Official Title: A Phase 1/2, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of VIR-2218

NCT Number: NCT03672188

Document Date: Amendment 2, 27 March 2019

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1/2, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of VIR-2218
Sponsor:	Vir Biotechnology, Inc. 499 Illinois Street, Suite 500 San Francisco, CA 94158, USA
Investigational Product:	VIR-2218
Clinicaltrials.gov ID:	To be determined
Indication:	Chronic Hepatitis B (HBV) Infection
Protocol ID:	VIR-2218-1001
Vir Study Director & Medical Monitor:	PPD [redacted]
Protocol Version/Date:	Amendment 2: 27 March 2019

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PROTOCOL SYNOPSIS

Study Title:	A Phase 1/2, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of VIR-2218
Clinical Investigative Sites Planned:	Part A is planned to be conducted at 1 clinical investigative site. Part B/C are planned to be conducted at multiple clinical investigative sites in the Asia-Pacific region.
Phase	**Part A:** Phase 1 Single Ascending Dose (SAD) **Part B/C:** Phase 2 Multiple Ascending Dose (MAD)
Number of Subjects Planned:	Up to 104 subjects
Target Population:	**Part A:** Up to 56 healthy adult subjects **Part B/C:** Up to 48 non-cirrhotic adult subjects with chronic hepatitis B virus (HBV) infection on nucleos(t)ide reverse transcriptase inhibitor (NUC) therapy
Diagnosis and Main Eligibility Criteria	Part A will include healthy adult subjects. Part B/C will include non-cirrhotic adult subjects with chronic HBV infection on NUC therapy.
Duration of Study Participation:	**Part A:** The estimated total time on study, inclusive of screening and follow-up, for each subject is up to 16 weeks. The duration of treatment is a single dose, which can consist of up to 3 subcutaneous (SC) injections based on the assigned dose level. **Part B/C:** The estimated total time on study, inclusive of screening and follow-up, for each subject is up to 20 weeks. For subjects requiring additional HBsAg monitoring, the estimated total time on study is up to 52 weeks. The duration of treatment is 2 doses 4 weeks apart, consisting of up to 2 SC injections per dose based on the assigned dose level.
Duration of Follow-up:	**Part A**: 12 weeks after study drug administration **Part B/C:** All subjects should be followed until Week 16. 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.

Objective(s):	**Part A** The primary objective is: • To evaluate the safety and tolerability of a single dose of VIR-2218 in healthy adult subjects The secondary objective is: • To characterize the pharmacokinetics (PK) of VIR-2218 in healthy adult subjects **Part B/C** The primary objective is: • To evaluate the safety and tolerability of multiple doses of VIR-2218 in non-cirrhotic subjects with HBeAg-negative (Part B) and HBeAg-positive (Part C) chronic HBV infection on NUC therapy The secondary objectives are: • To characterize the PK of VIR-2218 in non-cirrhotic subjects with chronic HBV infection on NUC therapy • To assess the antiviral activity of VIR-2218 in non-cirrhotic subjects with chronic HBV infection on NUC therapy CCI [redacted]
Study Design:	This is a randomized, double-blind, placebo-controlled study of VIR-2218 administered subcutaneously to healthy adult subjects and non-cirrhotic adult subjects with chronic HBV infection who are on NUC therapy. The study is designed to evaluate the safety, tolerability, PK, and antiviral activity of VIR-2218. A Safety Review Committee (SRC) will perform ongoing reviews of safety and tolerability based on available study data collected throughout the study. The study will be conducted in 3 Parts: • **Part A:** SAD phase in healthy adult subjects

- **Part B:** MAD phase in non-cirrhotic adult subjects with HBeAg-negative chronic HBV infection on NUC therapy for ≥ 6 months and serum HBV DNA < 90 IU/mL
- **Part C:** MAD phase in non-cirrhotic adult subjects with HBeAg-positive chronic HBV infection on NUC therapy for ≥ 6 months and serum HBV DNA < 90 IU/mL

Four dose-level cohorts are planned for Part A: 50 mg, 100 mg, 200 mg, and 400 mg. Two sentinel subjects will be randomized 1:1 to VIR-2218 or placebo. These subjects will be dosed concurrently and monitored for 24 hours; if the investigator has no safety concerns, the remainder of the subjects in the same cohort will be dosed. The remaining subjects will be randomized 5:1 to VIR-2218 or placebo. Two optional cohorts in Part A may be added following the same stratification, including sentinel dosing, up to a maximum dose of 900 mg. In addition to the optional cohorts, a total of 8 "floater" subjects may be added to expand any cohort in Part A. "Floater" subjects are to be added in increments of 4 and randomized 3:1 to VIR-2218 or placebo.

