



AMENDMENT 1 CLINICAL STUDY PROTOCOL

Study Title	A Phase 1, Open-Label, Single-Dose, Parallel-Group Study of the Pharmacokinetics and Safety of VIR-2218 in Adult Participants with Renal Impairment
Brief Title	A Study to Investigate the Effect of Renal Impairment on the Pharmacokinetics and Safety of VIR-2218
Study Number	VIR-2218-V108
Compound	VIR-2218 (elebsiran)
Indication	Chronic Hepatitis B
Study Phase	1
Study Sponsor	Vir Biotechnology, Inc. 1800 Owens Street, Suite 900 San Francisco, CA 94158, USA
Regulatory Agency Identifying Numbers	US IND: 153682 EudraCT: Not Applicable NCT: NCT05844228
Protocol Date	18 April 2024, Version 1.0

This study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

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STUDY ACKNOWLEDGMENT

A Phase 1, Open-Label, Single-Dose, Parallel-Group Study of the Pharmacokinetics and Safety of VIR-2218 in Adult Participants with Renal Impairment

This protocol has been approved by Vir Biotechnology, Inc. The following signature documents this approval.

Li Wang, PhD
Study Director, Clinical Pharmacology

[\[See Appended Electronic Signature Page\]](#)

Printed Name

Signature and 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 Vir Biotechnology, Inc. I will discuss this material with them to ensure they are fully informed about the drugs and the study.

Principal Investigator Printed Name

Signature

Date

TABLE OF CONTENTS

INVESTIGATOR SIGNATURE PAGE	2
PROTOCOL AMENDMENT 1 (18 APRIL 2024) SUMMARY OF CHANGES TABLE.....	7
Protocol Document History	7
Protocol Amendment 1 Summary of Changes.....	7
1. PROTOCOL SUMMARY.....	9
1.1. Synopsis.....	9
1.2. Study Schema	12
1.3. Schedule of Activities.....	13
2. INTRODUCTION	17
2.1. Background.....	17
2.2. Study Rationale.....	18
2.3. Benefit/Risk Assessment	18
2.3.1. Risk Assessment	19
2.3.2. Benefit Assessment.....	20
2.3.3. Overall Benefit/Risk Conclusion.....	20
3. OBJECTIVES AND ENDPOINTS.....	20
4. STUDY DESIGN	21
4.1. Overall Study Design.....	21
4.1.1. Number of Participants	21
4.1.2. Intervention Groups and Duration	21
4.2. Scientific Rationale for Study Design	22
4.3. Justification for Dose.....	22
4.4. End of Study Definition.....	24
5. STUDY POPULATION	24
5.1. Inclusion Criteria	24
5.2. Exclusion Criteria	26
5.3. Lifestyle Considerations	28
5.3.1. Meals and Dietary Restrictions.....	28
5.3.2. Caffeine, Alcohol, and Tobacco	28
5.3.3. Activity	28
5.4. Screen Failures.....	28

5.5.	Criteria for Temporarily Delaying Enrollment.....	29
6.	STUDY INTERVENTION(S) AND CONCOMITANT THERAPY	29
6.1.	Study Intervention(s) Administered	29
6.2.	Preparation, Handling, Storage, and Accountability	29
6.3.	Measures to Minimize Bias: Randomization and Blinding.....	30
6.4.	Study Intervention Compliance	30
6.5.	Dose Modification	30
6.6.	Continued Access to Study Intervention After the End of the Study	30
6.7.	Treatment of Overdose	30
6.8.	Concomitant Therapy	31
6.8.1.	Permitted Concomitant Medications	31
6.8.2.	Prohibited Concomitant Therapy	31
7.	STUDY STOPPING RULES	32
7.1.	Participant QTc Monitoring Guidance	32
7.2.	Participant Discontinuation/Withdrawal from the Study	32
7.3.	Lost to Follow-Up/Replacement of Participants	32
8.	STUDY ASSESSMENTS AND PROCEDURES.....	33
8.1.	Screening Period.....	33
8.1.1.	Screening Viral Serology Parameters	33
8.1.2.	Screening for Drugs of Abuse	33
8.2.	Pharmacokinetics	34
8.2.1.	Blood Sample Collection	34
8.2.2.	Urine Sample Collection.....	34
8.3.	Safety Assessments.....	34
8.3.1.	Physical Examinations.....	34
8.3.2.	Vital Signs	34
8.3.3.	Electrocardiograms	34
8.3.4.	Clinical Safety Laboratory Tests	35
8.3.5.	Pregnancy Testing	35
8.4.	Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting	36
8.4.1.	Time Period and Frequency for Collecting AE and SAE Information.....	36
8.4.2.	Follow-Up of AEs and SAEs.....	36

8.4.3.	Regulatory Reporting Requirements for SAEs.....	37
8.4.4.	Adverse Events of Interest.....	37
8.4.5.	Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs or SAEs.....	37
8.4.6.	Special Situation Reports.....	38
8.4.6.1.	Pregnancy	38
8.5.	Genetics	39
8.6.	Biomarkers.....	39
8.7.	Immunogenicity Assessments	39
8.8.	Health Economics OR Medical Resource Utilization and Health Economics	39
9.	STATISTICAL CONSIDERATIONS	39
9.1.	Statistical Hypotheses.....	39
9.2.	Sample Size Determination	39
9.3.	Analysis Sets.....	40
9.4.	Statistical Analysis.....	40
9.4.1.	General Considerations.....	40
9.4.2.	Background Characteristics	40
9.4.3.	Pharmacokinetic Analysis	41
9.4.4.	Safety Analyses	42
9.4.5.	Exploratory Endpoint Analysis.....	42
9.5.	Interim Analysis.....	42
10.	SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS.....	43
10.1.	Appendix 1: Regulatory, Ethical, and Study Oversight Considerations	43
10.1.1.	Regulatory and Ethical Considerations	43
10.1.2.	Financial Disclosure	43
10.1.3.	Informed Consent Process	44
10.1.4.	Data Protection	44
10.1.5.	Confidentiality	44
10.1.6.	Committees Structure	44
10.1.7.	Dissemination of Clinical Study Data	45
10.1.8.	Data Quality Assurance	45
10.1.9.	Source Documents	45

10.1.10.	Electronic Case Report Forms (eCRFs)	45
10.1.11.	Study and Site Start and Closure	46
10.1.11.1.	First Act of Recruitment	46
10.1.11.2.	Study/Site Termination	46
10.1.12.	Publication Policy	46
10.2.	Appendix 2: Clinical Laboratory Tests	47
10.3.	Appendix 3: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting AEs, SAEs, and SSRs	48
10.3.1.	Definition of AE	48
10.3.2.	Definition of SAE	49
10.3.3.	Definitions of Special Situations (SSR)	50
10.3.4.	Recording and Follow-Up of AEs, SAEs, and/or SSRs (including Pregnancies)	51
10.3.5.	Reporting of SAEs and SSRs (Including Pregnancies)	53
10.4.	Appendix 4: List of Abbreviations and Definitions of Terms	54
10.5.	Appendix 5: Contraceptive and Barrier Guidance	56
10.6.	Appendix 6: MDRD Equation Definition	58
11.	REFERENCES	59

LIST OF TABLES

Table 1:	Pharmacokinetic Assessment Timepoints	13
Table 2:	Schedule of Activities	14
Table 3:	Study Intervention(s) Administered	29
Table 4:	Protocol-Required Safety Laboratory Tests	47

PROTOCOL AMENDMENT 1 (18 APRIL 2024) SUMMARY OF CHANGES TABLE

Protocol Document History

Document	Date
Protocol Amendment 1	18 April 2024
Original Protocol	21 November 2022

Protocol Amendment 1 Summary of Changes

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 1.3. Schedule of Activities, 4.1.2. Intervention Groups and Duration	Removed exploratory VIR-2218 pharmacokinetic (PK) assessments	Emerging data indicates that no additional exploratory VIR-2218 samples need to be collected, therefore they were removed.
1.3. Schedule of Activities	Removed VIR-2218 pooled urine PK collection timepoint on Day 5 (96-120 hours)	Emerging data indicates majority of the drug excreted in urine within the first 96 hours. Participants are discharged on Day 5 (ie, end of inpatient period, 96 hours). The pooled urine PK collection of 96-120 hours will stretch the collection to Day 6 (ie, 120 hours).
2.3.1. Risk Assessment	Updated risk information for VIR-2218	To provide updated risk assessment information per the most recent VIR-2218 Investigator Brochure
5.1. Inclusion Criteria	Modified inclusion criteria (#1 and #3) regarding age and body mass index (BMI)	The age and BMI inclusion/exclusion (I/E) criteria are expanded to align with severe renal impairment population from published literature. Additionally, the expanded criteria will allow for inclusion of participants with severe RI in the ongoing and planned pivotal studies.
5.2. Exclusion Criteria	Updated exclusion criteria (#26) regarding use of other medications	To clarify medications that would exclude participants with RI from the study

Section # and Name	Description of Change	Brief Rationale
6.8.2. Prohibited Concomitant Therapy	Updated window for which participants must abstain from taking prescription or nonprescription drugs prior to study drug administration	To align with exclusion criteria
8. Study Assessments and Procedures	Removed the following language: Repeat samples and/or samples used to run reflex testing may be run at the site local laboratory to determine subject eligibility but must be confirmed by the central laboratory. The central laboratory results will be entered in the clinical database.	A protocol deviation was identified where a local lab result differed enough from the central lab result for it to be a deviation from the Inclusion/Exclusion criteria. This change will prevent similar deviations in the future.
9.4.2. Background Characteristics	Clarified how participant disposition, demographics, and baseline characteristics will be summarized	In addition to treatment cohort, background characteristics will also be summarized by RI status.
Entire document	Other administrative, formatting, and other minor changes	These changes were made to clarify, ensure consistency, provide up-to-date information, or rectify typographical errors.

