A Phase 2 Randomized, Placebo-Controlled Study in Mainland China to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of VIR-2218

NCT04507269

Protocol Amendment 2

23 September 2020

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Randomized, Placebo-Controlled Study in Mainland China to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of VIR-2218
Sponsor:	Brii Biosciences Ltd. Room 301, 3/F, Building 7, No. 1 Yongtaizhuang North Street, Haidian District, Beijing 100192, China
Investigational Product:	VIR-2218
Clinicaltrials.gov ID:	NCT04507269
Indication:	Chronic Hepatitis B (HBV) Infection
Protocol ID:	VIR-2218-1005
Study Director:	PPD [redacted]
Medical Monitor:	PPD [redacted]
Protocol Version/Date:	Amendment 2: 23 September 2020

CONFIDENTIALITY STATEMENT

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	23 September 2020
Amendment 1	07 April 2020
Original Protocol	06 September 2019

Amendment 2 (23 September 2020)

The changes and rationale for the changes from the Protocol Amendment 1 dated 07 April 2019 to Amendment 2 dated 23 September 2020 are as follows. Wording that has been deleted will be indicated with a strikethrough (ex. ~~Word~~) and new wording will be indicated in Bold type (ex. **Word**).

Affected Sections:	Section 5.3 Exclusion Criteria, Item 7
Original Text:	Each subject must not meet any of the following exclusion criteria to be eligible for enrollment in the study: 7. Subjects has the following laboratory parameters at screening by central laboratory: a. creatinine, total bilirubin, international normalized ratio (INR) or prothrombin time above the upper limit of normal (ULN)
Amended Text:	Each subject must not meet any of the following exclusion criteria to be eligible for enrollment in the study: 7. Subjects has the following laboratory parameters at screening by central laboratory: a. creatinine or total bilirubin above the upper limit of normal (ULN), **OR international normalized ratio (INR) above 1.1x ULN**
Rationale:	Based on the comparison of coagulation data in the same patient population from the central laboratory for this study and those from a different central laboratory and a certified local clinical laboratory, the central laboratory for this study reported higher PT results that were not considered either clinically significant or exclusive. INR is a standardized calculation based on the PT result of the specific sample versus the PT result of a reference sample. INR has been recognized extensively as a standardized marker to evaluate coagulation function in patients

	with all stages of liver diseases. Changes avoid unnecessary and medically inaccurate exclusion of eligible subjects for this study.
Categorization:	Non-substantial

Affected Sections:	Appendix 2 Part One/Two Schedule of Assessments (SoA) for Planned and Optional Cohorts in Subjects with Chronic HBV Infection, Footnote h of Vital signs
Original Text:	On Day 1, vital signs should be measured within 2 hours predose and 4 hours post-dose.
Amended Text:	On Day 1, vital signs should be measured within 2 hours predose and 4 hours **(± 30 minutes)** post-dose.
Rationale:	Clarification on the time window for collection of vital signs post-dose on Day 1.
Categorization:	Non-substantial

Affected Sections:	Appendix 2 Part One/Two Schedule of Assessments (SoA) for Planned and Optional Cohorts in Subjects with Chronic HBV Infection, Footnote j of Pregnancy test
Original Text:	A blood pregnancy test will be performed at screening and urine pregnancy tests will be performed thereafter.
Amended Text:	A blood pregnancy test will be performed at screening and urine pregnancy tests will be performed thereafter. **Urine pregnancy test results from local laboratories are acceptable.**
Rationale:	Clarification on allowing local laboratory results for urine pregnancy tests.
Categorization:	Non-substantial

Affected Sections:	Appendix 3 Part One/Two Pharmacokinetic Assessment Timepoints
Original Text:	Converted from the tabular format: PK blood will be collected at 1 hour, 2 hours, 4 hours, 8 hours, and 24 hours post-dose on Day 1 and Week 4.

Amended Text:	Converted from the tabular format: PK blood will be collected at 1 hour **(± 5 minutes)**, 2 hours **(± 10 minutes)**, 4 hours **(± 30 minutes)**, 8 hours **(± 30 minutes)**, and 24 hours **(± 2 hours)** post-dose on Day 1 and Week 4.
Rationale:	Clarification on the time windows for PK sample collections.
Categorization:	Non-substantial

Affected Sections:	Section 8.3.2 Serious Adverse Events
Original Text:	Email or fax the SAE form within 24 hours of the investigator's knowledge of the event. Contact information is as follows: PPD [redacted]
Amended Text:	Email ~~or fax~~ the SAE form within 24 hours of the investigator's knowledge of the event. Contact information is as follows: PPD [redacted]
Rationale:	Changes reflect the correct information of SAE reporting contact.
Categorization:	Non-substantial

Affected Sections:	Section 8.5.2 Special Situations Reports
Original Text:	All other special situations must be reported to PRA Pharmacovigilance within 24 hours of the investigator becoming aware of the situation. Contact information is as follows: PPD [redacted]
Amended Text:	All other special situations must be reported to ~~PRA Pharmacovigilance~~ **the Sponsor** within 24 hours of the investigator becoming aware of the situation. Contact information is as follows: PPD [redacted]

Rationale:	Changes reflect the correct information of special situations reporting contact.
Categorization:	Non-substantial

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PROTOCOL SYNOPSIS

Study Title:	A Phase 2 Randomized, Placebo-Controlled Study in Mainland China to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of VIR-2218
Clinical Investigative Sites Planned:	Planned to be conducted at multiple clinical investigative sites in mainland China.
Phase	Phase 2
Number of Subjects Planned:	Up to 30 subjects
Target Population:	Up to 30 adult subjects with HBeAg-negative or HBeAg-positive chronic hepatitis B virus (HBV) without cirrhosis on nucleos(t)ide reverse transcriptase inhibitor (NrtI) therapy.
Diagnosis and Main Eligibility Criteria	Adult subjects with chronic HBV infection without cirrhosis on NrtI therapy.
Duration of Study Participation:	Inclusive of screening to post-dose follow-up, the estimated total time on study for each subject is up to 20 weeks: screening period (4 weeks), dosing period (4 weeks) and post-dose follow-up period (12 weeks). Additional HBsAg monitoring is required for subjects with a ≥ 1 $1og_{10}$ change from baseline (Day 1 predose level) decrease in HBsAg achieved by the Week 16 visit. Subjects will be followed until the HBsAg level returns to > 90% of the Day 1 predose level or Week 48, whichever comes earlier. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.
Duration of Follow-up:	**Post-dose follow-up period:** All subjects will be followed until Week 16. **Extended follow-up period:** Extended follow-up visits will occur every 4 weeks starting at Week 20 and up to Week 48.

Objective(s):	Primary objective: • To evaluate the safety and tolerability of multiple doses of VIR-2218 in subjects with HBeAg-negative and HBeAg-positive chronic HBV infection without cirrhosis on NrtI therapy Secondary objectives: • To characterize the pharmacokinetics (PK) of VIR-2218 in subjects with chronic HBV infection without cirrhosis on NrtI therapy • To assess the antiviral activity of VIR-2218 in subjects with chronic HBV infection without cirrhosis on NrtI therapy CCI [redacted]
Study Design:	This is a phase 2 randomized, double-blind, placebo-controlled study of VIR-2218 administrated subcutaneously to adult subjects with chronic HBV infection without cirrhosis on NrtI therapy. The study is designed to evaluate the safety, tolerability, PK and antiviral activity of VIR-2218. This study will be conducted in close collaboration with an ongoing phase 1/2 regional study (VIR-2218-1001, ClinicalTrials.gov Identifier: NCT03672188) conducted at multiple sites in the Asia-Pacific region. The objective of the VIR-2218-1001 regional study is to evaluate safety, tolerability, PK and antiviral activity of VIR-2218 in healthy volunteers (HVs) and patients with chronic HBV infection. The VIR-2218-1001 regional study includes 3 Parts, which are a single ascending dose (SAD) study in HV adult subjects (Part A), and two multiple ascending dose (MAD) studies in adult subjects with HBeAg-negative (Part B) and HBeAg-positive (Part C) chronic HBV infection without cirrhosis on NrtI therapy, respectively. Safety and efficacy data collected from the VIR-2218-1001 regional study will be used to guide the conduct of this study. A Safety Review Committee (SRC) will perform ongoing reviews of safety and tolerability based on data collected through both this study and the VIR-2218-1001 regional study. This study (VIR-2218-1005) will include two Parts:

- Part One: adult subjects with HBeAg-negative chronic HBV infection without cirrhosis on NrtI therapy for ≥ 6 months and HBV DNA < 90 IU/mL at screening (by central laboratory)
- Part Two: adult subjects with HBeAg-positive chronic HBV infection without cirrhosis on NrtI therapy for ≥ 6 months and HBV DNA < 90 IU/mL at screening (by central laboratory)

The cohort dosing strategy of this study is based on data collected from the VIR-2218-1001 regional study. There are two planned cohorts (50 mg dose-level and 100 mg dose-level) for each of Part One and Part Two of the study. For each of the planned cohorts, 5 subjects will be randomized 4:1 to VIR-2218 or placebo administered 4 weeks apart on Day 1 and Week 4.

One optional cohort may be added to each study Part One and Part Two, wherein 5 subjects will be randomized 4:1 to VIR-2218 or placebo, administered on Day 1 and Week 4 at a maximum dose-level of up to 200 mg.

The optional cohorts may be initiated after SRC review of a minimum of 6 weeks of available safety and antiviral activity data from the 200 mg cohorts of the VIR-2218-1001 regional study.

Study Procedures:

Screening period:

Screening will be performed no more than 4 weeks before the Day 1 visit and will include written informed consent, determination of eligibility, collection of demographics and medical history as well as physical examination (including vitals), laboratory tests, 12-lead Electrocardiogram (ECG) and other assessments per the schedule of assessments. Adverse events related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All serious adverse events (SAEs) must be collected from the time of consent onwards.

Dosing period:

The dosing period is outpatient. Eligible subjects will be randomized to receive VIR-2218 or placebo within 48 hours before study drug administration on Day 1. Subjects will return to the clinical investigational site at Week 4 to receive a second dose of the same study drug administered on Day 1.