Three dose-level cohorts are planned for Part B: 50 mg, 100 mg, and 200 mg. One dose-level cohort is planned for Part C: 200 mg. These planned dose levels will be administered twice, with each subject receiving a dose on Day 1, and a second dose at Week 4, such that the cumulative dose received for these subjects will be 100 mg, 200 mg, and 400 mg (Part B) and 400 mg (Part C). Each cohort in Part B/C will be randomized 3:1 to VIR-2218 or placebo. Two optional cohorts in Part B and 2 optional cohorts in Part C may be added following the same stratification, up to a maximum dose of 450 mg per dose (900 mg cumulative dose). In addition to the optional cohorts, a pool of 16 "floater" subjects may be added to expand any cohort in Part B and/or C if further data are needed. "Floater" subjects are to be added in increments of 4 (3:1) to maintain the randomization ratio.

All dose levels explored in Part B/C must first be completed in Part A with data reviewed by the SRC prior to initiating the dose-level cohort in subjects with chronic HBV infection.

The cohort dosing strategy for Part B/C of this study is staggered; 2 dose levels in Part A (1a: 50 mg and 2a: 100 mg) must be completed and data must be reviewed by the SRC to begin dosing at the starting dose in Part B (1b: 50 mg). Part C will be initiated at the Part C starting dose (3c: 200 mg) at the same time that the equivalent Part B dose level cohort is initiated (3b: 200 mg).

Study Procedures:

Part A

Screening

- Screening will be performed no more than 4 weeks prior to 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 (SoA). Adverse events (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 serious adverse events (SAEs) must be collected from the time of consent onwards.

Inpatient Period (Day −1 to Day 2)

- Subjects will be admitted into the clinical investigative site on Day −1. Eligible subjects will be randomized to receive VIR-2218 or placebo within 48 hours prior to study drug administration on Day 1. Subjects will be discharged after all study assessments are performed on Day 2.

Outpatient/Follow-Up Period

- Subjects will return to the clinical investigative site for in-person assessments per the SoA including but not limited to physical examination (including vitals), laboratory testing (including safety), 12-lead ECG and review of AEs and concomitant medication for 12 weeks after study drug administration.

Part B/C

Screening

- Screening will be performed no more than 4 weeks prior to 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 ECG and other assessments per the SoA. 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 (Day 1 to Week 4) • The dosing period for Part B/C is outpatient. Eligible subjects will be randomized to receive VIR-2218 or placebo within 48 hours 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. Follow-Up Period • Subjects will return to the clinical investigative site for in-person assessments per the SoA including but not limited to physical examination (including vitals), laboratory testing (including safety), 12-lead ECG and review of AEs and concomitant medication until Week 16. Extended Follow-Up Period • Subjects that require additional HBsAg monitoring will return to the clinical investigative site for in-person assessments per the SoA. Visits will occur every 4 weeks starting at Week 20 for a maximum of 48 weeks from the first study drug administration.
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-acetyl-galactosamine (GalNAc) ligand that allows for specific uptake by hepatocytes. VIR-2218 will be supplied as a sterile solution for SC injection at a free acid concentration of 200 mg/mL. The starting dose for Parts A and B is 50 mg. The starting dose for Part C is 200 mg. The dose levels in Parts A, B, and C will not exceed the defined maximum administered dose of 900 mg (single or cumulative).
Reference Therapy:	Subjects randomized to placebo will be administered sterile, preservative-free normal saline 0.9% solution for SC injection.
Criteria for Evaluation:	**Part A** Primary Endpoints • Incidence of AEs • Clinical assessments including but not limited to laboratory test results Secondary Endpoints • PK parameters of VIR-2218 and possible metabolites (may include, but not be limited to, plasma: maximum 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; urine: fraction eliminated in the urine and renal clearance)

Part B/C

Primary Endpoints

- Incidence of AEs
- Clinical assessments including but not limited to laboratory test results

Secondary Endpoints

- PK parameters of VIR-2218 and possible metabolites (may include, but not be limited to, plasma: maximum 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 Week 16
- Number of subjects with serum HBsAg loss at any timepoint
- Number of subjects with sustained serum HBsAg loss for ≥ 6 months
- Number of subjects with anti-HBs seroconversion at any timepoint
- For HBeAg-positive subjects (Part C only): number of subjects with HBeAg loss and/or anti-HBe seroconversion at any timepoint

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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

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBe	hepatitis B extracellular antibody
anti-HBs	hepatitis B surface antibody
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the curve
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
ECG	Electrocardiogram
eCRF	electronic case report form
ET	early term
FDA	Food and Drug Administration
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
Hgb	Hemoglobin
HIV	human immunodeficiency virus
HLGT	High-Level Group Term
HLT	High-Level Term
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
NUC	nucleos(t)ide reverse transcriptase inhibitor
OTC	over-the-counter
PEG-IFN	pegylated interferon-alpha
PK	Pharmacokinetics
pgRNA	pregenomic RNA
PT	Preferred Term
Q1	first quartile
Q3	third quartile

RBC	red blood cell (count)
RT	reverse transcriptase
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
US	United States
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, 2017; 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).