1. PROTOCOL SUMMARY

1.1. Synopsis

Study Title:

A Phase 1, Open-Label, Single-Dose, Parallel-Group Study of the Pharmacokinetics and Safety of VIR-2218 in Adult Participants with Renal Impairment

Brief Title:

A Study to Investigate the Effect of Renal Impairment on the Pharmacokinetics and Safety of VIR-2218

Background and Rationale:

VIR-2218 (elebsiran) is a novel agent being investigated for the treatment of chronic hepatitis B virus (HBV) infection and chronic hepatitis D virus (HDV) infection. VIR-2218 is an investigational, N-acetylgalactosamine (GalNAc)-conjugated, double-stranded ribonucleic acid interference (RNAi) therapeutic, chemically modified using Enhance Stability Chemistry (ESC+) technology that stabilizes the small interfering RNA (siRNA) in vivo and decreases off-target effects.

VIR-2218 was well tolerated when administered as a single subcutaneous (SC) dose of up to 900 mg in healthy participants and when administered as multiple doses up to 200 mg SC in participants with chronic HBV infection.

It is estimated that approximately 30% of HBV patients will have mild renal disease and up to 4% will develop moderate to severe renal disease (Deray 2015). Among HDV-infected patients, up to 30% have mild renal impairment (RI) and up to 10% will have moderate to severe RI (“IQVIA PharMetrics® Plus database 2016-2021 ~HEMA”; data on file). In addition to RI, a subset of HBV and HDV patients will also have liver cirrhosis and hepatic impairment. Although VIR-2218 is primarily eliminated via liver metabolism (Gupta 2021), comorbid RI may further impact the pharmacokinetic (PK) and pharmacodynamic (PD) properties of VIR-2218 in patients with chronic HBV infection and chronic HDV infection.

The rationale of this study is to evaluate the impact of renal function on the PK, safety, and tolerability of VIR-2218 in participants with normal renal function and participants with varying degrees of renal dysfunction who are otherwise medically stable. The PK properties of VIR-2218 have been evaluated in participants with mild RI using preliminary population PK analyses. To date, no clinically significant differences in PK and safety have been observed in participants with mild RI dosed with VIR-2218 (data on file). In this study, up to a 200 mg single dose of VIR-2218 will be administered to assess the PK exposure, safety, and tolerability of VIR-2218 in participants with moderate to severe RI (*participants with end-stage renal disease [ESRD] or on hemodialysis will not be included in this trial*).

Primary and Secondary Objectives and Endpoints:

Objectives	Endpoints
Primary	
Assess the pharmacokinetics of VIR-2218 in adult participants with RI and in matched healthy adult participants with normal renal function	AUC_{last}, AUC_{inf}, C_{max}, %f_e, Ae, CL_R for VIR-2218 and its metabolite AS(N-1)3'VIR-2218
Secondary	
Assess the safety and tolerability of single-dose VIR-2218 in adult participants with RI and in matched healthy adult participants with normal renal function	Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

Overall Study Design:

This is a Phase 1, open-label, single-dose, parallel-group study conducted in adult participants with RI and in healthy adult participants matched (1:1) by race, sex, age (± 10 years), and body mass index (BMI) ($\pm 20\%$ of BMI at screening).

Each participant will receive a single SC dose of VIR-2218 up to 200 mg on Day 1.

Cohort 1: Participants with moderate RI and matched healthy participants will be evaluated first.

(Optional) Cohort 2: Participants with severe RI will be enrolled after sponsor's review of the safety, tolerability, and PK data from participants with moderate RI (Cohort 1) compared to matched healthy controls. Enrolled participants with severe RI may receive a reduced dose if the exposure (AUC_{last}, AUC_{inf}, C_{max}) in the moderate RI participants is > 3 -fold compared to their matched healthy controls. Alternatively, severe RI participants may not be enrolled if the plasma exposure reaches or exceeds the threshold exposure observed at the maximum administered dose of 900 mg and/or the safety/tolerability profile in participants with moderate RI is not supportive of dosing in severe RI as determined by the sponsor and investigator.

Brief Summary:

The purpose of the study is to evaluate single-dose PK and safety of VIR-2218 following a SC injection of VIR-2218 administered at a dose up to 200 mg in participants with moderate to severe RI compared with matched healthy participants with normal renal function.

Number of Participants:

Up to approximately 32 participants (up to 16 healthy participants and up to 16 participants with RI) will be enrolled across 2 cohorts. Participants are planned to be enrolled in multiple sites in the United States. Cohort 1 is planned to be enrolled first.

Intervention Groups and Duration:

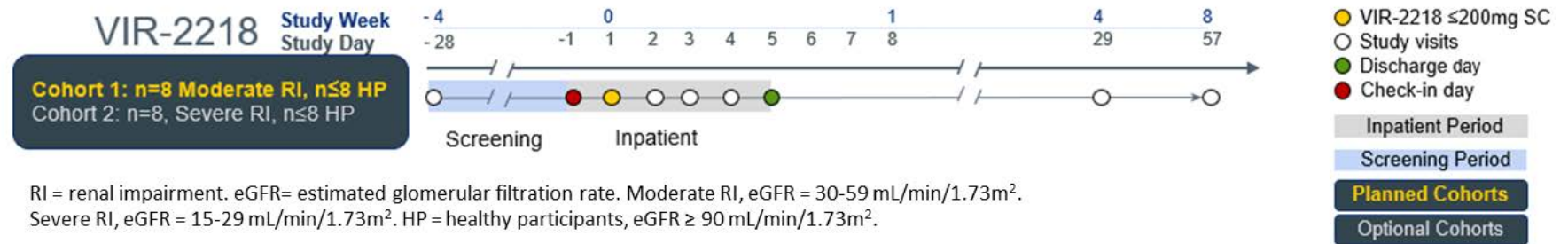
- Cohort 1: 8 (moderate RI) participants with estimated glomerular filtration rate (eGFR) = 30-59 mL/min/1.73m² as calculated by the Modification of Diet in Renal Disease (MDRD) equation, and up to 8 matched healthy participants with eGFR ≥ 90 mL/min/1.73m² will receive a single dose of SC VIR-2218 (200 mg)
- (Optional) Cohort 2: 8 (severe RI) participants with eGFR = 15-29 mL/min/1.73m² as calculated by the MDRD equation and up to 8 matched healthy participants with eGFR ≥ 90 mL/min/1.73m² will receive a single dose of SC VIR-2218 (≤ 200 mg)

Each participant will be in the study for approximately 12 weeks in total. Participation will include a screening evaluation within 28 days before dosing Day 1, and a 6-day (5-night) inpatient period (from Day -1 through Day 5). Participants will be discharged from the clinic after completing the Day 5 procedures (approximately 96 hours post-dose). Participants will return to the clinic for scheduled visits per the Schedule of Activities (SoA) until up to 8 weeks post-dose for safety assessments.

Independent Data Monitoring/Other Committee:

No data monitoring or other committee is warranted for this study.

1.2. Study Schema



1.3. Schedule of Activities

Table 1: Pharmacokinetic Assessment Timepoints

Study Day	Protocol Time $\pm$ Window	VIR-2218 PK	Plasma Protein Binding	VIR-2218 Pooled Urine PK
Day 1	Pre-dose (-2 hrs)	X	X	
	Dose			X (0-4 hours)
	15 min post-dose (± 2 min)	X		
	30 mins post-dose (± 5 min)	X		
	1 hour post-dose (± 10 min)	X		
	2 hours post-dose (± 20 min)	X		
	4 hours post-dose (± 30 min)	X		X (4-8 hours)
	6 hours post-dose (± 30 min)	X	X	
	8 hours post-dose (± 30 min)	X		X (8-12 hours)
	10 hours post-dose (± 30 min)	X		
	12 hours post-dose (± 1 hr)	X		X (12-24 hours)
	18 hours post-dose (± 1 hr)	X		
Day 2	24 hours post-dose (± 2 hrs)	X		X (24-36 hours)
	36 hours post-dose (± 2 hrs)	X		X (36-48 hours)
Day 3	48 hours post-dose (± 4 hrs)	X		X (48-72 hours)
Day 4	72 hours post-dose (± 6 hrs)	X		X (72-96 hours)
Day 5	96 hours post-dose (± 6 hrs)	X		

Table 2: Schedule of Activities

Study Stage	Screening		Inpatient Period					Follow-Up Period	
Visit Week			W1					W4	W8/ET ^a
Visit Day ± Visit Window	D-28 to D-1		D1 / Dosing Day ^b	D2	D3	D4	D5 / Discharge	D29±2	D57±4
Study Procedures									
Informed consent	X								
Inclusion/exclusion criteria	X		X ^c						
Demography	X								
Physical examination	X		X						
Symptom-directed examination ^d				X	X	X	X	X	X
Medical history	X		X						
Body weight	X		X						
Height and BMI	X								
Vital signs ^e	X		X	X	X	X	X	X	X
eGFR assessment	X ^f	X ^f							
12 Lead safety ECG ^g	X		X	X	X	X	X	X	X
Adverse event review/record ^h	X		X	X	X	X	X	X	X
Concomitant medication review	X		X	X	X	X	X	X	X
Laboratory Assessments ⁱ									
Liver function tests	X		X					X	
Serum chemistry	X		X	X	X	X	X	X	X
Hematology	X		X	X	X	X	X	X	X

Study Stage	Screening	Inpatient Period					Follow-Up Period	
Visit Week		W1					W4	W8/ET ^a
Visit Day ± Visit Window	D-28 to D-1	D1 / Dosing Day ^b	D2	D3	D4	D5 / Discharge	D29±2	D57±4
Screening viral serology	X							
Coagulation parameters	X	X					X	
Urinalysis	X	X	X	X	X	X	X	X
Urine for drugs of abuse ^j	X	X					X	X
Pregnancy test ^k	X	X					X	X
Study Intervention Administration								
VIR-2218		X						
PK Assessments								
Protein Binding ^l		X						
VIR-2218 PK ^m		X	X	X	X	X		
VIR-2218 Pooled Urine PK ^m		X	X	X	X			

AE = adverse event; BMI = body mass index; D = day; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; ICF = informed consent form; MDRD = Modification of Diet in Renal Disease; PK = pharmacokinetic; SAE = serious adverse event; W = week

^a If a participant discontinues from the study (eg, due to withdrawal of consent) post-dose but before the completion of the Week 8 visit, an ET visit should be performed as early as possible regardless of the Visit Day/Window of D57 ± 4.

