gilead PS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead's PS (Section 7.4.2).

Adverse events and SAEs resulting from SSRs must be reported in accordance with the AE and SAE reporting guidance (Section 7.3).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered study drug), that occurs after the participant first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead's PS utilizing the paper SSR (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

Special situations involving non-Gilead concomitant medications does not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situations Reports

7.4.1. Serious Adverse Event Reporting Process

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.

Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the participant's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Paper Serious Adverse Event Reporting Process

All SAEs will be recorded on the SAE report form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead PS from ICF signature throughout the duration of the study, including the protocol-required follow-up period. Additionally, the SAE must be captured on the applicable eCRF.

Gilead PS
Email: Safety_FC@gilead.com
or
Fax: +1-650-522-5477

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Study Drug

All SSRs will be recorded on the special situations report form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead PS from study drug initiation throughout the duration of the study, including the protocol required posttreatment follow-up period.

Gilead PS
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

7.4.2.2. Reporting Process for Gilead Concomitant Medications

Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead PS utilizing the paper SSR form and transmitted to:

Gilead PS
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs because of a non-Gilead concomitant medication, must be reported as an AE.

7.4.2.3. Pregnancy Reporting Process

The investigator should report pregnancies in female study participants who are identified after initiation of study drug and throughout the study, including the protocol required follow-up period to Gilead PS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

Gilead PS
Email: Safety_FC@gilead.com
or
Fax: +1-650-522-5477

The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome poststudy must be reported to the Gilead PS.

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to Gilead PS using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PS. Gilead PS contact information is as follows: email: Safety_FC@gilead.com and fax: +1-650-522-5477.

Refer to Appendix 11.4 for Pregnancy Precautions, Definition for Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable FDA Code of Federal Regulations, the European Union Clinical Trials Directive (2001/20/EC)/EU Regulation 536/2014], and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, which may be in the form of line-listings, serious adverse drug reactions, or suspected unexpected serious adverse reactions (SUSARs). In accordance with the European Union Clinical Trials Directive (2001/20/EC)/EU Regulation 536/2014, Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IRB or IEC in concerned member states of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using RSI specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2, respectively. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis (eg, anemia) will be recorded and not the laboratory result (ie, decreased hemoglobin).

Note: In accordance with the mechanism of action of BLV, asymptomatic elevation of BA with BLV dosing in this study will not be documented as laboratory toxicities.

Severity should be recorded and graded according to the CTCAE, toxicity grading scale, Version 5.0 (Section 7.2.2 and Appendix 11.5). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Toxicity Management

Bulevirtide injection will be administered to participants at the site under close supervision. Healthcare professionals administering the SC injections should have the appropriate medication available for immediate use in case of hypersensitivity or injection-related reactions. The participant should be treated according to the standard of care for management of hypersensitivity reaction or injection-related reactions.

All clinical and clinically significant laboratory toxicities will be managed as outlined below:

- Grade 3 or 4 clinically significant laboratory toxicities should be confirmed by repeat testing as soon as possible, and preferably within 3 calendar days after receipt of the original test results. The study drug may be continued without dose interruption for a clinically insignificant Grade 3 and 4 laboratory abnormality (eg, CK elevation after strenuous exercise, triglyceride elevation that is nonfasting, or that can be medically managed). Recurrence of laboratory abnormalities considered unrelated to the study drug may not require permanent discontinuation.

- Grade 3 or 4 clinical events if considered unrelated to the study drug may not require dose interruption and continuation of the investigational product is at the discretion of the investigator.

The Gilead medical monitor should be consulted prior to study drug discontinuation when medically feasible.

7.7.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

- Continue study drug at the discretion of the investigator.

7.7.2. Grade 3 and Grade 4 Laboratory Abnormality or Clinical Event

- For a Grade 3 or Grade 4 clinical event or clinically significant laboratory abnormality confirmed by repeat testing considered to be related to the study drug, study drug should be permanently discontinued, and the participant managed according to local practice. The participant should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 3 or Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor, and the appropriate course of action will be discussed and decided. Whether or not considered treatment related, all participants experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Any questions regarding toxicity management should be directed to the Gilead medical monitor.

8. STATISTICAL CONSIDERATIONS

Details of the statistical methods will be provided in the statistical analysis plan, including any deviations from the original statistical analyses planned.

8.1. Analysis Objectives and Endpoints

Objectives and endpoints are listed in Section 2.

8.2. Planned Analyses

8.2.1. Interim Analysis

Prior to the final analysis, interim analyses may be conducted and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program.

8.2.2. Final Analysis

The final analysis will be performed after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The analysis of the primary endpoints will be conducted at the time of the final analysis.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all participants enrolled into the study after screening. This is the primary analysis set for safety listings.