For subjects enrolled into the optional cohorts, eligible subjects will be randomized to receive VIR-2218 or placebo within 48 hours before study drug administration on Day 1. Subjects will return to the

	clinical investigational site at Week 4 to receive a second dose of the same study drug administered on Day 1. **Post-dose follow-up period:** Subjects will return to the clinical investigative site on an outpatient basis for safety, tolerability, PK, and antiviral activity monitoring at specified timepoints during this Post dose Follow up period (Week 5 to Week 16). Additional HBsAg monitoring is required for subjects with a ≥ 1 $1og_{10}$ change from baseline (Day 1 predose level) decrease in HBsAg achieved by the Week 16 visit. **Extended follow-up period:** Subjects who require additional HBsAg monitoring will return to the clinical investigational site for in-person assessments. Extended follow-up visits will occur every 4 weeks starting at Week 20, and subjects will be followed until the HBsAg level returns to > 90% of the Day 1 predose level or Week 48, whichever comes earlier. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.
Investigational Product, Dose, and Mode of Administration:	VIR-2218 is a synthetic, chemically modified small interfering RNA (siRNA) targeting HBV RNA with a covalently attached triantennary N-acetylgalactosamine (GalNAc) ligand that allows for specific uptake by hepatocytes. VIR-2218 will be supplied as a sterile solution for subcutaneous injection at a free acid concentration of 200 mg/mL. The starting dose level for the planned Cohorts in Parts One and Two will be 50 mg and 100 mg; the maximum dose level in the optional cohorts will not exceed 200 mg.
Reference Therapy:	Subjects randomized to placebo will be administered sterile, preservative-free normal saline 0.9% solution for subcutaneous injection.
Criteria for Evaluation:	Primary Endpoints • Incidence of treatment-emergent adverse events (TEAEs) • Clinical assessments including but not limited to laboratory test results Secondary Endpoints • PK parameters of VIR-2218 and possible metabolites (may include, but not limited to, maximum plasma concentration, time to reach maximum concentration, area under the concentration versus time curve [to last measurable timepoint and to infinity], percent of area extrapolated, apparent terminal elimination half-life, clearance, and volume of distribution)

- Maximum reduction of serum HBsAg from Day 1 until 12 weeks post last dose
- Number of subjects with serum HBsAg loss at any timepoint
- Number of subjects with sustained serum HBsAg loss for greater than or equal to 6 months post last dose
- Number of subjects with anti-HBs seroconversion at any timepoint
- For HBeAg-positive subjects (Part Two only): number of subjects with HBeAg loss and/or anti-HBe seroconversion at any timepoint

CCI [redacted]

Statistical Methods:	Statistical analyses will be primarily descriptive. All study data will be presented by subject data listings. Summary tables will present results by cohort for each VIR-2218 dose and placebo, where the placebo subjects will be combined across dose cohorts. Descriptive statistics will be presented for continuous variables, and frequencies and percentages will be presented for categorical and ordinal variables. Percentages will be based on the number of non-missing values in a dose group. Details will be provided in the Statistical Analysis Plan.

This study will be conducted in accordance in compliance with the protocol, International Conference on Harmonisation Good Clinical Practices (ICH GCP) and applicable state, local, and federal regulatory requirements including archiving of essential documents.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBe	hepatitis B extracellular antibody
anti-HBs	hepatitis B surface antibody
ALP	alkaline phosphatase
ASGPR	asialoglycoprotein receptor
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
BUN	blood urea nitrogen
cccDNA	covalently closed circular DNA
CL_{cr}	creatinine clearance
CRF	case report form
CTCAE	common terminology criteria for adverse events
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	electronic case report form
ET	early termination
ESC+	enhanced stabilization chemistry plus
GalNAc	N-acetyl-galactosamine
GCP	good clinical practice
GGT	gamma glutamyl transferase
GLP	good laboratory practice
GNA	glycol nucleic acid
CCI	[redacted]
HBcAg	hepatitis core antigen

HBeAg	hepatitis B e-antigen
HBsAg	hepatitis surface antigen
HBV	hepatitis B virus
HBx	hepatitis B protein X
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HEDs	human equivalent doses
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
HV	healthy volunteer
ICF	informed consent form
ICH	international conference on harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IWRS	interactive web response system
LDH	lactate dehydrogenase
LLN	lower limit of normal
LLOQ	lower limit of quantitation
LLT	lower-level term
MAD	multiple ascending dose
MedDRA	medical dictionary for regulatory activities
mRNA	messenger RNA
NHP	non-human primate
NOAELs	no observed adverse effect levels
NrtI	nucleos(t)ide reverse transcriptase inhibitor
OTC	over-the-counter
PEG-IFN	pegylated interferon-alpha

pgRNA	pregenomic RNA
PK	Pharmacokinetics
Pol/RT	polymerase, reverse transcriptase
PT	preferred term
Q1	first quartile
Q3	third quartile
RBC	red blood cell (count)
rcDNA	relaxed-circular DNA
SAD	single ascending dose
SADR	serious adverse drug reaction
SAE	serious adverse event
SC	Subcutaneous
SD	standard deviation
siRNA	small interfering RNA
SoA	schedule of assessments
SOC	system organ class
SRC	safety review committee
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir disoproxil fumarate
TDF	tenofovir alafenamide
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell (count)
WHO	world health organization
WOCBP	women of child-bearing potential

1. INTRODUCTION

1.1. Background

VIR-2218 is a synthetic small interfering RNA (siRNA) therapeutic being developed for the treatment of chronic hepatitis B virus (HBV) infection. Chronic HBV infection remains an important global public health problem with significant morbidity and mortality (Trepo, 2014). According to the World Health Organization (WHO) an estimated 257 million people are living with chronic HBV infection worldwide (WHO, 2019; Schweitzer, 2015). Over time, chronic HBV infection leads to serious sequelae including cirrhosis, liver failure, hepatocellular carcinoma (HCC), and death. Almost 800,000 people are estimated to die annually due to sequelae associated with chronic HBV infection (Stanaway, 2016). China has the highest chronic HBV burden in the world, with an estimated 90 million people, or almost 7% of China's population, who are chronically infected, resulting in 330,000 deaths each year (WHO, 2015).

More broadly, HBV prevalence varies geographically, with a range of less than 2% in low to greater than 8% in high prevalence countries (Schweitzer, 2015). In high prevalence countries, such as those in sub-Saharan Africa and East Asia, transmission occurs predominantly in infants and children by perinatal and horizontal routes. In more industrialized countries, new infections are highest among young adults and transmission occurs predominantly via injection drug use and high-risk sexual behaviors. The risk of developing chronic HBV infection depends on the age at the time of infection. While only ~10% of people infected as adults develop chronic HBV infection, 90% of infants infected perinatally or during the first 6 months of life, and 20–60% of children infected between 6 months and 5 years of age remain chronically infected. Twenty-five percent of people who acquire HBV during infancy and childhood will develop primary liver cancer or cirrhosis during adulthood.

HBV is a DNA virus that infects, replicates, and persists in human hepatocytes (Protzer, 2012). The small viral genome (3.2 kb), consists of partially double-stranded, relaxed-circular DNA (rcDNA) and has 4 open reading frames encoding 7 proteins: HBcAg (HBV core antigen, viral capsid protein), HBeAg (hepatitis B e-antigen), HBV Pol/RT (polymerase, reverse transcriptase), PreS1/PreS2/HBsAg (large, medium, and small surface envelope glycoproteins), and HBx (HBV × antigen, regulator of transcription required for the initiation of infection) (Seeger, 2015; Tong, 2016).

In hepatocytes, rcDNA, the form of HBV nucleic acid that is introduced by the infection virion, is converted into a covalently closed circular DNA (cccDNA), which persists in the host cell's nucleus as an episomal chromatinized structure (Allweiss, 2017). cccDNA serves as a transcription template for all viral transcripts (Lucifora, 2016). Pregenomic RNA (pgRNA) transcripts are reverse transcribed into new rcDNA for new virions, which are secreted without causing cytotoxicity. In addition to infectious virions, infected hepatocytes secrete large amounts of genome-free subviral particles, that may exceed the number of secreted virions by 10,000-fold (Seeger, 2015). Random integration of the virus into the host genome can occur as well, a mechanism that contributes to hepatocyte transformation (Levrero, 2016).

In acute resolving infections, the virus is cleared by effective innate and adaptive immune responses that include cytotoxic T cells leading to death of infected hepatocytes, and induction of

B cells producing neutralizing antibodies that prevent the spread of the virus (Bertoletti, 2016; Maini, 2016; Li, 2016). In contrast, chronic infection is associated with T and B cell dysfunction, mediated by multiple regulatory mechanisms including presentation of viral epitopes on hepatocytes and secretion of subviral particles (Bertoletti, 2016; Maini, 2016; Burton, 2018). Thus, the continued expression and secretion of viral proteins due to cccDNA persistence in hepatocytes is considered a key step in the inability of the host to clear the infection.

Chronic HBV infection is a dynamic process reflecting the interaction between HBV replication and host immune responses. The laboratory hallmark of chronic HBV infection is persistence of HBsAg in the blood for greater than 6 months, and a lack of detectable anti-HBs. Chronic infection is divided into 4 stages based on HBV markers in blood (HBsAg, HBeAg/anti-HBe, HBV DNA), and liver disease based on biochemical parameters (alanine aminotransferase (ALT)), as well as fibrosis markers (noninvasive or based on liver biopsy) (EASL, 2017). Overall, across the various phases of chronic HBV infection, only a minority of patients (less than 1% per year) clear the disease as measured by HBsAg seroclearance.

Currently, there are 2 main treatment options for patients with chronic HBV infection: treatment with nucleos(t)ide reverse transcriptase inhibitors (NrtIs) and pegylated interferon-alpha (PEG-IFN) (Liang, 2015). NrtIs inhibit the production of infectious virions, and often reduce serum HBV DNA to undetectable. However, NrtIs do not directly eliminate cccDNA, and therefore, transcription and translation of viral proteins continues. Consequently, expression of viral epitopes on hepatocytes, secretion of subviral particles, and immune dysfunction remain largely unaffected by NrtI therapy. In turn, this necessitates prolonged, often lifelong therapy; furthermore, while NrtI therapy reduces the incidence of HCC, it does not eliminate the increased risk of HCC that HBV infection confers. In contrast, PEG-IFN can induce long-term immunological control, but only in a small percentage of patients (< 10%) (Konerman, 2016). The high variability of response, in combination with an unfavorable safety profile make a significant number of patients ineligible or unwilling to undergo PEG-IFN treatment.