^b All assessments on Day 1 are to be performed prior to dosing unless otherwise specified. Some procedures may be performed on Day -1 per sites local practices.

^c Prior to study drug administration on Day 1, participant eligibility will be confirmed.

^d Symptom-directed physical examination will be performed in the event of new signs and symptoms only.

^e Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) should be measured after the participant has rested comfortably for approximately 10 minutes.

^f Two separate samples will be collected for the measurement of serum creatinine. Samples will be collected no more than 14 days apart, but at least 72 hours apart, with the first screening visit occurring within 28 days prior to dosing on Day 1. The mean of the two serum creatinine measurements will be used to determine renal function at screening per the MDRD equation.

- ^g 12-lead safety ECG will be recorded at screening, pre-dose (within 30 min) on Day 1, and as highlighted in the SoA. ECGs should be measured in the supine position after the participant has rested comfortably for 10 minutes.
- ^h After signing of the ICF, but prior to initiation of study intervention, all SAEs (regardless of cause or relationship) and AEs related to protocol-mandated procedures will be reported. Following initiation of study drug, all AEs/SAEs, regardless of cause or relationship, will be recorded for the entire duration of the study. Further details can be found in Section 8.4.
- ⁱ Detailed laboratory assessments can be found in Section 10.2.
- ^j Drugs of abuse included in the screen are described in Section 10.2. Collection of urine for drugs of abuse scheduled for Day 1 may be performed on Day -1 per local practices. Results for drugs of abuse must be reviewed prior to dosing. Local drugs of abuse assessment will be confirmed by central testing, but local results will be used for determination of eligibility.
- ^k Female participants who are women of childbearing potential (WOCBP) will have blood collected for pregnancy testing at screening and urine collected for pregnancy testing at check-in prior to dose and thereafter (ie, Weeks 4 & 8).
- ^l Pre-dose sample will be collected up to 2 hours before dosing and approximately 6 hours post-dose for protein binding assay.
- ^m Detailed blood PK and urine PK sample collection timepoints can be found in Table 1.

2. INTRODUCTION

2.1. Background

VIR-2218 is an investigational, N-acetylgalactosamine (GalNAc)-conjugated, double-stranded ribonucleic acids interference (RNAi) therapeutic that targets a region of the hepatitis B virus (HBV) genome that is common to all HBV viral transcripts. VIR-2218 is chemically modified using Enhance Stability Chemistry (ESC+) technology that stabilizes the small interfering RNA (siRNA) in vivo and decreases off-target effects. The GalNAc moiety enables targeted delivery of VIR-2218 into the liver via uptake by asialoglycoprotein receptors (ASGPR) expressed primarily and abundantly on the surface of hepatocytes ([Schwartz 1980](#)). Due to its high level of expression on hepatocytes, ability to mediate multiple rounds of uptake, and its ligand specificity, the ASGPR has been widely used for liver-specific drug and gene delivery in animals ([Wu 2002](#)). The ASGPR has been safely and effectively used in humans for targeted delivery to hepatocytes ([Nair 2014](#)).

In the 3 approved GalNAc-conjugated siRNA therapeutics (givosiran, lumasiran, and inclisiran), renal clearance is a minor pathway accounting for 5-26% of systemic clearance ([Givlaari® \(Givosiran\) 2022](#); [Leqvio® \(inclisiran\) 2021](#); [Oxlumo® \(lumasiran\) 2022](#)). The most significant increase (2.3-fold) in plasma exposure (AUC) was observed for inclisiran in participants with severe RI. Despite the changes in plasma exposure, no adjustments in doses were warranted for givosiran, inclisiran or lumasiran in participants with RI due to lack of changes in efficacy in the patient population.

VIR-2218 is a novel agent being investigated for the treatment of chronic HBV infection and chronic hepatitis D virus (HDV) infection. VIR-2218 was well tolerated in healthy participants when administered as a single dose of up to 900 mg and in participants with chronic HBV infection administered multiple doses of up to 200 mg subcutaneously (SC). Reductions in hepatitis B surface antigen (HBsAg) were observed across all VIR-2218 dosing levels, and greater reductions were associated with higher VIR-2218 doses ([Gane 2021](#)).

It is estimated that approximately 30% of HBV patients will have mild renal disease and up to 4% will develop moderate to severe renal disease ([Deray 2015](#)). Among HDV-infected patients, up to 30% have mild renal impairment (RI) and up to 10% will have moderate to severe RI (“IQVIA PharMetrics® Plus database 2016-2021 ~HEMA”; data on file). In addition to RI, a subset of HBV and HDV patients will also have liver cirrhosis and hepatic impairment. Although VIR-2218 is primarily eliminated via liver metabolism ([Gupta 2021](#)), comorbid RI may further impact the pharmacokinetic (PK) and pharmacodynamic (PD) properties of VIR-2218 in patients with chronic HBV infection and chronic HDV infection.

VIR-2218 has the potential to serve as an effective treatment strategy for patients with chronic HBV infection and chronic HDV infection, including for those with RI.

2.2. Study Rationale

Although VIR-2218 is primarily eliminated via liver metabolism ([Gupta 2021](#)), comorbid RI may further impact the PK and PD properties of VIR-2218 in patients with chronic HBV infection and chronic HDV infection. The rationale of this study is to evaluate the impact of renal function on the PK, safety, and tolerability of VIR-2218 in participants with normal renal function and participants with varying degrees of renal dysfunction who are otherwise medically stable. The PK properties of VIR-2218 have been evaluated in participants with mild RI using preliminary population PK analyses. To date, no clinically significant differences in PK and safety have been observed in participants with mild RI dosed with VIR-2218 (data on file). In this study, a single dose of up to 200 mg VIR-2218 will be administered to assess the PK exposure, safety, and tolerability of VIR-2218 in participants with moderate to severe RI (*participants with end-stage renal disease [ESRD] or on hemodialysis will not be included in this trial*).

2.3. Benefit/Risk Assessment

Detailed information about the known and potential benefits and risks of VIR-2218 in healthy adult participants and participants with chronic HBV infection and chronic HDV infection may be found in the Investigator's Brochure (IB). The potential benefits and risks for participants with RI are expected to be no different than those in the healthy adult population and in those with chronic HBV infection and/or chronic HDV infection.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: VIR-2218		
Injection site reactions (ISRs)	ISRs are a recognized risk of SC administered siRNA therapies and are typically transient.	Participants are monitored for local tolerability after injection and all adverse events (AEs) will be collected to reflect any ISRs that may be reported. Routine safety monitoring and reporting procedures are in place to provide safety overview.
Immunogenicity: Immunogenicity is a potential risk associated with siRNA molecules. In general, the development of anti-drug antibodies (ADA) may impact safety, efficacy, or both.	Interim immunogenicity data indicated a low incidence of ADA and low titers.	Immunogenicity will continue to be assessed in relation to associated VIR-2218 and clinical safety measures.
Liver function test abnormalities: VIR-2218 is targeted for delivery to the liver, and transient transaminase elevations have been observed with SC administration with other GalNAc-conjugated siRNA therapeutics. Liver function test abnormalities had been assessed as a potential risk for VIR-2218 in HBV/HDV patients.	Based on available preliminary clinical data from studies in participants with chronic HBV infection, Grade 1 or Grade 2 aminotransferase (ALT) elevations have been observed in participants receiving VIR-2218 monotherapy. No participants met Hy's law and the majority resolved the ALT elevations by the end of treatment.	Monitoring of liver function including ALT, aspartate aminotransferase (AST) and total bilirubin will be performed.

2.3.2. Benefit Assessment

This is a Phase 1 study being conducted in healthy participants with normal renal function and in participants with moderate and up to severe RI. There is no direct clinical benefit to study participants. Participation in this study will contribute to the clinical development of VIR-2218 as a potential therapy for participants with chronic HBV infection and chronic HDV infection.