8.3.1.2. Safety Set

The Safety Analysis Set will include all enrolled participants who received at least 1 dose of study drug BLV.

8.3.1.3. Pharmacokinetics Set

The plasma PK Analysis Set will include all enrolled participants who received at least 1 dose of BLV and had at least 1 measurable plasma PK concentration data reported by PK laboratory for the respective analyte. The urine PK Analysis Set will include all enrolled participants who received at least 1 dose of BLV and had at least 1 measurable urine PK concentration data reported by PK laboratory for BLV.

8.3.1.4. Pharmacodynamics Set

The plasma PD Biomarker Analysis Set will include all enrolled participants who received at least 1 dose of study drug BLV and had at least 1 measurable plasma PD concentration value reported for each respective analyte. The urine PD Analysis Set will include all enrolled participants who received at least 1 dose of study drug BLV and had at least 1 measurable urine PD concentration value reported for BA.

8.3.1.5. Immunogenicity Set

The Immunogenicity Analysis Set will include all enrolled participants who received at least 1 dose of BLV, had at least 1 blood sample collected for immunogenicity evaluation before any BLV administration and had at least 1 blood sample collected after administration of BLV.

8.3.2. Data Handling Conventions

For summary statistics, PK and PD concentration values below the limit of quantitation will be treated as zero at predose and missing for postdose time points.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation (LLOQ) or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is less than 20, a value of 19 will be assigned; if the result of a continuous laboratory test is less than 20.0, a value of 19.9 will be assigned).

Missing data can have an impact upon the interpretation of the study data. As this study is of short duration, it is anticipated that missing data will be minimal. In general, values for missing data will not be imputed. However, a missing pretreatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized and descriptive statistics will be provided. Demographic summaries will include sex, race/ethnicity, and age. Baseline data will include a summary of height, weight, BMI, and eGFR by the CKD-EPI equation.

8.5. Safety Analysis

All safety data collected on or after the date that study drug was first administered up to the date of last dose of study drug plus 7 days (± 2 days) will be summarized by renal function group and dose level (according to the study drug dose received) using the Safety Analysis Set.

8.5.1. Extent of Exposure

A participant’s extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be listed.

8.5.2. Adverse Events

Clinical and laboratory AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high-level group term, high-level term, preferred term (PT), and lower-level term will be attached to the clinical database.

Adverse event data will be listed by participant. Treatment-emergent AEs (TEAEs), serious TEAEs, and TEAEs leading to permanent study drug discontinuation will be summarized by renal function group, dose, and SOC and PT using the current version of MedDRA.

8.5.3. Laboratory Evaluations

Listings of individual participant laboratory results will be provided. Laboratory results and changes from baseline values for selected laboratory tests will be summarized by renal function group and dose at scheduled visits. The incidence of treatment-emergent graded laboratory abnormalities will be summarized by renal function group and dose.

8.5.4. Other Safety Evaluations

Vital signs and ECG data will be summarized by renal function group and dose.

8.6. Pharmacokinetic and Pharmacodynamic Analysis

The following plasma PK parameters will be calculated for BLV, as applicable: AUC_{tau}, $C_{max\ ss}$, $AUC_{0\text{-}24,}$ C_{max}, T_{max}, $t_{1/2}$, CL_{ss}/F, and V_{ss}/F.

The following PD parameters in plasma for total BA will be calculated, as applicable: C_{trough}, C_{max}, $AUC_{0\text{-}24}$, and T_{max}. In addition, concentrations of individual BA may be measured and exposure parameters may be summarized.

Plasma concentrations and PK parameters of BLV, and plasma concentrations and PD parameters of total BA, will be listed and summarized by renal function group and dose level using descriptive statistics.

In addition, a one-way analysis of variance (ANOVA) model appropriate for a parallel-design with renal function group as a fixed effect will be fit to the natural logarithmic transformation of plasma PK parameters (AUC_{tau} and $C_{max\ ss}$) for BLV. The 90% CIs will be constructed for the geometric least-squares mean (GLSM) ratio of PK parameters for BLV in the RI group versus the matched control (normal renal function) group.

The same analysis will be conducted for plasma PD parameters of total BA, as applicable.

The PK-PD relationship using plasma BLV PK concentrations/parameters and plasma BA concentrations/parameters may be explored using a graphical approach and correlation coefficients as appropriate. Additional PK and PD parameters may be estimated as necessary.

8.7. Immunogenicity Analysis

Plasma will be evaluated for the presence of ADA to BLV as applicable. ADA may be further characterized for neutralizing activity.