The failure of NrtI therapy to eradicate the virus, and the limitations of PEG-IFN therapy highlight the clinical need for new HBV therapies that are effective, well tolerated, and do not require lifelong administration. To address this unmet need, Vir is developing an investigational agent, VIR-2218, for the treatment of chronic HBV infection. In preclinical models, VIR-2218 inhibits viral replication, translation, and secretion of HBsAg. Therefore, VIR-2218 has the potential, alone or in combination with other therapies, to achieve a functional cure of chronic HBV infections.

1.2. VIR-2218

1.2.1. VIR-2218 Description

VIR-2218 is an siRNA targeting a region of the HBV genome that is common to all HBV viral transcripts. The siRNA is chemically modified using Enhanced Stabilization Chemistry Plus (ESC+) consisting of 2'-fluoro (2'F), 2'-O-methoxy (2'OMe) ribose sugar modifications, phosphorothioate backbone modifications, glycol nucleic acid (GNA) modification, and conjugation to a triantennary N-acetyl-galactosamine ligand (GalNAc) at the 3' end of the sense strand, to facilitate delivery to hepatocytes through the asialoglycoprotein receptor (ASGPR). The drug product, VIR-2218, is the drug substance VIR-2218 formulated in water for subcutaneous (SC) injection.VIR-2218 is pharmacologically active against HBV genotypes A through J; see the Investigator's Brochure for additional information on VIR-2218.

1.2.2. Rationale for VIR-2218 for the Treatment of HBV Infection

The use of siRNA offers a novel strategy for the treatment of chronic HBV infection. siRNAs are 19-21 base-pair RNA duplexes that exploit the endogenous RNA-interference pathway to enable sequence-specific RNA cleavage and degradation. One siRNA can have multiple antiviral effects, including degradation of the pgRNA, thus inhibiting viral replication, and degradation of all viral messenger RNA (mRNA) transcripts, thereby preventing expression of viral proteins. This may result in the return of a functional immune response directed against HBV, either alone or in combination with other therapies.

By contrast, NrtIs act at a distinct part of the viral life cycle and have a different mechanism of action than VIR-2218. NrtIs inhibit the action of HBV DNA polymerase, blocking the reverse transcription of the viral pgRNA to viral DNA and preventing the production of infectious virions. NrtIs, however, do not directly impact the production of viral proteins such as HBsAg. Reduction of HBsAg-containing noninfectious subviral particles by VIR-2218 is considered an important differentiator from current treatments.

Subjects randomized to active treatment for this study will receive VIR-2218 added to their ongoing NrtI therapy. Such subjects have already been determined by their physician to require treatment. Based on the known mechanisms of action there is no risk for pharmacodynamic drug-drug interactions or overlapping toxicities between NrtIs and siRNA.

1.2.3. Nonclinical Data

Refer to the Investigator's Brochure for VIR-2218 Nonclinical data.

1.2.4. Rationale for Dose Selection

VIR-2218 doses were determined using a combination of animal toxicology data and available clinical data from the ongoing VIR-2218-1001 regional study.

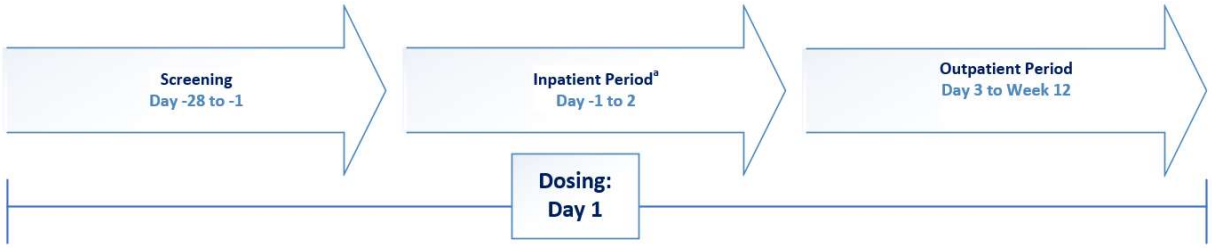
Although dosing in the GLP-toxicology studies was weight based, subjects will receive a fixed dose rather than a body weight-based dose because VIR-2218, like other GalNAc-conjugated siRNAs, is preferentially taken up by the liver, the therapeutically targeted organ with extended tissue half-life, and to a lesser extent distributed to other organs and tissues (Nair, 2014). Nonclinical data suggested receptor level changes had minimal impact on efficiency of this ASGPR mediated uptake process at pharmacologically relevant dose levels (Willoughby, 2018). Therefore, body weight-based dosing is not anticipated to reduce the inter-subject variability in the pharmacokinetics (PK) of VIR-2218 in adults, and a fixed dose has the advantage of avoiding potential dose calculation errors.

VIR-2218-1001 regional study

The ongoing VIR-2218-1001 regional study (ClinicalTrials.gov Identifier: NCT03672188) is a randomized, double-blind, placebo-controlled study of VIR-2218 administered subcutaneously to healthy adult subjects and adult subjects with chronic HBV infection without cirrhosis who are on NrtI therapy. This study is designed to evaluate the safety, tolerability, PK, and antiviral activity of VIR-2218. Single ascending dose (SAD) levels are being evaluated in healthy volunteers (HVs). Safety data from HVs are then used to support the dose levels evaluated in a multiple ascending dose (MAD) study in adult subjects with HBeAg-negative (Part B) and

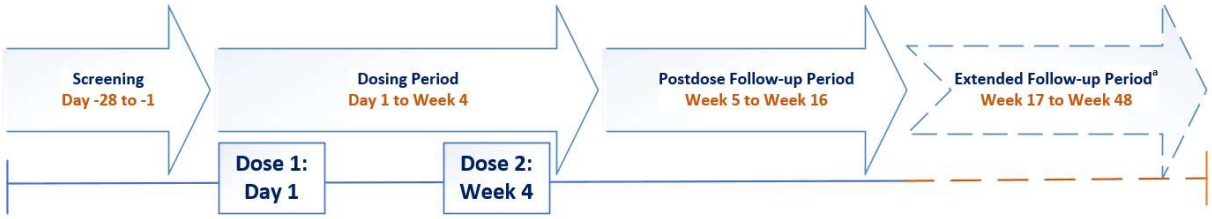
HBeAg-positive (Part C) chronic HBV infection without cirrhosis on NrtI therapy, currently being conducted at multiple clinical investigative sites in the Asia-Pacific region. Significant ethnic Asian representation is expected in the ongoing healthy volunteer and patient studies. The study designs for Part A SAD and Part B/C MAD studies are presented in Figure 1 and Figure 2, respectively.

Figure 1. SAD Study Design for Part A (VIR-2218-1001 Regional Study)



[a] Subject discharge will occur after all assessments are completed on Day 2

Figure 2. MAD Study Design for Part B/C (VIR-2218-1001 Regional Study)



[a] Additional HBsAg monitoring is required for subjects with HBsAg levels with a > 10% decrease from the Day 1 predose level at the Week 16 visit. Visits will occur every 4 weeks starting at Week 20 up to Week 48 or until the HBsAg level returns to ≥ 90% of the Day 1 predose level. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.

VIR-2218-1001, Part A: Single Ascending Dose (SAD) Study in Healthy Volunteers (Table 2):

HVs received a single ascending dose of VIR-2218, ranging from 50 to 900 mg. Doses were increased stepwise by a factor of 2-fold up to a dose of 400 mg followed by 1.5-fold increases to doses of 600 and 900 mg. As of 16 July 2019, data generated in the ongoing VIR-2218-1001 study demonstrated that single doses of up to 600 mg had an acceptable safety and tolerability profile in 41 healthy subjects, 8 of which (20%) are of Asian ethnicity. Based upon review of the clinical data from the Safety Review Committee (SRC), the optional dose level of 900 mg will be initiated in HVs.

Table 2. Part A Dose Escalation Plan

Cohort	Fixed dose (mg)	Dose Escalation Factor
1a	50	-
2a	100	2.0-fold
3a	200	2.0-fold
4a	400	2.0-fold
5a	600	1.5-fold
6a	900	1.5-fold

VIR-2218-1001, Part B/C: Multiple Ascending Dose (MAD) Study in HBeAg-negative and HBeAg-positive Subjects with Chronic HBV Infection (Table 3):

For this part of the ongoing VIR-2218-1001 regional study, HBeAg-negative subjects with chronic HBV infection are enrolled in Part B, and HBeAg-positive subjects with chronic HBV infection are enrolled in Part C. Dose levels were increased stepwise by a factor of 2 up to a maximum planned dose level of 200 mg and a cumulative dose of 400 mg in 3 dose-level cohorts for HBeAg-negative subjects. To accommodate the anticipated lower prevalence of HBeAg-positive patients on NrtI therapy, only 1 dose level cohort (200 mg) was planned for HBeAg-positive subjects.

Data generated in the ongoing VIR-2218-1001 study, as of 16 July 2019, show that multiple doses of VIR-2218 up to 100 mg x 2 doses had an acceptable safety and tolerability profile in 13 subjects with HBV infection, a majority of which (85%) are of Asian ethnicity. Initiation of the next higher dose cohort (200 mg) in subjects with HBV infection has been recommended based on SRC review on 25 July 2019. Additionally, based on the antiviral activity data collected thus far, notable reductions in HBsAg were observed across subjects with HBV infection in both the 50 mg and 100 mg dose cohorts. Based upon review of the clinical data from the SRC, two optional dose levels of 20 mg and 50 mg were initiated in HBeAg-positive subjects. An additional optional dose level not to exceed 300 mg may also be initiated based on review of available safety data collected.

Table 3. Part B/C Dose Escalation Plan

Cohort	Fixed Dose (mg)	Dose Escalation Factor
1b	50	-
2b	100	2.0-fold
3b and 3c	200	2.0-fold
4b	20	-
4c	50	-
Optional: 5b and 5c	Up to 300	Up to 1.5-fold

1.3. VIR-2218-1005 study

The cohort dosing strategy of this study is based on data collected from the VIR-2218-1001 regional study (Appendix 4). There are 2 planned cohorts (50 mg dose-level and 100 mg dose-level) for both Part One and Part Two of the study. For each of the planned 50 and 100 mg dose-level cohorts, 5 subjects will be randomized 4:1 to VIR-2218 or placebo administered 4 weeks apart on Day 1 and Week 4.

One optional cohort may be added to each study part (Part One and Part Two), wherein 5 subjects will be randomized 4:1 to VIR-2218 or placebo administered 4 weeks apart on Day 1 and Week 4 at a dose-level of up to 200 mg.