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 (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 (NUCs) and pegylated interferon-alpha (PEG-IFN) (Liang, 2015). NUCs inhibit the production of infectious virions, and often reduce serum HBV DNA to undetectable. However, NUCs 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 NUC therapy. In turn, this necessitates prolonged, often lifelong therapy; furthermore, while NUC 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 NUC 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. VIR2218

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, NUCs act at a distinct part of the viral life cycle and have a different mechanism of action than VIR-2218. NUCs inhibit the action of HBV RNA polymerase, blocking the reverse transcription of the viral pgRNA to viral DNA and preventing the production of infectious virions. NUCs, 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 in Part B/C of this study will receive VIR-2218 added to their ongoing NUC 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 NUCs 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

The recommended starting dose for VIR-2218 was determined by calculating the human equivalent doses (HEDs) of the no observed adverse effect levels (NOAELs) in the definitive animal toxicology studies and applying a safety margin to those HEDs. Body surface area (m/kg^2) conversion factors were used to calculate HEDs of animal doses.

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Although dosing in the GLP-toxicology studies was weight based, subjects will receive a fixed dose rather than a weight-based dose because VIR2218, like other GalNac-conjugated siRNAs, is taken up by the liver and minimally distributed to other organs and tissues. Therefore, weightbased dosing is not anticipated to reduce the inter-individual variation in the pharmacokinetics (PK) of VIR2218 in adults and a fixed dose has the advantage of avoiding potential dose calculation errors.

The planned and optional dose levels for Part A, were determined to support Part B/C. The planned and optional dose levels for Part B/C are based on what is estimated to result in meaningful biological activity in humans, specifically the observation that other siRNAs using the GalNac platform have demonstrated meaningful liver target engagement at 1 to 15 mg/kg.

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Part A: Single Ascending Dose Study in Healthy Volunteers (Table 2):

Planned dose levels*:* Healthy volunteers will receive a single ascending dose. Four dose-level cohorts are planned. Doses will be increased stepwise by a factor of 2-fold up to a maximum planned dose of 400 mg (Section 4.5. describes the criteria used for dose escalation).

Optional dose level*:* Two optional dose levels may be added. The additional dose levels will not exceed 900 mg. Doses higher than 400 mg will only be administered if 400 mg is well tolerated in subjects based on review of all available safety data collected through Week 4.

Table 2. Part A Dose Escalation Plan

Cohort	Weight-based dose (mg/kg)	Fixed dose[a] (mg)	Dose Escalation Factor
1a	0.8	50	-
2a	1.7	100	2.0-fold
3a	3.3	200	2.0-fold
4a	6.7	400	2.0-fold
Optional: 5a and 6a	Up to 15	Up to 900	Up to 2.25-fold

[a] Based on average adult weight of 60 kg

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

Planned dose levels*:* HBeAg-negative subjects with chronic HBV infection will be enrolled in Part B and HBeAg-positive subjects with chronic HBV infection will be enrolled in Part C. Three dose-level cohorts for HBeAg-negative subjects are planned; dose levels will be increased stepwise by a factor of 2 up to a maximum planned dose level of 200 mg and a cumulative dose of 400 mg (Section 4.5. describes the criteria used for dose escalation). To accommodate the anticipated lower prevalence of HBeAg-positive patients on NUC therapy, only 1 dose level cohort (200 mg) is planned for HBeAg-positive subjects.

Initiation of Part B*:* Part B, Cohort 1b will be initiated after cumulative review of all available safety data, inclusive of the Week 4 laboratory and clinical data of the last available healthy volunteer subject in the 100 mg cohort (Cohort 2a).

Initiation of Part C*:* The only planned cohort in Part C, Cohort 3c, will initiate at the same time as Cohort 3b after review of all available safety data inclusive of Week 6 clinical and laboratory data from Cohort 2b, and according to the criteria outlined in Section 4.5. Subjects in Cohort 3c will receive VIR-2218 at the same dose level as subjects in Cohort 3b (200 mg administered twice at a dosing interval of 4 weeks).