8.8. Sample Size

For study Group A, with 16 (8 RI and 8 matched control [normal renal function]) evaluable participants, the estimated upper limit of the one-sided 95% CIs of the GLSM ratio of RI group versus matched control group with regards to AUC_{tau} and C_{max} of BLV, would be less than 200% with ≥ 80% probability if the expected GLSM ratio is 1.0. This assumes a percentage coefficient of variation (CV%) of no more than 51%, which is supported by previously conducted Study MYR102. Accounting for a 20% dropout rate, a total sample size of 20 participants (10 RI and 10 matched control each) will be required.

Furthermore, given the lower degree of variability in BA concentrations compared to BLV, plasma concentrations observed in Study MYR102 {Blank 2018}, this sample size will also provide ≥ 80% probability that the estimated upper limit of the one-sided 95% CIs of the GLSM ratio of RI group versus matched control group with regards to AUC_{tau} and C_{max} of total plasma BA would be less than 200% if the expected GLSM ratio is 1.0. If additional optional groups (Groups B, C, and D) are conducted, a total of up to 20 participants (10 RI and 10 matched controls with normal renal function) will be enrolled in each conducted study group in order to adequately power each subgroup.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with ICH E6(R2) GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with the sponsor or proprietary interests in the study drug. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last participant completes the protocol-defined activities.

9.1.3. Institutional Review Board or Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study participant activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC for any modifications made to the protocol or any accompanying material to be provided to the participant after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study participants.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB-approved ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the participant, the person conducting the consent discussion, and also by an impartial witness if required by the IRB/IEC or local requirements.

The ICF will inform participants about genomic testing and planned sample retention. CCI [redacted]

9.1.5. Confidentiality

The investigator must ensure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB/IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all participants screened and enrolled in the study. Participant data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the investigational site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of 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. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) participant clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRFs, IRB/IEC, and governmental approval with correspondence, ICF, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each participant:

- Participant identification (name, date of birth, gender)

- Documentation that participant meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented participant is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Start and end dates (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity), and documentation that adequate medical care has been provided for any AE
- Concomitant medication (including start and end dates, dose if relevant, and dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the participant, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the electronic data capture (EDC) system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of

events and procedures, unless collected by a nonelectronic data capture vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the CRF Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor (clinical research associate) may perform source data verification (SDV). System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study after database lock, ICON will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRB/IEC, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications may be implemented.

9.2.2. Study Reports and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. For

studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 3.5.2).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator's meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal and/or travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation and any participant records in order to verify the adherence to the protocol and accuracy of the data recorded in the eCRFs. The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The investigator agrees to cooperate with the study monitor to ensure that any problems detected through any type of monitoring (central, off-site, onsite) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead study monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Gilead reserves the right to terminate the study at any time, and the investigator has the right to terminate the study at his or her site. Should this be necessary, both parties will arrange discontinuation procedures and notify the participants, appropriate regulatory authority(ies), and IRB/IEC. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the participants' interests.

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11. APPENDICES

11.1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404
USA

STUDY ACKNOWLEDGEMENT

A Phase 1 Open-Label, Parallel-Design, Multiple-Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Bulevirtide in Participants with Normal and Impaired Renal Function

Amendment 1: 02 February 2023

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD
Director, Clinical Development

[See appended electronic signature]
Signature

[See appended electronic signature]
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

11.2. Authorization Status of Study Interventions

Study Intervention Name	Category	Authorized in at Least 1 Country Following EU Regulation No. 536/2014	Authorized in at Least 1 ICH Country	Authorized by Swissmedic
Bulevirtide	Study drug	No	Yes	No

EU = European Union, ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals

11.3. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with participants being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Participant safety monitoring and follow-up:

   a) Participants may be unable or unwilling to come to the investigational site for their in-clinic stay or other requested visits as required per protocol.

      Mitigation plan: Participants who may be unable or unwilling to visit the investigational site for their in-clinic stay as required per protocol, will not be able to receive treatment and will be discontinued. Participants who have received treatment and have been discharged either at the end of treatment or early as the result of a pandemic, will receive a follow-up telephone call to collect safety data as specified in the protocol follow-up procedures. During the follow-up telephone call, the following information at minimum will be reviewed:

      i) Confirm if participant has experienced any AEs/SAEs/special situations (including pregnancy) and follow-up on any unresolved AEs/SAEs.

      ii) Review the current list of concomitant medications and document any new concomitant medications.

   b) Participants may be unable or unwilling to travel to the investigational site for unplanned laboratory assessments (eg, safety blood draws); hence samples may not be sent for central laboratory analyses.

      Mitigation plan: Local laboratories or other vendors may be utilized as appropriate to monitor safety until the participant can return to the site for their follow-up assessment. Any changes in the party conducting laboratory assessments for the study because of the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

   c) Participants may be unable or unwilling to attend a study visit to sign an updated informed consent form version.