The optional cohorts may be initiated after SRC review of a minimum of 6 weeks of available safety and antiviral activity data from the 200 mg cohorts of the VIR-2218-1001 regional study.

1.4. Overall Risk/Benefit Assessment

This study will provide information on the safety, PK, and antiviral activity of VIR-2218, an siRNA therapeutic targeting HBV, which has the potential to functionally cure chronic HBV infection alone or in combination with other treatment modalities.

The potential benefits of VIR-2218 over the current standard of care for the treatment of chronic HBV infection are:

- A pan-genotypic therapy for HBV infection that is well-tolerated and administered via SC injection for a finite duration of time
- A reduction in serum HBsAg, which may break immune tolerance against HBV and lead to a functional cure

As VIR-2218 is taken up by the liver, ALT and other liver function tests will be monitored during this study. Along with safety reviews performed by the Sponsor during the conduct of the

ongoing VIR-2218-1001 regional study, an SRC will perform ongoing reviews of safety and tolerability for this study.

In summary, there is no approved therapy that reduces serum HBsAg in a significant percentage of patients. If serum HBsAg can be effectively reduced with a pangenotypic regimen, the anticipated safety profile would offer a favorable risk-benefit determinant in patients with chronic HBV infection.

2. OBJECTIVES

2.1. Primary Objective

To evaluate the safety and tolerability of multiple doses of VIR-2218 in subjects with HBeAg-negative and HBeAg-positive chronic HBV infection without cirrhosis on NrtI therapy

2.2. Secondary Objectives

- To characterize the PK of VIR-2218 in subjects with chronic HBV infection without cirrhosis on NrtI therapy
- To assess the antiviral activity of VIR-2218 in subjects with chronic HBV infection without cirrhosis on NrtI therapy

CCI [redacted]

- [redacted]
- [redacted]

3. ENDPOINTS

3.1. Primary Endpoint

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical assessments including but not limited to laboratory test results

3.2. Secondary Endpoints

- PK parameters of VIR-2218 and possible metabolites (may include, but not limited to, maximum plasma concentration, time to reach maximum concentration, area under the concentration versus time curve [to last measurable timepoint and to infinity], percent of area extrapolated, apparent terminal elimination half-life, clearance, and volume of distribution)
- Maximum reduction of serum HBsAg from Day 1 until 12 weeks post last dose
- Number of subjects with serum HBsAg loss at any timepoint
- Number of subjects with sustained serum HBsAg loss for greater than or equal to 6 months post last dose
- Number of subjects with anti-HBs seroconversion at any timepoint
- For HBeAg-positive subjects (Part Two only): number of subjects with HBeAg loss and/or anti-HBe seroconversion at any timepoint

CCI [redacted]

- [redacted]
- [redacted]

4. STUDY DESIGN

4.1. Treatment Plan and Regimen

This is a phase 2 randomized, double-blind, placebo-controlled study of VIR-2218 administered SC to adult subjects with chronic HBV infection without cirrhosis on NrtI therapy. The study is designed to evaluate the safety, tolerability, PK and antiviral activity of VIR-2218. This study will be conducted in close collaboration with an ongoing phase 1/2 regional study being conducted in multiple sites in the Asia-Pacific region (VIR-2218-1001, ClinicalTrials.gov Identifier: NCT03672188) described in more detail in Section 1.2.4.

The study will include two Parts:

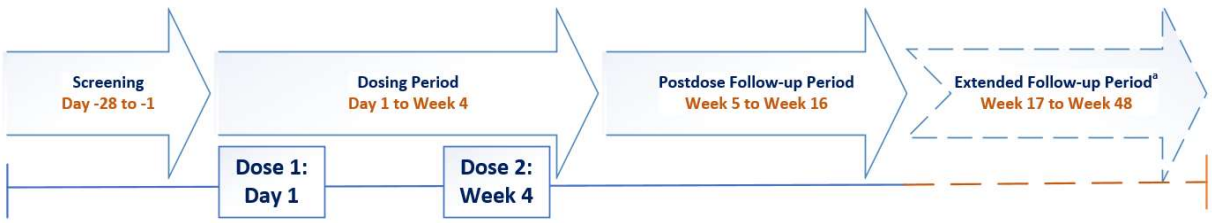
- Part One: adult subjects with HBeAg-negative chronic HBV infection without cirrhosis on NrtI therapy for ≥ 6 months and HBV DNA < 90 IU/mL at screening (by central laboratory)

- Part Two: adult subjects with HBeAg-positive chronic HBV infection without cirrhosis on NrtI therapy for ≥ 6 months and HBV DNA < 90 IU/mL at screening (by central laboratory)

Each cohort in Part One/Two will be composed of 5 subjects randomized 4:1 to VIR 2218 or placebo, respectively. There are two planned cohorts (50 mg dose-level and 100 mg dose-level) and 1 optional cohort (≤ 200 mg dose-level) for each of Part One and Part Two of the study. Enrollment of the Part One/Two optional cohorts will be according to the same randomization scheme and eligibility criteria as the Part One/Two planned cohorts. The optional cohorts may be initiated after SRC review of a minimum of 6 weeks of available safety and antiviral activity data from the 200 mg cohorts of the VIR-2218-1001 regional study.

The estimated total duration for each subject is up to 52 weeks, including screening period (4 weeks), dosing period (4 weeks), post-second dose follow-up period (12 weeks) and extended follow-up period (up to 48 weeks) (Figure 3). Additional HBsAg monitoring is required for subjects with a ≥ 1 $1og_{10}$ change from baseline (Day 1 predose level) decrease in HBsAg achieved by the Week 16 visit. Extended follow-up visits will occur every 4 weeks starting at Week 20, and subjects will be followed until the HBsAg level returns to > 90% of the Day 1 predose level or Week 48, whichever comes earlier. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.

Figure 3. Study Design for Cohorts



The assessments performed at each visit are described in Appendix 2 for Part One/Two planned and optional cohorts. Fasting is not required for any study procedure/assessment.

Screening period:

Screening will be performed no more than 4 weeks before the Day 1 visit and will include written informed consent, determination of eligibility, collection of demographics and medical history as well as physical examination (including vitals), laboratory tests, 12-lead Electrocardiogram (ECG) and other assessments per the schedule of assessments. To exclude the presence of cirrhosis, screening will include a mandatory noninvasive assessment of liver fibrosis such as a FibroScan evaluation, unless the subject has results from a FibroScan evaluation performed within 6 months prior to screening or a liver biopsy performed within 1 year prior to screening that confirms the absence of Metavir F3 fibrosis or F4 cirrhosis. Adverse events related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards.

Dosing period:

Subjects enrolled will remain outpatient. Subjects will be randomized 4:1 to receive VIR-2218 or placebo within 48 hours prior to study drug administration on Day 1. Subject eligibility must be confirmed prior to study drug administration on Day 1. Subjects will return to the clinical investigative site at Week 4 to receive a second dose of the same study drug administered on Day 1. The decision to administer a second dose will be made based on Week 3 laboratory values in accordance with dose suspension/stopping criteria in Section 4.6.CCI [redacted]

Subjects enrolled into the optional cohorts will receive VIR-2218 or placebo on Day 1 and Week 4 at a maximum dose-level of 200 mg.

Post-dose follow-up period:

Subjects will return to the clinical investigative site on an outpatient basis for safety, tolerability, PK, and antiviral activity monitoring at specified timepoints during this Post-dose Follow-up period (Week 5 to Week 16). Additional HBsAg monitoring is required for subjects with a ≥ 1 $1og_{10}$ change from baseline (Day 1 predose level) decrease in HBsAg achieved by the Week 16 visit.

Extended follow-up period:

Subjects who require additional HBsAg monitoring will return to the clinical investigational site for in-person assessments. Extended follow-up visits will occur every 4 weeks starting at Week 20, and subjects will be followed until the HBsAg level returns to > 90% of the Day 1 predose level or Week 48, whichever comes earlier. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.

4.2. Discontinuations

Subjects who discontinue prematurely will be followed for safety, and under certain circumstances, subjects who discontinue study drug (as described in Section 4.3) may be replaced. If a subject discontinues from the study post-dose but before completion of the Week 16 visit, an Early Termination (ET) visit should be performed.

4.3. Replacement of Subjects

Replacement subjects may be enrolled to ensure that the minimum data requirements for SRC decisions and study progression are met, as described in Section 4.5. Subjects who do not receive the full planned dose, do not receive a second dose, discontinue due to an AE that does not meet study progression and dose suspension/stopping rules (Section 4.6), or who withdraw from the study, may be replaced with confirmation by the SRC. Subjects who are discontinued from treatment for reasons other than experiencing an AE may be replaced following discussion between the Sponsor and investigator.

The replacement subject will be assigned a unique study identification number and will receive the same study drug assignment and dose level as the subject who is being replaced and in the same blinded fashion.

4.4. Safety Review Committee

An SRC will perform ongoing reviews of safety, tolerability, and available study data collected throughout the study with the primary purpose of protecting the safety of subjects participating in this clinical study. The SRC will be governed by an SRC Charter that will be finalized prior to screening the first subject.

The SRC will undertake safety data review prior to initiation of dosing the optional cohorts of the study in accordance with the SRC Charter. In addition, ad hoc SRC meetings may take place as needed, e.g., for a significant safety event such as a subject or cohort stopping criterion being reached (Section 4.6).

Decisions to suspend dosing or discontinue individual subjects from study drug will be made according to predetermined stopping rules (Section 4.6). Additionally, the SRC may recommend discontinuation of the study to the Sponsor. The SRC membership composition is described in detail in the SRC Charter.

4.5. Study Drug Dosing and Study Progression

Progression rules are based on the absence of prespecified safety signals. Standard toxicity grading according to the current Common Terminology Criteria for Adverse Events (CTCAE) Version 5 will be used to grade AEs. The decision to enroll an optional cohort or expand an existing cohort will be made by the SRC based on available safety, tolerability, and antiviral activity data, if further data are considered necessary to better understand dose response and/or safety and tolerability.

Subjects will receive VIR-2218 or placebo via SC injection according to the schedules provided in Appendix 2.