2.3.3. Overall Benefit/Risk Conclusion

This study will provide information on the PK and safety of VIR-2218 in participants with moderate to severe RI. The risks to participants enrolled in this study are provided in Section 2.3.1. There is no direct clinical benefit to study participants, and this study may only provide additional safety and PK data for future participants with chronic HBV infection or chronic HDV infection with RI. The risk of AEs is mitigated for the intended population by selection of VIR-2218 dose that has been previously determined to be safe and generally well tolerated in healthy participants and participants with chronic HBV infection. Exclusion criteria and extended safety monitoring have been incorporated into the study to mitigate long term safety risk for participants enrolled in this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Assess the pharmacokinetics of VIR-2218 in adult participants with RI and in matched healthy adult participants with normal renal function	AUC_{last}, AUC_{inf}, C_{max}, %f_e, Ae, CL_R for VIR-2218 and its metabolite AS(N-1)3'VIR-2218
Secondary	
Assess the safety and tolerability of single-dose VIR-2218 in adult participants with RI and in matched healthy adult participants with normal renal function	Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
Exploratory/Other	
Determine the plasma protein binding of VIR-2218 in participants with RI and participants with normal renal function	VIR-2218 pre-dose and post-dose unbound fraction

4. STUDY DESIGN

4.1. Overall Study Design

This is a Phase 1, open-label, single-dose, parallel-group study conducted in adult participants with RI and in healthy adult participants matched (1:1) by race, sex, age (± 10 years), body mass index (BMI) ($\pm 20\%$ of BMI at screening).

Each participant will receive a single SC dose of VIR-2218 up to 200 mg on Day 1.

Cohort 1: Participants with moderate RI and matched healthy participants will be evaluated first.

(Optional) Cohort 2: Participants with severe RI will be enrolled after sponsor's review of the safety, tolerability, and PK data from participants with moderate RI (Cohort 1) compared to matched healthy controls. Enrolled participants with severe RI may receive a reduced dose if the exposure (AUC_{last} , AUC_{inf} , C_{max}) in the moderate RI participants is > 3 -fold compared to their matching healthy controls. Alternatively, severe RI participants may not be enrolled if the plasma exposure reaches or exceeds the threshold exposure observed at the maximum administered dose of 900 mg and/or the safety/tolerability profile in participants with moderate RI is not supportive of dosing in severe RI as determined by the sponsor and investigator.

4.1.1. Number of Participants

Up to approximately 32 participants will be enrolled. Participants are planned to be enrolled in multiple sites in the United States. Cohort 1 is planned to be enrolled first.

4.1.2. Intervention Groups and Duration

- Cohort 1: 8 (moderate RI) participants with estimated glomerular filtration rate ($eGFR$) = 30-59 mL/min/1.73m² as calculated by the Modification of Diet in Renal Disease (MDRD) equation and up to 8 matched healthy participants with $eGFR \geq 90$ mL/min/1.73m² will receive a single dose SC VIR-2218 (200 mg)
- (Optional) Cohort 2: 8 (severe RI) participants with $eGFR = 15$ -29 mL/min/1.73m² as calculated by the MDRD equation and up to 8 matched healthy participants with $eGFR \geq 90$ mL/min/1.73m² will receive a single dose SC VIR-2218 (≤ 200 mg)

Each participant will be in the study for a total of approximately 12 weeks. Participation will include a screening evaluation within 28 days prior to dosing Day 1, and a 6-day (5-night) inpatient period (from Day -1 through Day 5). Participants will be discharged from the clinic after completing the Day 5 procedures (approximately 96 hours post-dose). Participants will return to the clinic for scheduled visits per the Schedule of Activities (SoA) until up to 8 weeks post-dose for safety assessments (Section 1.3).

4.2. Scientific Rationale for Study Design

Renal impairment may alter the absorption, disposition, and elimination of drugs resulting in PK and subsequently pharmacodynamics changes. The objective of this RI study is to investigate potential clinically relevant changes in the PK and safety of VIR-2218 and its major metabolite AS(N-1)3'VIR-2218 in the context of RI. The data from this study will directly inform dosing recommendations for participants with chronic HBV infection and chronic HDV infection who have varying levels of renal dysfunction.

The GalNAc moiety in VIR-2218 enables targeted delivery into the liver via ASGPR expressed primarily and abundantly on the surface of hepatocytes. In rats and nonhuman primates, hepatic metabolism was determined to be the primary route of elimination of VIR-2218 ([Gupta 2021](#)). Consistent with hepatic uptake, VIR-2218 was rapidly absorbed and eliminated from the systemic circulation with undetectable plasma levels beyond 48 hours in healthy participants and participants with chronic HBV infection. Due to the short systemic half-life of VIR-2218, plasma accumulation was not observed after multiple doses of VIR-2218 administered 4 weeks apart ([Gupta 2021](#)). Based on the similar PK characteristics of VIR-2218 after single or repeat doses, a single dose of VIR-2218 was deemed appropriate for this study.

4.3. Justification for Dose

The safety, tolerability, PK, and antiviral activity of VIR-2218 has been evaluated in Parts A-C of Study VIR-2218-1001. A single SC dose of VIR-2218 from 50 to 900 mg was administered to healthy participants (Part A) and 2 doses of VIR-2218 up to 200 mg were administered 4 weeks apart to participants with chronic hepatitis B (Parts B-C).

VIR-2218 was well tolerated in healthy participants when administered as a single dose of up to 900 mg and in participants with chronic HBV infection administered multiple doses up to 200 mg SC. No clinically significant laboratory, electrocardiogram (ECG), or vital sign abnormalities were observed. No clinically significant hyperbilirubinemia, changes in functional status of the liver (eg, albumin, coagulation parameters), or clinical signs/symptoms of hepatic dysfunction were observed. In healthy participants, VIR-2218 was absorbed after SC injection with median T_{max} of 4-7 hours and was not measurable in plasma beyond 48 hours for any participant ([Gupta 2021](#)).

Available PK data from participants with chronic HBV infection were similar to healthy adults. No accumulation of VIR-2218 in plasma was evident following a second dose of VIR-2218 in participants with chronic HBV infection. Refer to the VIR-2218 IB for a detailed summary of the PK properties of VIR-2218.

The antiviral activity of VIR-2218 was also evaluated to assess the effect on HBsAg following VIR-2218 administration in participants with chronic HBV infection. Reductions in HBsAg were observed across all VIR-2218 dosing levels, and greater reductions were associated with higher VIR-2218 doses ([Gane 2021](#)). At the highest dose level of 200 mg, all patients achieved ≥ 1 log HBsAg reduction from baseline. Additionally, PK assessments in healthy participants at doses up to 200 mg SC suggest that renal route of elimination is a secondary pathway for VIR-2218. Over the initial 24-hour period, approximately 17–23% and 2–3% of the administered dose (50–200 mg) was excreted in urine as unchanged VIR-2218 and AS(N-1)3'VIR-2218, respectively, with the majority of the drug excreted within the first 12 hours ([Gupta 2021](#)). Thus, evaluation of 200 mg VIR-2218 SC in this RI study is supported by the PK, safety and tolerability profile of VIR-2218.

Preliminary population PK (PopPK) covariate analysis conducted on pooled plasma PK in healthy participants and participants with chronic HBV infection administered VIR-2218 at 200 mg SC, showed no clear effect of mild RI on the PK properties of VIR-2218. As reference, no clinically relevant difference in plasma exposure was observed in patients with mild, moderate or severe RI compared to patients with normal renal function with givosiran, a GalNAc-conjugated RNAi therapeutic approved for the treatment of adults with acute hepatic porphyria ([Givlaari® \(Givosiran\) 2019](#)). This assessment was conducted using a PopPK model from data in 3 trials that included patients with various degrees of renal function. Similar to VIR-2218, givosiran is selectively targeted via ASGPR to the hepatocytes in the liver and as such renal function did not impact the plasma concentration of givosiran.

In healthy participants administered a single dose of VIR-2218, the observed C_{max} and AUC_{last} of VIR-2218 were 711 ng/mL and 6630 h·ng/mL respectively at 200 mg, compared to a C_{max} and AUC_{last} of 5010 ng/mL and 58800 h·ng/mL respectively at 900 mg. In a moderate RI population administered 200 mg VIR-2218 SC, an up to 4-fold increase in exposure of VIR-2218 would equate to a C_{max} and AUC_{last} of approximately 2844 ng/mL and 26520 h·ng/mL respectively. These increases in plasma exposures would be covered by the suprathreshold dose of 900 mg for which no clinically significant safety signals have been observed in healthy participants.

The enrollment of severe RI participants will be gated on the preliminary safety and PK data from moderate RI participants. Enrolled participants with severe RI, may receive a reduced dose if the exposure (AUC_{last} , AUC_{inf} , and C_{max}) in the moderate RI participants is > 3 -fold compared to their matched healthy controls. Alternatively, the severe RI cohort would not be enrolled if plasma exposure has reached or exceeded the threshold exposure observed at the maximum administered single dose of 900 mg and/or if the safety/tolerability profile in participants with moderate RI is not supportive of dosing in severe RI as determined by the sponsor and investigator. Furthermore, participants will be monitored closely throughout the treatment period and for at least 8 weeks following the dose of VIR-2218 for any potential AEs or laboratory abnormalities.

In summary, based on the safety and PK profile of VIR-2218 and historical data from another GalNAc siRNA, the selected starting dose of 200 mg administered SC is considered a safe starting dose in participants with moderate RI.

4.4. End of Study Definition

The end of study is defined as the last scheduled visit (or completed contact) of the last participant.

5. STUDY POPULATION

Adult male and female participants with moderate to severe RI and matched healthy participants with normal renal function.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Inclusion Criteria: Criteria for All Participants

Age

1. Participant must be aged 18 to 80 years (inclusive) at screening.

Type of Participant and Disease Characteristics

2. Participants must have stable renal function as defined by less than 20% change in eGFR between the first and second screening sample with the first screening visit occurring within 28 days prior to dosing on Day 1 and the second screening visit occurring no more than 14 days apart, but at least 72 hours apart from the first.