      Mitigation plan: The site staff will follow their approved consent process and remain in compliance with the local ethics committee/institutional review board and national laws and regulations. Remote consent will be allowed if has been approved by the local ethics committee/institutional review board. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

2) Protocol and monitoring compliance:

   a) Protocol deviations may occur in case scheduled visits cannot be conducted as planned per protocol.

      Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed participant visits or deviation to the protocol because of the pandemic must be reported in the eCRF and described in the clinical study report. Any remote study visits that are conducted in lieu of clinic visits because of the pandemic will be documented as a protocol deviation related to the pandemic.

   b) Study monitors may be unable to carry out source data review or SDV, or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in SDV, an increase in protocol deviations, or underreporting of AEs.

      Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. Remote SDV may be arranged if allowed by local regulation and the Study Monitoring Plan. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct an off-site monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or on site, must be tracked centrally and updated on a regular basis.

3) Missing data and data integrity:

   There may be an increased amount of missing data because of participant missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

   Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (eg, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of participants who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of BLV in study participants remains unchanged.

11.4. Pregnancy Precautions, Definition of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a participant assigned female at birth is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the participant is permanently sterile or has medically documented ovarian failure.

Participants assigned female at birth are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause. In addition, participants assigned female at birth younger than 54 years with amenorrhea of at least 12 months also may be considered postmenopausal if their FSH level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a participant assigned female at birth of any age.

b. Definition of Fertility in a Participant Assigned Male at Birth

For the purposes of this study, a male born participant is considered fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Participants

a. Investigational Product Effects on Pregnancy, Lactation and Hormonal Contraception

There are no adequate and well-controlled studies with BLV in pregnant women. Bulevirtide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In nonclinical reproductive toxicity studies, BLV demonstrated no adverse effect on embryofetal development when administered to pregnant rats and rabbits at systemic exposures (AUC) 12- and 124-fold relative to exposure in humans at the recommended human dose.

It is not known whether BLV is secreted in human milk. In nonclinical pre- and post-natal developmental rat studies, BLV was not measured in the plasma of pups or in the milk of nursing animals. However, due to its high protein binding, liver tropism, and high specificity for the NTCP, BLV is not likely to be secreted in milk.

Available data indicate that BLV is not anticipated to reduce the clinical efficacy of hormonal contraception. Please refer to the latest version of the IB for additional information.

b. Assigned Female at Birth and of Childbearing Potential

The inclusion of participants assigned female at birth and of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at screening and a negative pregnancy test at the admission (Day –1) visit before

enrollment. In the event of a delayed menstrual period (over 1 month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is applicable also for participants assigned female at birth and of childbearing potential with infrequent or irregular periods.

Duration of required contraception for participants assigned female at birth and of childbearing potential in this clinical study should start from the screening visit until the end of study.

Participants assigned female at birth and of childbearing potential must agree to 1 of the following contraceptive methods:

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the participant's preferred and usual lifestyle.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Hormonal or nonhormonal intrauterine device (IUD)
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Or

Female participants who initiate use of a hormonal contraceptive greater than 5 days after onset of menses as one of their birth control methods should use additional backup contraception (eg, condoms) or avoid sexual intercourse for 7 days. Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Subdermal contraceptive implant
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring
- Barrier methods
  - Male condom (with or without spermicide)

- Female condom (with or without spermicide)
- Diaphragm with spermicide
- Cervical cap with spermicide
- Sponge with spermicide

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Participants assigned female at birth and of childbearing potential must also refrain from egg donation and in vitro fertilization during study drug dosing and until end of contraception requirement.

3) Contraception Requirements for Participants Assigned Male at Birth

No contraception measures are needed.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to Be Followed in the Event of Pregnancy

Participants assigned female at birth will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 7 days of last study drug dose. Participants who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3.

11.5. Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

The CTCAE toxicity grading scale Version 5.0 dated 27 November 2017 is available at the following location:
(https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf).

11.6. Country-Specific Requirements

Not applicable.

11.7. Amendment History

A high-level summary of this amendment is provided in tabular form in the subsection below, with changes listed in order of importance. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

A separate tracked change (red-lined) document comparing the original protocol to this amendment will be made available upon the publication of this protocol.

11.7.1. Amendment 1 (02 February 2023)

Rationale for Key Changes Included in Amendment 1	Affected Sections
Footnote “d” was modified to specify and correctly mention the schedule of collection for safety laboratory tests during the study.	Study Procedures Table (footnote “d”)
Red blood cell morphology was added as a hematology parameter applicable for each scheduled hematology laboratory assessment during the study.	Sections 6.4.5 (Table 3) and 6.4.5.1
Minor changes to correct typographic errors.	Throughout, as needed

Amend 1-Protocol_GS-US-589-6160

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	03-Feb-2023 16:59:18