4.6. Stopping Rules

The following stopping rules are based on potential safety signals. Standard toxicity grading according to the CTCAE Version 5.0 will be used to grade AEs. When a cohort is stopped, no further study drug will be administered at the dose level and further progression will be suspended. An ad hoc SRC meeting will be held, and only following SRC approval, may dosing be resumed; if required, additional approval from the concerned regulatory authority and the independent ethics committee (IEC)/institutional review board (IRB), in accordance with applicable requirements, will be obtained. De-escalation to a lower dose will be allowed at Sponsor discretion.

4.6.1. Cohort Stopping Rules

If any of the criteria described below are met, as determined by the Sponsor medical monitor or designee, cohort dosing will be suspended or stopped:

- If 1 or more subjects experience a Grade 3 study drug-related rash
- If 2 or more subjects experience the same study drug-related Grade 3 or higher AE
- If 1 or more subjects experience a study drug-related serious adverse event (SAE)
- If 1 or more subjects experiences a Grade 4 AE of rash, regardless of assessed causality

4.6.2. Individual Subject Stopping Rules

Individual subjects who have received 1 dose of study drug will not receive a second dose if any the following criteria are met:

- Serum ALT > 10 × upper limit of normal (ULN)
- Serum ALT > 5 × ULN, with no change (< 50% of baseline) in HBsAg
- Serum ALT or AST > 3 × ULN with a concomitant total bilirubin > 2 × ULN
- Any clinical manifestations of hepatic decompensation including but not limited to jaundice, ascites, variceal hemorrhage, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome

The investigator should contact the medical monitor in the event that any of the above criteria are met, prior to dose discontinuation, unless the investigator believes that immediate action is warranted to ensure the continued safety of the subject.

5. SUBJECT POPULATION

5.1. Number of Subjects and Subject Selection

A total of up to 30 adult subjects with chronic HBV infection without cirrhosis on NrtI therapy are planned to complete this study.

- **Part One Planned/Optional Dose Cohorts:** Up to 15 adult subjects with chronic HBV infection without cirrhosis who are HBeAg-negative on NrtI therapy
- **Part Two Planned/Optional Dose Cohorts:** Up to 15 adult subjects with chronic HBV infection without cirrhosis who are HBeAg-positive on NrtI therapy

5.2. Inclusion Criteria

Each subject must meet all the following inclusion criteria at screening to be eligible for enrollment in the study. All laboratory test requirements for inclusion will be performed by central laboratory:

1. Age 18 (or age of legal consent, whichever is older) to 65 years at the time of screening
2. 12-lead ECG within normal limits; or, with no clinically significant abnormalities at screening, as determined by the clinical investigator
3. Female subjects must have a negative pregnancy test or confirmation of post-menopausal status. Post-menopausal status is defined as 12 months with no menses without alternative medical cause. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test (using central laboratory) at screening and a negative urine pregnancy test on Day 1, cannot be breast feeding, and must be willing to use highly effective methods of contraception 14 days before study drug administration through 12 weeks after last study drug administration. Refer to Section 6.6 for more information on highly effective methods of contraception.
4. Male subjects with female partners of child-bearing potential must agree to meet 1 of the following contraception requirements from the time of study drug administration until the last follow-up visit: vasectomy with documentation of azoospermia, or male condom use plus partner use of 1 of the contraceptive options listed for contraception for WOCBP. Male subjects must also agree not to donate sperm for the 12 weeks following last study drug administration. Refer to Section 6.6 for more information on highly effective methods of contraception.
5. Agrees to not donate blood during the duration of the study
6. Willing to comply with the study requirements and able to provide written informed consent
7. Weight $\geq$ 40 kg to $\leq$ 125 kg
8. Chronic HBV infection as defined by a positive serum HBsAg for $\geq$ 6 months

9. On NrtI therapy for at least 6 months

10. HBsAg > 150 IU/mL

11. HBV DNA < 90 IU/mL

12. Part One only: HBeAg-negative

13. Part Two only: HBeAg-positive

14. Agrees not to increase physical activity from the time of screening through 4 weeks after final administration of VIR-2218

5.3. Exclusion Criteria

Each subject must not meet any of the following exclusion criteria to be eligible for enrollment in the study:

1. Any clinically significant chronic medical condition other than chronic HBV infection that, in the opinion of the investigator makes the volunteer unsuitable for participation in the study

2. Any clinically significant acute condition such as fever (> 38° C) or acute respiratory illness within 7 days of first study drug administration

3. Significant fibrosis or cirrhosis as defined by having either a FibroScan result of > 8.5kPa at screening or a liver biopsy within 1 year with Metavir F3 fibrosis or F4 cirrhosis. Refer to Section 7.2.8 for more information.

4. Receipt of a vaccine 14 days prior to Day 1

5. Previous or current psychiatric condition that precludes compliance with the protocol. Specifically excluded are persons with psychoses, ongoing risk for suicide, or history of suicide attempt or gesture within the past 5 years

6. Systolic blood pressure > 140 mmHg and a diastolic blood pressure of > 90 mmHg after approximately 10 minutes resting at screening

7. Subject has the following laboratory parameters at screening by central laboratory:

    a. Creatinine or total bilirubin above the upper limit of normal (ULN), OR international normalized ratio (INR) above 1.1x ULN

    b. hemoglobin, ANC, platelets, or albumin below the lower limit of normal (LLN)

    c. White blood cell (WBC), potassium, or sodium above the ULN or below the LLN

    d. serum ALT or AST > 2 × ULN

Study Screening laboratory tests may be repeated once (e.g., for values thought to be erroneous) with medical monitor approval.

8. Received an investigational agent within 90 days before study drug administration or are active in the follow-up phase of another clinical study involving interventional treatment. Subjects must also agree not to take part in any other study at any time during their participation in this study, inclusive of the follow-up period.

9. Used prescription drugs within 14 days before study drug administration except for a stable dose of medication to treat hypertension, inhaler or nebulizer to treat asthma, hormone replacement therapy, antihistamines, and contraceptive therapy (refer to Section 6.4.1 for more information). Hypertension must be well controlled on no more than 2 medications or 1 medication with two active components for > 6 months. Asthma must be well controlled, requiring, on average, use of a rescue bronchodilator no more than twice per week.

10. Use of over-the-counter (OTC) medication or herbal remedy within 14 days before Day 1 and throughout the study, with the following exceptions of permitted OTC medications: Paracetamol (acetaminophen) ≤ 2g/day, aspirin ≤ 3g/day or ibuprofen < 1.2 g/day.

11. Active infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis Delta virus as determined by the central laboratory

12. Consume more than 7 units of alcohol per week (unit: 1 glass of wine [125 mL] = 1 measure of spirits [30 mL] = one-half pint of beer [284 mL]). Alcohol is limited to no more than 1 unit per day for the duration of the study

13. History or clinical evidence of alcohol or drug abuse, within the 12 months before screening or a positive drug screen for amphetamines, cocaine, methadone or opiates at screening unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved by the investigator. Screening results must be reviewed by the investigator to confirm eligibility prior to dosing.

14. Known hypersensitivity or contraindication to an siRNA or GalNAc

15. History of intolerance to SC injection

16. Any conditions which, in the opinion of the investigator, would make the subject unsuitable for enrollment or could interfere with the subject's participation in or completion of the study

17. Donated more than 500 mL of blood within 90 days before study drug administration

18. Creatinine clearance (CLcr) < 60 mL/min as calculated by the Cockcroft-Gault formula at screening

19. History of chronic liver disease from any cause other than chronic HBV infection

20. History of hepatic decompensation, including ascites, hepatic encephalopathy and/or esophageal or gastric varices

6. INVESTIGATIONAL MEDICINAL PRODUCTS

6.1. Randomization, Blinding, and Treatment Codes

An Interactive Web Response System (IWRS) will be employed to manage subject randomization and treatment assignments.

6.1.1. Procedures for Breaking of Treatment Codes

Blinding of study treatment will be managed by the clinical investigative site's pharmacy in accordance with the Pharmacy Manual. In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment for that subject. IWRS should be used as the primary method of breaking the blind. If IWRS cannot be accessed, the investigator should contact the Sponsor medical monitor to break the blind. Treatment assignment should remain blinded unless that knowledge is necessary to guide subject emergency medical care. The investigator is requested to contact the Sponsor medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical study and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

The Sponsor or designee may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) as required by regulators.

6.2. Description and Handling of VIR-2218 and Placebo

6.2.1. Formulation

VIR-2218 is a clear, colorless to pale yellow solution, which will be supplied by the Sponsor as a sterile solution for SC injection at a free acid concentration of 200 mg/mL. Placebo is a sterile, preservative-free normal saline 0.9% solution for SC injection, which will be supplied by the clinical investigative site or the Sponsor where required.

6.2.2. Packaging and Labeling

VIR 2218 (solution for SC injection) is packaged in 2-mL glass vials with a fill volume of no less than 0.7 mL to allow for complete withdrawal of 0.5 mL of drug product at the pharmacy. The container closure system consists of a Type I glass vial, a Teflon-faced 13-mm stopper, and a flip-off aluminum seal.

VIR-2218 and Placebo will be packaged and labeled in a manner consistent with the study design and applicable regulations.

6.2.3. Storage and Handling

Study drug may be dispensed only by the investigator, by a staff member specifically authorized by the investigator, or by pharmacy staff, as appropriate.

Each clinical investigative site will be responsible for assembly and labeling of injection syringe(s) according to procedures detailed in the Pharmacy Manual. The pharmacy staff will prepare the study drug using an aseptic technique. The amount (in mg) of study drug to be administered will be determined based on the assigned dose level for the cohort for subjects with chronic HBV infection. All syringes will be covered to ensure the study blind is maintained since the IP solution may have a slight yellow coloring and the placebo (sterile normal saline) is clear. Additional details regarding the procedure for preparing study drug, the volume to be loaded into each syringe, and how the syringes are to be 'blinded' are provided in the Pharmacy Manual.

No special procedures for the safe handling of VIR-2218 are required. Study drug will be stored upright and refrigerated at 2 to 8°C protected from light in the storage area of the clinical investigative site pharmacy, in a secure, temperature-controlled, locked environment with restricted access. Any deviation from the recommended storage conditions should be reported to the Sponsor and use of the study drug halted until authorization for its continued use has been provided by the Sponsor or designee. Refer to the Pharmacy Manual for additional storage details.