Weight

3. Body mass index (BMI) within the range 18.5 to 40.0 kg/m² (inclusive) at screening.

Sex and Contraceptive/Barrier Requirements

4. Female participants must have a negative pregnancy test or confirmation of post-menopausal status. Post-menopausal status is defined as 12 months with no menses without an alternative medical cause (see Section 10.5 for additional details). Women of childbearing potential (WOCBP) must have a negative blood pregnancy test at screening and a negative urine pregnancy test on dosing Day 1, cannot be breastfeeding, and must be willing to use highly effective methods of contraception (Section 10.5) 14 days before study intervention administration through 8 weeks after study intervention administration. Female participants must also agree to refrain from egg donation and in vitro fertilization from the time of study intervention administration through 8 weeks after study intervention administration.

5. Male participants with female partners of childbearing potential must agree to meet 1 of the following contraception requirements from the time of study intervention administration through 8 weeks after study intervention administration: documentation of vasectomy or azoospermia, or male condom use plus partner use of 1 of the contraceptive options listed for contraception for WOCBP (Section 10.5). Male participants must also agree to not donate sperm from the time of study intervention administration through 8 weeks after study intervention administration.

Informed Consent

6. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other Inclusions

7. 12-lead ECG within normal limits; or, with no clinically significant abnormalities at screening, as determined by the clinical Investigator
8. Absolute neutrophil count ≥ 1000 cells/mm³
9. Hemoglobin ≥ 8 g/dL

Inclusion Criteria: Additional Criteria Specific to Healthy Participants

10. Must in the opinion of the investigator, be in good health based upon medical history, physical examination, vital signs, and screening laboratory evaluations.
11. Must have normal renal function as defined by $\text{eGFR} \geq 90$ mL/min/1.73m² based on the MDRD equation determined from the mean of two measurements of serum creatinine at screening.

Inclusion Criteria: Additional Criteria Specific to Participants with Renal Impairment

12. Apart from renal insufficiency, participants must, in the opinion of the investigator, be sufficiently healthy for study participation based on medical history, physical examination, vital signs, and screening laboratory evaluations
13. The participant with RI must have chronic moderate or severe RI and be clinically stable per investigator assessment for at least 3 months prior to screening
 - a. Moderate RI as defined by eGFR level 30-59 mL/min/1.73m² based on the MDRD equation, or
 - b. Severe RI as defined by eGFR level 15-29 mL/min/1.73m² based on the MDRD equation

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Exclusion Criteria: Criteria for All Participants

Medical Conditions: General

1. Any clinically significant medical condition (other than RI for participants intended for the RI arm(s)) or psychiatric condition that may interfere with study intervention, assessment, or compliance with the protocol or otherwise makes the participant unsuitable for participation in the study OR require intervention during the study, as determined by the investigator
2. Participants with uncontrolled hypertension, asthma, and/or diabetes (Type I or II).
 - a. Participants with diabetes and Hemoglobin A1C > 9 % at screening
3. Participants with any active malignancy
4. Participants with vasculitis or conditions associated with vasculitis.
5. Participants who have undergone major surgery (eg, requiring general anesthesia) within 12 weeks before screening, or will have not fully recovered from surgery, or have surgery planned during the time the subject is expected to participate in the study, or within 8 weeks after dosing of study

Medical Conditions: Cardiovascular

6. Participants with unstable cardiac function or evidence of previous myocardial infarction in the past 12 months or any clinically significant active cardiovascular disease that, in the opinion of the investigator, could interfere with the safety of the participant
7. Any clinically significant conduction abnormality or arrhythmia (including non-sustained or sustained ventricular tachycardia as per investigator's assessment)
8. Corrected QT interval (QTc) > 470 ms
9. Participants who have undergone vascular procedures such as coronary artery bypass, angioplasty with or without stent placement, or procedures for other vascular insufficiency within 6 months of dosing.
10. Clinically significant or unstable heart failure that could interfere with the safety of the participant per investigator's assessment

Medical Conditions: Infectious or at Increased Risk of Infection

11. Infection with human immunodeficiency virus (HIV), hepatitis A virus (HAV), HBV (positive HBsAg or positive hepatitis B core antibody with negative hepatitis B surface antibody), hepatitis C virus (HCV), HDV or hepatitis E virus (HEV). HCV antibody positive participants with a negative HCV RNA are eligible. HDV antibody positive participants with a negative HDV RNA and negative HBsAg are eligible.

12. Any clinically significant acute condition such as fever ($> 38^{\circ}\text{C}$) or acute respiratory illness within 7 days of study drug administration
13. Participants with signs of active infection as deemed by the investigator
14. History of bone marrow or solid organ transplantation

Medical Conditions: Renal

15. Participants with electrolyte imbalance that poses a risk to participation in the opinion of the investigator at screening or Day 1 (D1)
16. Participants with end-stage renal disease or nephrotic syndrome as defined by:
 - a. Participants requiring hemodialysis or peritoneal dialysis
 - b. Participants who have undergone or are listed for transplant
 - c. Participants who have chronic kidney disease with nephrotic syndrome
17. Participants with active nephritis

Medical Conditions: Hepatic

18. Participants with clinically significant liver disease

Prior/Concomitant Therapy

19. Receipt of an oligonucleotide (eg, siRNA, antisense oligonucleotide) within 48 weeks before study intervention administration.

Prior/Concurrent Clinical Study Experience

20. Participation in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer)

Other Exclusions

21. History or clinical evidence of alcohol or drug abuse within 3 months before screening or a positive alcohol or drug screen at screening, per investigator assessment, unless it can be explained by a prescribed medication (the diagnosis and prescription must be approved by the investigator).

Note: cannabis use is permitted

22. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator, contraindicates their participation
23. Blood or blood products donated or substantial loss of blood (more than 500 milliliters [mL]) within 3 months before the study starts
24. Unwillingness or inability to follow the procedures outlined in the protocol

Exclusion Criteria: Additional Criteria Specific to Healthy Participants

25. Use of any prescription medications or over-the-counter medications (with the exception of vitamins and/or hormonal contraceptive medications) including herbal products within 30 days prior to D1 of study participation

Exclusion Criteria: Additional Criteria Specific to Participants with Renal Impairment

26. Not on stable dose and regimen of any medication(s) (prescription or over-the-counter) that the participants is taking regularly (eg, medications for chronic conditions such as hypertension, high cholesterol, or depression must not be changed in dose or type for at least 2 weeks prior to study drug administration). Use of other prescription or over-the-counter medications that are not for chronic conditions (with the exception of vitamins and/or hormonal contraceptive medications) including herbal products within 30 days prior to D1 of study participation.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

There will be no additional dietary restrictions in this study beyond dietary restrictions typically employed in the management of persons with RI.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants will abstain from consuming alcohol for 72 hours before the start of dosing and until after collection of the final PK sample. Participants should abstain from alcohol or avoid consuming more than 10 units of alcohol per week (1 unit = 1 glass of wine [125 mL] = 1 measure of spirits [30 mL] = one-half pint of beer [284 mL]), or more than 2 units of alcohol per day for the duration of the study.

Light smoking is allowed in this study. (Participants should not use tobacco or nicotine containing products in excess of the equivalent of more than 10 cigarettes per day) ([Boulos 2009](#)).

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during study period.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are subsequently not eligible to be enrolled or dosed in the study.

5.5. Criteria for Temporarily Delaying Enrollment

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. For eligibility purposes, clinical laboratory evaluations or vital sign measurements may be repeated once, if abnormal result is observed at the initial reading.

For inclusion, clinical laboratory results that are deemed inconsistent with the stage of RI may be repeated once.

Participants who do not qualify based on a reversible medical condition or mild intercurrent illness may be re-evaluated after further testing/examination or rescreened after the condition has resolved.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention, marketed product, or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Table 3: Study Intervention(s) Administered

Intervention Label	VIR-2218
Intervention Name	VIR-2218
Type	Oligonucleotide
Dose Formulation	Liquid in vial
Unit Dose Strength(s)	200 mg/mL at 0.5 mL
Dosage Level(s)	Up to 200 mg
Route of Administration	Subcutaneous injection
Use	Experimental
IMP and NIMP/AxMP	IMP
Sourcing	Provided centrally by the sponsor/designee
Packaging and Labeling	Single-use vial labeled as required by country requirement
Current or trade name(s)	VIR-2218

IMP = investigational medicinal product; NIMP/AxMP = non-investigational medicinal product/auxiliary medicinal product

6.2. Preparation, Handling, Storage, and Accountability

Detailed instructions on the preparation, handling and storage of study interventions will be provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a Phase 1 open-label, single-dose, parallel-group, inpatient, non-randomized study conducted in adult participants with RI and in healthy adult participants (1:1) matched by race, sex, age (± 10 years), BMI ($\pm 20\%$ of BMI at screening). Thus, the probability of bias for this study is minimal.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

6.5. Dose Modification

Based on safety, tolerability, and PK data from participants with moderate RI (Cohort 1), enrolled participants with severe RI (Cohort 2) may receive a reduced dose if the exposure (AUC_{last} , AUC_{inf} , C_{max}) in the moderate RI participants is > 3 -fold compared to their matched healthy controls.

6.6. Continued Access to Study Intervention After the End of the Study

No access to study intervention will be available to participants after the end of the study.