6.2.4. Dosage and Administration of VIR-2218

Dose and dose cohorts for this study are described in Sections 1.2.4 and 4.1, respectively. Study drug dose and administration are summarized by dose cohort in Table 4. On dosing days, the pharmacist or designee will withdraw the required amount of study drug into 1 or more syringes containing up to 1.5 mL/ syringe. A qualified clinical investigative site staff member under the supervision of the investigator or designee will administer study drug to subjects via SC injection. The injection site(s) will be marked and mapped for later observation and should be documented. If a local reaction around the injection site occurs, photographs may be obtained. Refer to the Pharmacy Manual for detailed study drug preparation and administration instructions.

Table 4. Study Drug Dose and Administration

Cohort	Visit Dose Level (mg)	Visit Dose Volume (mL)	Cumulative Dose (mg)	Injections Per Dose Administration	Injections Total	Cumulative Dose Volume (mL)
Part One						
Low dose	50	0.25	100	1	2	0.50
High dose	100	0.50	200	1	2	1.0
Optional	≤ 200	≤ 1.0	≤ 400	1	2	≤ 2.0
Part Two						
Low dose	50	0.25	100	1	2	0.50
High dose	100	0.50	200	1	2	1.0
Optional	≤ 200	≤ 1.0	≤ 400	1	2	≤ 2.0

6.3. Investigational Product Accountability

The investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including but not limited to, date of receipt, quantity, and temperature. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each subject in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drugs.

Further instructions about drug accountability and disposal are detailed in the Pharmacy Manual.

6.4. Concomitant Therapy

6.4.1. Permitted Concomitant Medications

The following medications/treatments are permitted:

- Hormone replacement therapy
- Oral, injectable, subdermal, intravaginal, or implantable contraceptives, as well as intrauterine device, and intrauterine hormone-releasing system are permitted for contraception
- Paracetamol (≤ 2g/day), aspirin (≤ 3g/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.

- A stable dose and regimen of any medication(s) (prescription or OTC) that the subject is taking regularly (i.e. medications for chronic conditions such as hypertension, high cholesterol, or depression must be unchanged in dose or type for at least 6 months), is permitted, except those listed in Section 6.4.2.

Investigators may initiate new prescription and non-prescription concomitant medications or treatments deemed necessary to provide adequate care for AEs or other new onset medical conditions, except those listed in Section 6.4.2.

6.4.2. Prohibited Concomitant Medications

The following medications/treatments are prohibited:

- Any OTC medications or herbal remedy within 14 days before Day 1 and throughout the study, except for those specified in Section 6.4.1
- Any prescription medications within 14 days before study drug administration except for those specified in Section 6.4.1 and NrtI therapy

6.5. NrtI Therapy

Examples of allowed NrtI therapy are listed below, but not limited to:

- Tenofovir (tenofovir alafenamide (TDF) or tenofovir disoproxil fumarate (TAF) at recommended dose for the given tablet)
- Entecavir
- Lamivudine
- Adefovir/adefovir dipivoxil

6.6. Contraceptive Requirements

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

WOCBP must be willing to use highly effective methods of contraception 14 days before dose, throughout study participation, and for 12 weeks after last dose of study drug administration. Highly effective methods of birth control 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) throughout the study and for 12 weeks after last study drug 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 subjects on the study, the vasectomized male partner should be the sole partner for that subject)
- True sexual abstinence, when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent subjects have to agree to use 1 of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 12 weeks after last dose of study drug administration, or for as long as the subject is followed on study, whichever is longer.
- 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.

Male subjects with female partners of child-bearing potential must agree to meet 1 of the following contraception requirements from the time of study treatment administration until the last follow-up visit.

- 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 subjects must also agree not to donate sperm for the 12 weeks following last study drug administration.

7. STUDY PROCEDURES

7.1. Procedures and Specifications

The Schedule of Assessments (SoA) is provided in Appendix 2 for Part One/Two planned and optional cohorts. Unscheduled visits are permitted at the discretion of the investigator as needed for safety assessment.

7.1.1. Medical History

A complete medical history, including details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing, medication history, including prior HBV treatment history and HBV genotype history (if available), will be collected on all subjects during screening and should be updated prior to dosing.

7.1.2. Assessment of Antiviral Activity and Development of Resistance

During the study, assessments of antiviral activity will include: HBsAg, HBeAg, CCI anti-HBs, anti-HBe, HBV DNA, CCI and assessment of HBV and NrtI resistance if indicated. HBV genome will be sequenced and analyzed for mutations that can confer resistance to VIR-2218 and NrtIs in subjects with confirmed HBV breakthrough as defined by HBV DNA ≥ 500 IU/mL measured at 2 consecutive study visits. HBV RNA may be sequenced to determine if nucleotide changes within the VIR-2218 target site may impact responsiveness. Details regarding the processing, shipping, and analysis of the samples are provided in the Laboratory Manual.

7.1.3. Screening Viral Serology Parameters

Screening viral serology parameters include active infection with HIV infection, HCV infection, chronic HBV infection and hepatitis Delta virus infection. Chronic HBV infection is defined as serum HBsAg for > 6 months. In cases of occult HBV, chronic HBV infection is defined as serum HBV DNA positive for > 6 months.

7.1.4. Pharmacokinetic Assessments

Blood samples will be collected to assess concentrations of VIR-2218 and metabolites, as applicable. Timepoints for the collection of samples for VIR-2218 PK analysis of the study are provided in Appendix 3.

Details regarding the processing, shipping, and analysis of the samples are provided in the Laboratory Manual.

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7.2. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medications, physical examination findings, alcohol assessment, ECG, and laboratory tests. All AEs related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards.

7.2.1. Physical Examination

A full physical examination will include general appearance, head, neck, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, extremities, skin, and screening neurological assessments.

A symptom-directed physical examination will be performed according to investigator discretion.

7.2.2. Alcohol Assessment

Alcohol intake during the study will be recorded.

7.2.3. Height and Weight

Height and body weight will be measured. Body mass index will be calculated from height and weight.

7.2.4. Vital Signs

Vital sign measurements include blood pressure, pulse rate, temperature (oral preferred), and respiratory rate. Vital signs should be measured after the subject has rested comfortably for approximately 10 minutes. When scheduled at the same timepoints, the assessments of vital signs and 12-lead ECGs must be performed before blood sample collections.

7.2.5. Electrocardiogram

12-lead safety ECGs will be recorded and reviewed on-site by the investigator as outlined in Appendix 2.

7.2.6. Pregnancy Testing

A pregnancy test or confirmation of post-menopausal status must be confirmed for all female subjects. Post-menopausal status is defined as 12 months with no menses without alternative medical cause. 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 serum 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 drug administration. A WOCBP determined to be pregnant while on study will be followed until the pregnancy outcome is known, as described in Section 8.5.2.

7.2.7. Clinical Laboratory Assessments

Clinical laboratory tests that will be performed in this study are presented in Table 5. In the event of an unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the investigator until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality.

Table 5. Clinical Laboratory Tests

Hematology	
• Complete blood count with differential	
Chemistry	
• Albumin	• Creatinine clearance
• Blood urea nitrogen (BUN)	• Gamma glutamyl transferase (GGT)
• Calcium	• Glucose
• Carbon dioxide/bicarbonate	• Lactate dehydrogenase (LDH)
• Chloride	• Potassium
• Creatine kinase	• Sodium
• Creatinine	• Uric acid
Liver Function Tests	
• Alkaline phosphatase (ALP)	• AST
• ALT	• Bilirubin (total and direct)
Coagulation Parameters	
• International normalized ratio (INR) time	• Prothrombin
Urinalysis	
• Bilirubin	• Proteins
• Glucose	• Red blood cells (RBCs)
• Ketones	• Screen for drugs of abuse
• Leukocytes	• Specific gravity
• Microscopy (if clinically indicated)	• Urobilinogen
• Nitrite	• Visual inspection for appearance and color
• pH	
Pregnancy Testing	
• Beta-human chorionic gonadotropin (WOCBP	• Urine pregnancy test
Serology	
• Hepatitis B, C, and Delta	• Human immunodeficiency virus I and II

7.2.8. FibroScan

To exclude the presence of cirrhosis, subjects will have a FibroScan evaluation, unless the subject has results from a FibroScan evaluation performed within 6 months prior to screening or liver biopsy performed within 1 year prior to screening that confirm the absence of Metavir F3 fibrosis or F4 cirrhosis. If a subject has had both procedures in the specified timeframes, the most recent result should be used to determine eligibility.

8. ADVERSE EVENTS MANAGEMENT

8.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

8.1.1. Adverse Events

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. 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. Pre-existing conditions (recorded as medical history), which change in nature or severity should also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose of study drug without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history Case Report Form (CRF).
- Unless associated with signs or symptoms, laboratory abnormalities (e.g., low platelets) should not be recorded as AEs, as these abnormalities will be captured as laboratory abnormalities
- Procedures should not be recorded as AEs; however, the condition that led to the procedure may be an AE

8.1.2. Serious Adverse Events

An SAE is any event that results in the following:

- Death

- Life-threatening: An AE is life threatening if the subject was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

- Inpatient hospitalization or prolongation of existing hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria. In general, hospitalization signifies that the subject has been detained (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. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

- Persistent or significant disability/incapacity: an AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions

- Congenital anomaly/birth defect in the offspring of a subject who received VIR-2218

Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm

- Blood dyscrasias or convulsions that do not result in inpatient hospitalization

- Development of drug dependency or drug abuse

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

Per Section 8.1.1, 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 (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 8.1.1 and 8.1.2. If the laboratory abnormality is part of a clinical syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

8.2. Assessment of Adverse Events and Serious Adverse Events

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

8.2.1. Assessment of Causality for Study Drugs and Procedures

Causality (Yes or No) should be determined by the investigator or qualified sub-investigator. An answer of Yes, should be entered when, in their opinion, there is either (a) a *reasonable* possibility that the AE is associated with study drug **or** (b) no reasonable alternative explanation can be identified. Otherwise, causality to study drug should be categorized as No. A mere possibility of a causal relationship is not grounds for a Yes categorization.

8.2.2. Assessment of Severity

AE severity should be graded using the CTCAE Version 5.0.

8.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Sponsor

Requirements for collection prior to study drug initiation:

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

8.3.1. Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 12 weeks after last administration of study drug.

All AEs should be followed up until resolution or until the AE is stable, if possible. Sponsor may request that certain AEs be followed beyond the protocol-defined follow-up period.

8.3.2. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (i.e., signing the informed consent) and throughout the duration of the study, including the protocol-required follow-up period, must be reported as instructed. This also includes any SAEs resulting from protocol-mandated procedures performed after informed consent is signed.

Investigators are not obligated to actively seek SAEs after the protocol--defined follow-up period. However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, he/she should promptly document and report the event to Sponsor.

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

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

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's electronic case report form (eCRF) and the event description section of the SAE form.

- Email the SAE form within 24 hours of the investigator's knowledge of the event. Contact information is as follows:

  PPD

8.4. Sponsor Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US Food and Drug Administration Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, the Sponsor may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or SUSARs. In accordance with the EU Clinical Trials Directive (2001/20/EC), the Sponsor or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure.

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

8.5. Special Situations Reports

8.5.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

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, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

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 subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject 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 subject.

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

8.5.2. Instructions for Reporting Special Situations

Pregnancy Reporting

If a female subject becomes pregnant after the first study drug administration through the follow-up period (12 weeks after last study drug administration), the investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. The subject should receive any necessary counseling regarding the risk of continuing the pregnancy and the possible effects on the fetus.

The pregnancy should be followed by the investigator until completion. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death or congenital anomaly, then the investigator should follow the procedures for reporting an SAE as outlined in Section 8.3.

If the partner of a male subject becomes pregnant after study drug administration through the follow up period, the subject should report this to the investigator and a Partner Pregnancy Information and Consent Form will be provided to allow follow up of the pregnancy as described above.

Reporting Other Special Situations

All other special situations must be reported to the Sponsor within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug and/or protocol-required concomitant medications, but do not apply to non-required concomitant medications. Contact information is as follows:

PPD

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

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 special situation reports will be reported as AEs or SAEs at the same time. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

9. STATISTICAL CONSIDERATIONS

9.1. Objectives

The objectives are listed in Section 2.

9.2. Endpoints

The endpoints are listed in Section 3.

9.3. Analysis Conventions

Descriptive statistics will be presented for continuous variables, and frequencies and percentages will be presented for categorical and ordinal variables. Percentages will be based on the number of nonmissing values in a dose group.

9.3.1. Analysis Sets

Safety

The primary analysis set for safety analyses will be the Safety Analysis Set, which includes all subjects who received at least 1 dose of study drug.

Pharmacokinetic

The primary analysis set for PK analyses will be the PK Analysis Set, which includes all subjects in the Safety Analysis Set who have at least 1 nonmissing concentration data to provide interpretable results for the specific parameters of interest for the analyte under evaluation.

Antiviral Activity

The primary analysis set for antiviral activity analyses will be the Antiviral Analysis Set, which includes all subjects in the Safety Analysis Set who have at least 1 nonmissing data to provide interpretable results for the specific antiviral activity parameters of interest.

9.3.2. Data Handling Conventions

PK concentration values and PK parameter values below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listings. For purposes of graphic presentation, BLQ values that occur prior to study drug administration will be treated as 0, BLQ values at all other timepoints will be treated as one-half of the lower limit of quantitation (LLOQ).

Laboratory data that are continuous in nature but are less than the LLOQ or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (e.g., if the result of a continuous laboratory test is < 30, a value of 29 will be assigned; if the result of a continuous laboratory test is < 30.0, a value of 29.9 will be assigned).

9.4. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized using standard descriptive statistics including sample size, mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum for continuous variables and numbers and of subjects for categorical variables.

9.5. Safety Analysis

All safety analyses will be performed using the Safety Analysis Set. Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, ECGs, vital signs measurements at various timepoints during the study, and by the documentation of AEs.

All safety data collected up to 12 weeks after the last study drug administration will be summarized by cohort for each VIR-2218 dose and placebo.

9.5.1. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Treatment-Emergent Adverse Events (TEAEs) are defined as any AEs with an onset date of on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug.

Summaries (number and percentage of subjects) of TEAEs by SOC and PT will be provided by cohort. TEAEs will also be summarized by relationship to study drug and severity.

9.5.2. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by cohort and study visit along with corresponding change from baseline.

Graded laboratory abnormalities will be defined using CTCAE Version 5.0 grading scale.

The incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any postbaseline timepoint up to 30 days after permanent discontinuation of study drug will be summarized by treatment group. If the relevant baseline laboratory data are missing, then any abnormality of at least Grade 1 will be considered as treatment-emergent.

9.5.3. Other Safety Evaluations

Individual data for physical examination findings, prior and concomitant medications and medical history will be provided. Twelve-lead ECGs and vital signs measurements will be listed

by subject and summarized by incidence of events/abnormalities or descriptive statistics as appropriate.

9.6. Pharmacokinetic/Pharmacodynamic Analysis

Plasma PK parameters of VIR-2218 and possible metabolites will be computed using standard noncompartmental methods. Parameters may include, but not be limited to maximum concentration, time to reach maximum concentration, area under the concentration versus time curve (to the last measurable timepoint and to infinity), percent of area extrapolated, apparent terminal elimination half-life, clearance, and volume of distribution. Other parameters may be calculated, if deemed necessary.

PK/pharmacodynamic analyses will be conducted to explore exposure-response relationships between PK parameters and selected antiviral variables. These analyses may include graphical plots, tabular summaries, and various linear and/or nonlinear analyses. Details of the analysis will be provided in the Statistical Analysis Plan.

9.7. Antiviral Activity Analysis

Selected data relating to the antiviral activity of VIR-2218, such as HBsAg, HBeAg, CCI anti-HBs, anti-HBe, CCI and HBV DNA levels, will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by cohort and study visit along with corresponding change from baseline. Summaries (number and percentage of subjects) of HBsAg loss, anti-HBs seroconversion, HBeAg loss, and anti-HBe seroconversion will be provided by cohort and study visit.

9.8. Sample Size

No formal sample size calculation was conducted. Up to 30 subjects with chronic HBV infection are planned to complete the study.

10. RESPONSIBILITIES

10.1. Investigator and Sponsor Responsibilities

10.1.1. Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.2. Informed Consent

The investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that participation is completely voluntary and that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The investigator must maintain the original, signed Informed Consent Form (ICF). A copy of the signed ICF must be given to the subject.

10.1.3. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject 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 subjects screened and for all subjects enrolled in the study.

The investigator agrees that all information received from the Sponsor, including but not limited to the Investigator's Brochure, this protocol, CRFs, 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.

In compliance with local and/or regional regulations, this clinical study may be registered and study results may be posted on public registries, such as ClinicalTrials.gov.

10.1.4. Study Files and Retention of Records

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.

10.1.5. Electronic Case Report Forms (eCRF)

Study data must be recorded on electronic CRFs (eCRFs) provided by the Sponsor or designee on behalf of the Sponsor. eCRFs must be completed only by the investigator or person designated by the investigator. eCRF data must be entered by trained clinical investigative site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Correction on source documents must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

10.1.6. Good Clinical Practice

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study subjects are protected consistent with the principles that have their origin in the Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

10.1.7. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational product and placebo. Refer to the Pharmacy Manual for further information.

10.1.8. Quality Control and Assurance

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core study process and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reports according to the protocol, GCP guidelines of ICH, an 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. Protocol Compliance

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

10.1.10. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

10.1.11. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies).

The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

After conclusion of the study and without prior written approval from the Sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media ***only after the following conditions have been met:***

- the results of the study in their entirety have been publicly disclosed by or with the consent of the Sponsor in an abstract, manuscript, or presentation form; or
- the study has been completed at all clinical investigative sites for at least 2 years

No such communication, presentation, or publication will include the Sponsor's confidential information (Section 10.1.3).

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with the Sponsor's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days to obtain patent protection if deemed necessary.

10.2. Study Monitoring

In accordance with ICH GCP guidelines, the study monitor must have access to the investigator's source documentation to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to

verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

10.2.1. Study Discontinuation

The Sponsor reserves the right to terminate the overall study at any time. The investigator reserves the right to discontinue the study at their institution at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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12. APPENDICES

Appendix 1. Investigator Signature Page

Sponsor:

Brii Biosciences Ltd.
Room 301, 3/F,
Building 7,
No. 1 Yongtaizhuang North Street,
Haidian District, Beijing 100192, China

STUDY ACKNOWLEDGMENT

A Phase 2 Randomized, Placebo-Controlled Study in Mainland China to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral activity of VIR-2218

VIR-2218-1005, Amendment 2, 23 September 2020

This protocol has been approved by Brii Biosciences Ltd. The following signature documents this approval.

CCI [redacted]

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 Brii Biosciences Ltd. 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

Appendix 2. Part One/Two Schedule of Study Assessments (SoA) for Planned and Optional Cohorts in Subjects with Chronic HBV Infection

Study Stage	**Screening**	**Dosing Period**						**Post-dose Follow-up Period** [b]						**Extended Follow-up Period** [c]		
Study Visit Week				W1	W2	W3	W4[a]	W5	W6	W7	W8	W12	W16/ET	W20	W24	
Study Visit Day ±Visit Window	D-28 to -1	D1[a]	D2	D8 ±2	D15 ±2	D22 ±2	D29[a] ±2	D36 ±2	D43 ±2	D50 ±2	D57 ±2	D85 ±7	D113 ±7/ET	D141 ±7	D169 ±7	Q28D ±7
Informed consent	X															
Demography	X															
Medical history including HBV genotype[d]	X															
Inclusion/exclusion criteria	X	X[e]														
Full physical examination[f]	X						X						X			
Symptom-directed physical examination		X	X	X	X	X		X	X	X	X	X				
Alcohol intake assessment[g]		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X															
Height and BMI	X															
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Safety ECG[i]	X	X	X				X									
Pregnancy test[j]	X	X					X				X	X	X			
FibroScan[k]	X															
Screening viral serology[l]	X															

Study Stage	**Screening**	**Dosing Period**						**Post-dose Follow-up Period** [b]						**Extended Follow-up Period** [c]		
Study Visit Week				W1	W2	W3	W4[a]	W5	W6	W7	W8	W12	W16/ET	W20	W24	
Study Visit Day ±Visit Window	D-28 to -1	D1[a]	D2	D8 ±2	D15 ±2	D22 ±2	D29[a] ±2	D36 ±2	D43 ±2	D50 ±2	D57 ±2	D85 ±7	D113 ±7/ET	D141 ±7	D169 ±7	Q28D ±7
Laboratory assessment[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]	X[n]	X[n]
Urinalysis[m]	X	X														
Urine for drugs abuse[o]	X															
Randomization		X														
Study drug administration[p]		X					X									
Blood samples for PK analysis[q]		X	X	X			X[r]	X			X		X		X	
Blood sample for HBsAg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for anti-HBs	X										X		X		X	X[s]
Blood sample for HBeAg qualitative	X															
Blood sample for HBeAg quantitative for Part Two only[t]		X					X				X	X	X		X	X[s]
Blood sample for anti-HBe for Part Two only	X										X		X		X	X[s]
Blood sample for HBV DNA quantitation[u]	X	X					X				X	X	X	X	X	X[s]

Study Stage	Screening	Dosing Period						Post-dose Follow-up Period [b]						Extended Follow-up Period [c]		
Study Visit Week				W1	W2	W3	W4[a]	W5	W6	W7	W8	W12	W16/ET	W20	W24	
Study Visit Day ±Visit Window	D-28 to -1	D1[a]	D2	D8 ±2	D15 ±2	D22 ±2	D29[a] ±2	D36 ±2	D43 ±2	D50 ±2	D57 ±2	D85 ±7	D113 ±7/ET	D141 ±7	D169 ±7	Q28D ±7
CCI																
Review/record AEs[x]	X															
Concomitant Medications	X															
NrtI medication adherence	X															

AE = adverse event; ECG = electrocardiogram; ET = early termination; CCI HBeAg = hepatitis e-antigen; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; NrtI = nucleoside/nucleotide; PK = pharmacokinetics

Note: When scheduled at the same timepoints, the assessments of vital signs and 12-lead ECGs must be performed before blood sample collections.