6.7. Treatment of Overdose

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine whether study intervention should be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until VIR-2218 can no longer be detected systemically (at least 5 days). Participant will be observed until any AE/SAE, laboratory abnormality, and/or until the overdose is considered to be resolved, has stabilized, or is otherwise explained at the discretion of the investigator and the medical monitor.
- Refer to Section [10.3.5](#) for reporting of overdose to sponsor.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Permitted Concomitant Medications

- Hormone replacement therapy
- Oral and injectable medications to treat diabetes mellitus type 1 or 2
- Oral, injectable, subdermal, intravaginal, or implantable contraceptives, as well as intrauterine device, and intrauterine hormone-releasing system are permitted for contraception
- Prescription drugs necessary to treat hypertension. Hypertension must be well controlled and on stable dose.
- Paracetamol (≤ 2 g/day), aspirin (≤ 3 g/day), or ibuprofen (< 1.2 g/day)
- Antihistamines
- Prescription inhaler or nebulizer to treat asthma (inhaled bronchodilator or inhaled steroid). Asthma must be well controlled, defined as historical use of a rescue bronchodilator on average no more than twice per week.
- Participants with RI may be taking medications which, in the opinion of the investigator, are believed to be therapeutic, and these medications should not interfere with the conduct of the study. Participants with RI should be on stable regimen of chronic medications for at least 14 days prior to study drug administration until completion of last follow-up visit.
- Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the medical monitor.

6.8.2. Prohibited Concomitant Therapy

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements), unless specified in Section 6.8.1 within 30 days prior to study drug administration.

The administration of any potentially hepatotoxic medications during the study should be considered only if no therapeutic alternative can be identified and after consideration of the potential risks and benefits for the participant as per investigator's assessment.

7. STUDY STOPPING RULES

If either of the following criteria are met within a cohort, all dosing in the cohort, as well as any other active cohort containing the same study drug(s), will be paused:

- 3 or more subjects experience Grade ≥ 3 study drug-related AEs or study drug-related SAEs in the same System Organ Class (SOC)
- 2 or more subjects experience Grade ≥ 4 study drug-related AEs or study drug-related SAEs in the same SOC
- Death in any subject in whom the cause of death is judged to be related to study drug

In the event the stopping criteria are met, an ad hoc safety meeting with the investigators(s) or their representative and sponsor medical monitor will be convened to review all available safety and PK data from all study subjects. The investigators and sponsor will document the decision whether to proceed with further dosing and enrollment in the cohort(s), and whether modification to the study protocol is needed.

7.1. Participant QTc Monitoring Guidance

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after baseline ECG and/or study drug administration, the investigator or qualified designee will determine if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.2. Participant Discontinuation/Withdrawal from the Study

If a participant discontinues from the study (eg, due to withdrawal of consent) post-dose but before the completion of the Week 8, an early termination (ET) visit should be performed.

7.3. Lost to Follow-Up/Replacement of Participants

Participants who are lost to follow-up or withdraw from the study may be replaced at the discretion of the sponsor. The replacement participant will be assigned a unique participant identification number and will be placed in the same cohort.

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Should the participant continue to be unreachable, or the vital status be determined as deceased, he/she will be considered to have withdrawn from the study. If the investigator becomes aware of an AE/SAE, the information must be recorded per Section 10.3.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Repeat or unscheduled laboratory samples may be taken for safety reasons or for technical issues with the samples.

8.1. Screening Period

Informed consent must be obtained before conducting any study-related procedures. Participant eligibility will be evaluated during the screening period and includes the assessments outlined in the SoA. The screening period duration is up to 28 days before a participant's first dose of study intervention.

8.1.1. Screening Viral Serology Parameters

Screening viral serology parameters are as follows: active infection with HIV, HAV, HBV, HCV, HDV and HEV. Participants who have positive HCV serology result must have HCV RT-PCR reflex testing to determine eligibility. HDV antibody positive participants must have HDV RT-PCR testing to determine eligibility.

8.1.2. Screening for Drugs of Abuse

Urine will be collected at the screening visit for drugs of abuse screening, per the SoA. The panel will include amphetamines, barbiturates, benzodiazepines, marijuana metabolites, cocaine, methadone, opiates, MDMA, methamphetamines, oxycodone, and phencyclidine.

8.2. Pharmacokinetics

8.2.1. Blood Sample Collection

- PK blood sample will be collected for measurement of plasma concentrations of VIR-2218 and metabolites as specified in the SoA. Concentration of the analytes of interest will be quantified using a validated assay.
- Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual.
- Blood samples will be collected pre-dose and post-dose for plasma protein binding assessment as specified in the SoA.

8.2.2. Urine Sample Collection

Pooled PK urine samples for the analysis of VIR-2218 and metabolite will be collected at the timepoints specified in the SoA. Detailed PK urine sample processing, storage and shipping procedures are provided in the Laboratory Manual.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.3.1. Physical Examinations

- A full physical examination will be conducted to determine the overall physical health of the participant, and any abnormal findings will be recorded as medical history. The physical examination may include but is not limited to general appearance, head, neck, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, extremities, skin, and screening neurological assessment. Height, weight, and BMI will be measured and recorded at screening. Weight will be reassessed at check-in.
- Symptom-directed physical examination will be performed in the event of new signs and symptoms only.

8.3.2. Vital Signs

Vital sign measurements include blood pressure, pulse rate, temperature (oral preferred), and respiratory rate. Vital signs should be measured after the participant has rested comfortably for approximately 10 minutes. When scheduled at the same timepoints, the assessments of vital signs must be performed before blood sample collections and study drug administration.

8.3.3. Electrocardiograms

A single 12-lead ECG will be obtained in a supine position after 10 minutes rest as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Electrocardiograms should be obtained prior to any vital sign measurements or blood draws scheduled on the same assessment day. Refer to Section 7.1 for QTc monitoring criteria and any additional QTc readings that may be necessary.

8.3.4. Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE or SAE, if applicable (refer to Section 10.3.4). The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study, or within 8 weeks after the last dose of study intervention, should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
 - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
 - All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the Laboratory Manual and the SoA.
 - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.3.5. Pregnancy Testing

A pregnancy test or confirmation of post-menopausal status must be confirmed for all female participants. Post-menopausal status is defined as no menses for 12 months without an alternative medical cause. An elevated follicle stimulating hormone (FSH) level in the post-menopausal range should be used to confirm a post-menopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). In the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required. Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Pregnancy tests will be performed for WOCBP only. Pregnancy testing will be performed per the SoA and any time pregnancy is suspected. A WOCBP who is known to be pregnant or who does not have a negative pregnancy test at screening is not eligible for study participation. A blood pregnancy test will be performed at screening and urine pregnancy tests will be performed thereafter. During the study, the results of these pregnancy tests must be known prior to study intervention administration. A WOCBP determined to be pregnant while on study will be followed until the pregnancy outcome is known, as described in Section 8.4.6.1.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs, SAEs, and other safety events are provided in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (Section 10.3.4).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.5.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs, regardless of causal relationship, will be collected from signing of the ICF until the end of the study.

After signing of the ICF, but prior to initiation of study intervention, AEs related to protocol-mandated procedures should be reported. Following initiation of study intervention, all AEs, regardless of causal relationship, will be recorded for the entire duration of the study.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent and are not considered related to protocol-mandated procedures, will be recorded as medical history/current medical conditions, not as AEs.

All SAEs must be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours from the investigator or designee awareness of the event, as indicated in Section 10.3.5. The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, pregnancy, and special situation reports (as defined in Section 10.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.4.

8.4.3. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met. The investigator will record the SAE information on the appropriate form and submit it to sponsor or designee within 24 hours of awareness of the event.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review the information, document the review in the electronic safety notification portal (if applicable) or file the safety report along with the relevant study documents, and will notify the IRB/IEC, if appropriate according to local requirements.

Assessment of expectedness for SAEs will be determined by the sponsor using the reference safety information (RSI) as specified in the IB.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.4. Adverse Events of Interest

Adverse events of interest are not applicable to this study.

8.4.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs or SAEs

Laboratory abnormalities without an associated AE (signs or symptoms) and/or which do not require medical intervention, are not themselves recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study intervention interruption, modification, or discontinuation must be recorded as an AE or as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, 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 Section 10.3. If the laboratory abnormality is part of a clinical syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 or later (presented in Section 10.3.4).

8.4.6. Special Situation Reports

All special situation reports (SSR) will be collected from the start of intervention until the end of follow-up period and include all reports of medication error, abuse, misuse, overdose, pregnancy, drug interactions, exposure via breastfeeding, unexpected benefit, occupational exposure, transmission of infectious agents via the product, counterfeit or falsified medicine, and product complaints (definitions presented in Section 10.3.3).

The investigator will record the special situation information on the appropriate form and submit it to the sponsor or designee within 24 hours of learning of the situation. These reports must consist of situations that involve study intervention and/or protocol-required concomitant medications but do not apply to non-required concomitant medications.

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 (from required and non-required medication) will also be reported as AEs or SAEs. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8.4.6.1. Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the end of study.

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor or designee within 24 hours of learning of the female participant or female partner of male participant pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner (after obtaining the necessary signed informed consent from the female partner) will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.3. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, if he/she learns of any SAE and considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

Any female participant who becomes pregnant while participating in the study may continue study participation and continue safety follow-up visits as per SoA.

The study participant and/or pregnant female partner, as applicable, should receive any necessary counseling regarding the risk of continuing the pregnancy and the possible effects on the fetus.

8.5. Genetics

Genetics are not evaluated in this study.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

There will be no immunogenicity assessments in this study.

8.8. Health Economics OR Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The primary objective of this study is to assess the pharmacokinetics of VIR-2218 in adult participants with RI and in matched healthy adult participants with normal renal function. The secondary objective is to assess the safety and tolerability of single-dose VIR-2218 in adult participants with RI and in matched healthy adult participants with normal renal function.

This section presents a summary of the principal features of the planned PK and safety analysis for this study. Statistical analysis details for both safety and clinical pharmacology will be in the statistical analysis plan (SAP), which will be finalized before clinical database lock.