[a] Assessments performed predose unless otherwise specified.

[b] If a subject withdraws prematurely from the study prior to their Week 16 visit, ET assessments should be performed.

[c] Additional HBsAg monitoring is required for subjects with a ≥ 1 $1og_{10}$ change from baseline (Day 1 predose level) decrease in HBsAg achieved by the Week 16 visit. Extended follow-up visits will occur every 4 weeks starting at Week 20, and subjects will be followed until the HBsAg level returns to > 90% of the Day 1 predose level or Week 48, whichever comes earlier. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.

[d] A complete medical history will be taken at screening including HBV genotype if available. Any changes should be updated prior to dosing.

[e] Evaluation of inclusion and exclusion criteria related to pregnancy testing, urine drug screen, medical history and concomitant medications prior to dosing.

[f] See Section 7.2.1 for assessments to be performed during a full physical examination.

[g] Subjects' alcohol intake will be recorded while on study.

[h] Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) should be measured in the supine position after the subject has rested comfortably for approximately 10 minutes. On Day 1, vital signs should be measured within 2 hours predose and 4 hours (± 30 minutes) post-dose. On all other visit days, vital signs are only required to be recorded once during the visit.

[i] 12-lead safety ECGs should be measured in the supine position after the subject has rested comfortably for 10 minutes.

[j] WOCBP are required to have pregnancy tests. A blood pregnancy test will be performed at screening and urine pregnancy tests will be performed thereafter. Urine pregnancy test results from local laboratories are acceptable. Negative pregnancy test must be confirmed prior to study drug administration.

[k] Does not need to be performed if the subject has had a FibroScan in the 6 months prior to screening or liver biopsy in the year prior to screening that confirmed the absence of Metavir F3 fibrosis or F4 cirrhosis.

[l] See Section 7.1.3 for viral serology parameters.

[m] Clinical laboratory and urinalysis parameters are described in Section 7.2.7.

[n] Liver function tests only.

[o] Drugs of abuse included in the screen are described in the inclusion/exclusion criteria. Screening results for drugs of abuse must be reviewed prior to dosing.

[p] Study drug will be administered via SC injection as described in Section 6.2.4.

[q] Blood samples for PK analysis will be collected at the timepoints listed in Appendix 3.

[r] As a part of the Week 4 visit, subjects will return to the study center 24-hours after their initial post dose Week 4 PK sample is drawn to have a 24-hour post dose PK sample drawn.

[s] Testing should occur again only at Week 36 and Week 48.

[t] For subjects in Part Two, if HBeAg has become undetectable for 2 consecutive assessments, no further quantitative testing is needed.

[u] If a subject experiences ALT flare (as defined by ALT > 2x ULN) additional HBV DNA quantitation sample(s) may be collected

[v] CCI [redacted]

[w] CCI [redacted].

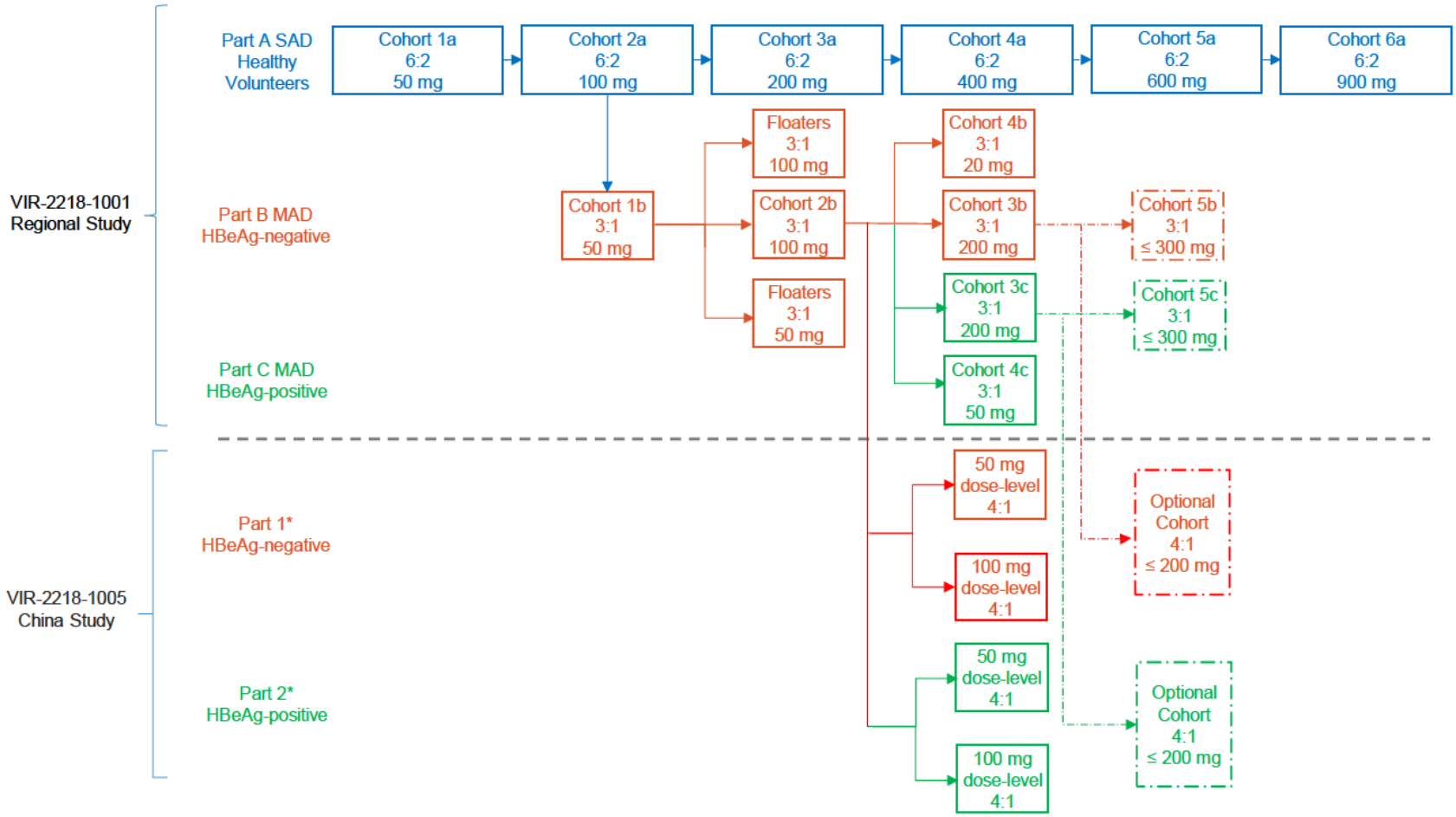
[x] All AEs related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards.

Appendix 3. Part One/Two Pharmacokinetic Assessment Timepoints

Study Day/Week	Protocol Time (Time Window)	PK Blood
Screening		
Day 1	Predose	X[a]
	Dose	
	1 hour ± 5 minutes	X
	2 hours ± 10 minutes	X
	4 hours ± 30 minutes	X
	8 hours ± 30 minutes	X
Day 2	24 hours ± 2 hours	X
Week 1		X
Week 4	Predose	X[a]
	Dose	
	1 hour ± 5 minutes	X
	2 hours ± 10 minutes	X
	4 hours ± 30 minutes	X
	8 hours ± 30 minutes	X
	24 hours ± 2 hours	X
Week 5		X
Week 8		X
Week 16		X
Week 24[b]		X

[a] At ≤ 15 minutes prior to dosing
[b] Collected only from subjects in extended follow up.

Appendix 4. Cohort Dose Schedule of the Regional Study and the China Study



HBeAg = hepatitis B e-antigen; MAD = multiple ascending dose; SAD = single ascending dose

Note: The ongoing VIR-2218-1001 regional study is being conducted independently of this study (VIR-2218-1005).

* The doses designated in the Part One/Two schedule are indicative of a single dose of VIR-2218 or placebo (4:1); subjects will receive up to 2 doses total for each cohort.

Appendix 5 Protocol Amendment History

The Protocol Amendment Summary of Changes for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1: 07 April 2020

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Inclusion Criteria and the relevant sections	Women of child-bearing potential (WOCBP) will be assessed by urine pregnancy test on Day 1 instead of by serum pregnancy test by central laboratory.	Changes allow for same day confirmation of pregnancy status prior to dosing on Day 1 of the study.
Table 4 Study Drug Dose and Administration; Table 5 Clinical Laboratory Tests	Remove unessential footnotes concerning the injection volume per administration and Creatine Kinase testing.	Changes eliminate confusion concerning related topics.
Appendix 2 Schedule of Assessments	Removal of inappropriate time points of the exploratory endpoints.	Changes reflect adequate time points to assess the exploratory endpoints.
Section 8.3.2 Serious Adverse Events; Section 8.5.2 Reporting Other Special Situations	Correct the contact information for reporting SAEs and other special situations.	Changes reflect correct contact information.

Document History Table for Protocol Amendments

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	23 September 2020
Amendment 1	07 April 2020
Original Protocol	06 September 2019