9.1. Statistical Hypotheses

No statistical hypothesis and multiplicity adjustment are planned in this study.

9.2. Sample Size Determination

A sample size of 8 participants per renal function group per cohort will be enrolled to ensure the precise estimation of relevant PK parameters, AUC_{last} and C_{max} of VIR-2218 and metabolite AS(N-1)3'VIR-2218, so that the 95% confidence interval of the geometric mean estimate is within 60% and 140% of the estimate in each renal function group with at least 80% power. The assumption is based on the PK data obtained from a prior clinical study of VIR-2218 administered as a single SC dose in healthy participants (Study VIR-2218-1001).

9.3. Analysis Sets

Participant Analysis Set	Description
All Enrolled Set	The All Enrolled Set includes all participants who were assigned to study intervention. This analysis set will be used for individual participant listings and disposition summary table.
Pharmacokinetic (PK) Analysis Set	The PK Analysis Set includes all enrolled participants who received at least one dose of study drug and at least one measurable post-dose concentration. The PK Analysis Set will be used for all PK analyses.
Safety Analysis Set	The Safety Analysis Set includes all participants who received any amount of study drug. All safety, demographics, baseline characteristics, and concomitant medications will be summarized based on the Safety Analysis Set.

9.4. Statistical Analysis

9.4.1. General Considerations

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (n), mean, SD, median, minimum value (min), and maximum value (max). The precision of the measurement for each continuous variable will be specified in the SAP.

Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

Baseline value, unless otherwise specified, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the initial administration of study intervention. Baseline of eGFR will be the mean of two measurements of samples that are collected during screening.

Treatment-emergent Adverse Events (TEAE) will include any AE that is reported with an onset date on or after administration of study intervention until the last follow-up visit.

9.4.2. Background Characteristics

Participant disposition (eg, completed treatment, prematurely discontinued the treatment and the reason for discontinuation) will be summarized by treatment cohort and RI status.

Demographic and baseline characteristics will be summarized by treatment cohort and RI status. No statistical tests will be carried out to evaluate baseline imbalance between treatment cohorts and RI status.

Medications used will be coded using the World Health Organization Drug Dictionary (WHODrug) and summarized descriptively.

9.4.3. Pharmacokinetic Analysis

The pharmacokinetic analysis will be performed on PK analysis set. Plasma and urine concentrations of VIR-2218 and metabolite will be analyzed using noncompartmental analysis (NCA) methods using Phoenix WinNonlin version 8.3.2 or higher. Based on the individual concentration-time data the estimated PK parameters may include but not be limited to:

Parameter	Description
Plasma	
AUC _{inf}	Area under the concentration-time curve from time 0 (pre-dose) extrapolated to infinite time
AUC _{last}	Area under the concentration-time curve from time 0 (pre-dose) to time of last quantifiable concentration
C _{max}	Maximum observed concentration
λ_z	Terminal-phase rate constant
t _{1/2}	Terminal-phase half-life
T _{max}	Time to first occurrence of C _{max}
CL/F	Apparent oral clearance
Vz/F	Apparent volume of distribution
Urine	
Ae	Amount of drug excreted in urine in a time intervals indicated in the SoA
fe%	Percentage of the given dose of drug excreted in urine, calculated as: fe% = (Ae total/Dose) × 100
CL _R	Renal clearance of drug, calculated as: Ae total/AUC(0-t)

Blood and urine samples for PK analysis will be obtained from each participant prior to study drug administration and at selected times after study drug administration. Plasma pharmacokinetics will be analyzed for VIR-2218 and metabolite using a validated analytical method. Blood samples will be collected at pre-dose and post-dose for protein binding assay.

The primary PK endpoints will include AUC_{last}, AUC_{inf}, and C_{max}, for VIR-2218 and its metabolite AS(N-1)3'VIR-2218. The natural log-transformed plasma AUC_{last}, AUC_{inf}, and C_{max} values for VIR-2218 and its metabolite AS(N-1)3'VIR-2218 in the RI groups and healthy group will be compared using an analysis of variance. The ratio of least squared (LS) geometric mean between RI groups and healthy group and corresponding 90% CIs of AUC_{inf}, AUC_{last}, and C_{max} for VIR-2218 will be presented.

No-interaction criteria will be met if the 90% confidence intervals (CIs) for the ratios of least squares means (LSM) for the natural log-transformed PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) of participants with mild RI or severe RI, compared to healthy participants fall between 80.0% and 125.0%.

Additional PK parameters will include, but may not be limited to, T_{max}, t_{1/2}, CL/F, Vz/F, Ae and %fe as appropriate, for VIR-2218 and its metabolite AS(N-1)3'VIR-2218.

The relationships between estimated renal function (CL_R) and relevant PK parameters (C_{max} and AUCs) will be established using linear regression models with the PK parameters as the dependent variable and estimated renal function (CL_R) as the independent variable. Regression model parameters with graphs will be reported.

Plasma concentrations and urine concentrations of VIR-2218 and its metabolite and the PK parameters will be listed, and summary statistics (n, mean, SD, min, max, and coefficient of variation [CV]) will be presented for each cohort. Mean individual plasma concentration versus time profiles will be presented graphically on linear or semilogarithmic scales.

9.4.4. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

The safety profile of VIR-2218 will be assessed in terms of the following safety endpoints:

- TEAEs
- Clinical laboratory values (ie, hematology, serum chemistry, and urinalysis)
- ECGs
- Vital signs
- Physical examinations

For safety analysis, no statistical hypothesis testing will be conducted, and analyses will be performed based on descriptive summary statistics. Additional details will be provided in the SAP.

9.4.5. Exploratory Endpoint Analysis

Plasma protein binding at pre-dose and ~6 h post-dose may be assessed via a qualified bioanalytical method. Unbound fraction of VIR-2218 in plasma may be assessed in healthy participants and participants with RI.

9.5. Interim Analysis

No formal interim analysis will be performed for this study.

A safety review meeting will be held between the sponsor and investigators to evaluate PK, safety, and tolerability results of VIR-2218 from participants in Cohort 1 (moderate RI) prior to enrolling Cohort 2 (severe RI). See Section 9.4.3 for the details on the estimation of PK parameters.

Enrolled participants with severe RI, may receive a reduced dose if the exposure (AUC_{last} , AUC_{inf} , C_{max}) in the moderate RI is > 3-fold compared to their matching healthy controls. Alternatively, severe RI participants may not be enrolled if the plasma exposure reaches or exceeds the threshold exposure observed at the maximum administered dose of 900 mg and/or the safety/tolerability profile in participants with moderate RI is not supportive of dosing in severe RI as determined by the sponsor and investigator.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable ICH Good Clinical Practice (GCP) guidelines
 - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
 - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
 - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators, sub-investigators and applicable site staff are responsible for providing information on financial interests during the course of the study and for 1 year after site closure.

10.1.3. Informed Consent Process

The participant's signed and dated informed consent (either signed by participant or their legally authorized representative [LAR]) must be obtained before conducting any study procedures.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will be anonymized except for the identifier; participant names or any information which would make the participant identifiable will not be transferred.
- All participants must provide informed consent to the use and disclosure of their information obtained during the study. This includes informing the participant how his/her personal study-related data will be used by the sponsor, and the level of disclosure.
- The participant must also be informed and consent to the possible examination of his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Confidentiality

The investigator must assure that participant's anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only participant initials and date of birth (where local regulations allow) and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all participants screened and for all participants enrolled in the trial.

The investigator agrees that all information received from the sponsor, including but not limited to the IB, this protocol, case report forms, the investigational new drug, and any other study information, remain the sole and exclusive property of the sponsor 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 the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the clinical investigative site to any third party or otherwise into the public domain.

10.1.6. Committees Structure

No safety or other monitoring committees have been identified for this study.

10.1.7. Dissemination of Clinical Study Data

- Where required by applicable law, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to appropriate study information and results.
- Sponsor or designee will provide all investigators who enrolled participants into the study with a summary of the study results.
- The procedures and timing for public disclosure of study results summary will be in accordance with applicable laws.

10.1.8. Data Quality Assurance

Periodically, the sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial process and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the clinical investigative site to perform audits or inspections, including source data verification. The investigator should contact the sponsor, or its designee, immediately if contacted by a regulatory agency about an inspection.

10.1.9. Source Documents

All documentation relating to the study should be retained for the period of time required by applicable local law. If it becomes necessary for the sponsor or designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the sponsor in writing and giving the sponsor the opportunity to store the records for a longer period of time at the sponsor's expense.

10.1.10. Electronic Case Report Forms (eCRFs)

- Data collected during the study (except clinical laboratory results, PK analysis, study disease testing results, immunogenicity) will be recorded in each participant's eCRF provided by the sponsor or designee.
- The study site(s) will use an electronic data capture (EDC) system that is compliant with relevant Food and Drug administration (FDA) regulatory requirements per 21 CFR Part 11.
- Data queries and data correction on the eCRF will be handled through the same system.
- All transactions within the EDC system are fully documented within an electronic audit trail.
- Data reported on the eCRF must be transcribed from a source document with consistency and accuracy.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm the accuracy of data entered into the eCRF. Each set of completed eCRFs must be reviewed after being source verified by the monitor and electronically signed and dated by the investigator.

10.1.11. Study and Site Start and Closure

10.1.11.1. First Act of Recruitment

The first act of recruitment is the first participant dosed and will be the study start date.

10.1.11.2. Study/Site Termination

The sponsor or designee reserves the right to close the study site and/or terminate one or more individual cohorts, or the overall study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. If the investigator terminates or suspends a trial without the prior agreement of the sponsor, the investigator should inform the institution (where applicable) of the suspension or termination at the investigative site. The investigator / institution should promptly inform the IRB/EC and the sponsor of the termination/ suspension with a detailed, written explanation of the reason for the suspension or termination of the trial.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.12. Publication Policy

Site-specific results of this study may be published or presented at scientific meetings subject to the terms and requirements of the clinical trial agreement.

10.2. Appendix 2: Clinical Laboratory Tests

Table 4: Protocol-Required Safety Laboratory Tests

Chemistry	Hematology
Albumin Blood urea nitrogen (BUN) Calcium Bicarbonate Chloride Creatinine Gamma-glutamyltransferase Glucose (non-fasting) Lactate dehydrogenase (LDH) Potassium Protein (total) Sodium <u>Liver Function Tests:</u> Alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total and direct)	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit <u>White blood cell (WBC) count with differential:</u> neutrophils, lymphocytes, monocytes, eosinophils, basophils Hemoglobin A1C (HbA1C) <u>RBC indices:</u> mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), % reticulocytes
Coagulation Parameters	Pregnancy Testing
D-dimer International normalized ratio (INR) time Partial thromboplastin time (PTT)/activated PTT (aPTT) Prothrombin time (PT) Vitamin K	Highly sensitive (serum/plasma or urine) human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) Follicle stimulating Hormone (FSH) (required for confirmation of menopause as applicable)
Urinalysis	Screening Viral Serology
Specific gravity Glucose, pH, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick Microscopic examination (if blood or protein is abnormal) Alcohol and drug screen (to include: amphetamines, barbiturates, benzodiazepines, marijuana metabolites, cocaine, methadone, opiates, MDMA, methamphetamines, oxycodone, and phencyclidine)	Hepatitis A ^a , B, C ^b , D ^c and E ^a HIV I and II

^a Participants with positive HAV IgM or HEV IgM but asymptomatic and with a positive HAV IgG or HEV IgG are eligible.

^b Participants with positive HCV screening serology must have HCV RT-PCR performed to determine eligibility.

^c Participants with positive HDV screening serology must have HDV RT-PCR performed to determine eligibility.

10.3. Appendix 3: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting AEs, SAEs, and SSRs

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • AEs may also include pre- or post-treatment complications that occur as a result of protocol-specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements) that require medical or surgical intervention or lead to study intervention interruption, modification, discontinuation, or are considered clinically significant in the medical and scientific judgment of the investigator • Laboratory or other abnormal assessments (eg, 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. If the laboratory abnormality is part of a clinical syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin). • Exacerbation of a chronic or intermittent pre-existing condition (recorded as medical history) including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected study intervention interaction, including drug/drug, drug/food, drug/device and drug/alcohol interactions • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE

Events <u>NOT</u> Meeting the AE Definition
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition - The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition - Medical or surgical procedure (eg, endoscopy, appendectomy, transfusion, tooth extraction): the condition that leads to the procedure is the AE - Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen - Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, hospitalization for elective surgery) - Overdose of study intervention without clinical sequelae - Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the screening visit that do not worsen

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:
1. Results in death
2. Is life-threatening 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, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization - In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:
4. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption
5. Is a congenital anomaly/birth defect
6. Other medically important events • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. – Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse, suspected transmission of any infectious agent via an authorized medicinal product

10.3.3. Definitions of Special Situations (SSR)

Special Situation Report (SSR) Definitions
• Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, participant, or consumer. • Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a participant. • Misuse is defined as any intentional and inappropriate use of a medicinal product 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 medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol (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 pharmacist cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the additional dose(s) were administered to the participant. • Occupational exposure is defined as exposure to a study intervention as a result of one's professional or nonprofessional occupation. • Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Special Situation Report (SSR) Definitions

- 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 Vir study intervention.
- Counterfeit or falsified medicine: Any study intervention with a false representation of (a) its identity, (b) its source, or (c) its history.
- Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

The signs, symptoms, and/or clinical sequelae resulting from a special situation will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

10.3.4. Recording and Follow-Up of AEs, SAEs, and/or SSRs (including Pregnancies)

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- All SAEs should be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For fatal or life-threatening events, copies of hospital case reports, discharge summaries, autopsy reports, and other documents should be submitted 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 AE/SAE must be recorded onto the concomitant medication section of the participant's eCRF and the event description section of the SAE form.

Assessment of Severity	
The investigator will assess severity for each AE and SAE reported during the study according to the standard toxicity grading in the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.	
Severity	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

ADL = activities of daily living
For each event, the highest grade attained should be reported.
Source: ([NCI 2017](#))

Assessment of Causality
- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship (Yes or No). - A <i>reasonable possibility</i> of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. - Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. - An answer of Yes should be entered when, in the investigator's opinion, there is a reasonable possibility that the AE is associated with study intervention. Otherwise, relationship to study intervention should be categorized as No. - The investigator will also consult the Investigator's Brochure (IB) and/or product information, for marketed products, in his/her assessment. - For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

Assessment of Causality

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| <ul style="list-style-type: none">• The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.• The causality assessment is one of the criteria used when determining regulatory reporting requirements. |
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Follow-up of AEs, SAEs, and/or SSRs (including Pregnancies)
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| <ul style="list-style-type: none">• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.• If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.• New or updated information will be recorded in the originally submitted documents.• The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information. |
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10.3.5. Reporting of SAEs and SSRs (Including Pregnancies)

Safety (SAE, SSR, and Pregnancy) Reporting to Sponsor
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| <ul style="list-style-type: none">• Email or Facsimile transmission of the paper data collection tool is the preferred method to transmit this information to the sponsor within 24 hours.• The investigator is responsible for assessing SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments on the reporting forms.• Sponsor's designee for receipt of all reports is UBC Pharmacovigilance.• Contacts for safety reporting is as follows: |
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UBC Pharmacovigilance:

Email: VirBioPV@ubc.com

US Fax: (+1) 877-867-1822

Europe and Asia-Pacific Fax: (+44) 20 3936 2286

10.4. Appendix 4: List of Abbreviations and Definitions of Terms

ADA	anti-drug antibodies
AE	adverse events
ALT	alanine aminotransferase
ASGPR	asialoglycoprotein receptors
AST	aspartate aminotransferase
BMI	body mass index
CIOMS	Council for International Organizations of Medical Sciences
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ESC+	Enhance Stability Chemistry
ESRD	end-stage renal disease
ET	early termination
FDA	Food and Drug administration
FSH	follicle stimulating hormone
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committees

IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional review boards
ISR	injection site reaction
LSM	least square means
MDRD	Modification of Diet in Renal Disease
NIMP/AxMP	non-investigational medicinal product/auxiliary medicinal product
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic
PopPK	Population PK
QTc	Corrected QT
QTcF	changes from baseline in QT interval corrected using Fridericia's formula
RBC	red blood cell
RI	renal impairment
RNAi	ribonucleic acid interference
RSI	Reference Safety Information
SAE	serious adverse events
SAP	statistical analysis plan
SC	subcutaneous
siRNA	small interfering ribonucleic acid
SoA	Schedule of Activities
SOC	system organ class
SSR	special situation reports
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	treatment-emergent adverse event
WBC	white blood cell
WOCBP	women of childbearing potential

10.5. Appendix 5: Contraceptive and Barrier Guidance

WOCBP may be included in this study and include any female participant who has experienced menarche and who is not post-menopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).

WOCBP must be willing to use highly effective methods of contraception from 14 days before the first dose of study intervention to 8 weeks after the final dose of study intervention. Highly effective methods of birth control are defined as those that result in a low failure rate (ie, less than 1% per year). Birth control methods which are considered highly effective include:

- Established use of combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal methods of contraception associated with inhibition of ovulation OR established use of progestogen-only oral, injectable, or implantable hormonal methods of contraception associated with inhibition of ovulation. It is not currently known whether VIR-2218 will impact the effectiveness of hormonal contraceptive methods; therefore, it is recommended to use an additional form of contraception (ie, barrier method) for 8 weeks after study intervention administration.
- Placement of an intrauterine device
- Placement of an intrauterine hormone-releasing system
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female participants on the study, the vasectomized male partner should be the sole partner for that participant)
- True sexual abstinence from heterosexual contact, when in line with the preferred and usual lifestyle of the participant. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent participants must agree to use 1 of the above-mentioned contraceptive methods for 8 weeks after study intervention administration if they start heterosexual relationships during the study.
- Barrier method in combination with hormonal contraceptive, as described above

Post-menopausal status is defined as 12 months with no menses without an alternative medical cause. An elevated FSH level in the post-menopausal range should be used to confirm a post-menopausal state in women not using hormonal contraception or HRT. In the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Female participants must also refrain from egg donation and in vitro fertilization from the time of study treatment administration until 8 weeks after study intervention administration.

Male participants with female partners of childbearing potential must agree to meet 1 of the following contraception requirements from the time of study treatment administration until 8 weeks after study intervention administration.

- Vasectomy with documentation of azoospermia
- Male condom plus partner use of 1 of the contraceptive options listed above for contraception for WOCBP (hormonal contraceptive, intrauterine device)

Male participants must also agree not to donate sperm for the 8 weeks following last study intervention administration.

10.6. Appendix 6: MDRD Equation Definition

$$\text{eGFR} = 175 \times (\text{SerumCr}^{-1.154}) \times (\text{age}^{-0.203}) \times 1.212 \text{ (if patient is Black or African American)} \\ \times 0.742 \text{ (if female)}$$

Units for eGFR (estimated glomerular filtration rate) = mL/min/1.73 m²

Units for SerumCr (standardized serum creatinine) = mg/dL

age = years

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