Optional dose levels*:* Two optional dose level cohorts may be added for each subject population. Doses higher than 200 mg will only be administered if 200 mg is well tolerated in subjects with chronic HBV infection based on review of all available safety data collected through 8 weeks after the first dose (4 weeks after the second dose). Doses can be increased stepwise by a factor of 1.5-fold up to a maximum optional single dose of 450 mg (cumulative dose of 900 mg).

Table 3. Part B/C Dose Escalation Plan

Cohort	Weight-based Dose (mg/kg)	Fixed Dose[a] (mg)	Dose Escalation Factor
1b	0.8	50	-
2b	1.7	100	2.0-fold
3b and 3c	3.3	200	2.0-fold
Optional: 4b and 4c	Up to 5	Up to 300	Up to 1.5-fold
Optional: 5b and 5c	Up to 7.5	Up to 450	Up to 1.5-fold

[a] Based on average adult weight of 60 kg

1.3. 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 pangenotypic 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

The safety profile of VIR-2218 has not yet been established. CCI [redacted] CCI [redacted] To further mitigate risk, a "sentinel" dose design will be used in Part A as follows.

- Two subjects will be randomized 1:1 to VIR-2218 or placebo and dosed concurrently
- These subjects will be monitored for 24 hours and if the investigator has no safety concerns, the other subjects in the same cohort are dosed. The remaining 6 subjects will be randomized 5:1 to VIR-2218 or placebo.

During the conduct of the study, the Sponsor will perform ongoing safety reviews and the SRC will meet to review safety data.

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. Part A Objectives

The primary objective is:

- To evaluate the safety and tolerability of a single dose of VIR-2218 in healthy adult subjects

The secondary objective is:

- To characterize the PK of VIR-2218 in healthy adult subjects

2.2. Part B/C Objectives

The primary objective is:

- To evaluate the safety and tolerability of multiple doses of VIR-2218 in non-cirrhotic subjects with HBeAg-negative (Part B) and HBeAg-positive (Part C) chronic HBV infection on NUC therapy

The secondary objectives are:

- To characterize the PK of VIR-2218 in non-cirrhotic subjects with chronic HBV infection on NUC therapy
- To assess the antiviral activity of VIR-2218 in non-cirrhotic subjects with chronic HBV infection on NUC therapy

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3. ENDPOINTS

3.1. Part A Endpoints

The primary endpoints are:

- Incidence of AEs
- Clinical assessments including but not limited to laboratory test results

The secondary endpoints are:

- PK parameters of VIR-2218 and possible metabolites (may include, but not limited to plasma: maximum 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; urine: fraction eliminated in the urine and renal clearance)

3.2. Part B/C Endpoints

The primary endpoints are:

- Incidence of AEs
- Clinical assessments including but not limited to laboratory test results

The secondary endpoints are:

- PK parameters of VIR-2218 and possible metabolites (may include, but not limited to plasma: maximum concentration, time to reach maximum concentration, area under the concentration versus time curve [to the last measurable timepoint and to infinity], apparent terminal elimination half-life, clearance, and volume of distribution)
- Maximum reduction of serum HBsAg from Day 1 until Week 16
- Number of subjects with serum HBsAg loss at any timepoint
- Number of subjects with sustained serum HBsAg loss for ≥ 6 months
- Number of subjects with anti-HBs seroconversion at any timepoint
- For HBeAg-positive subjects (Part C only): number of subjects with HBeAg loss and/or anti-HBe seroconversion at any timepoint

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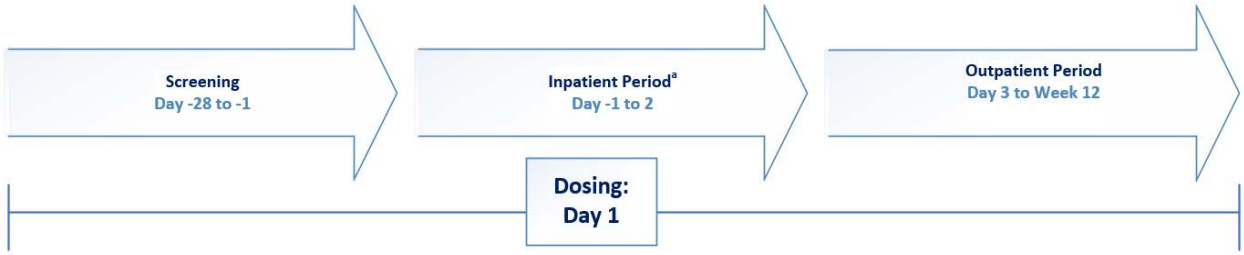
[redacted]

4. STUDY DESIGN

4.1. Treatment Plan and Regimen

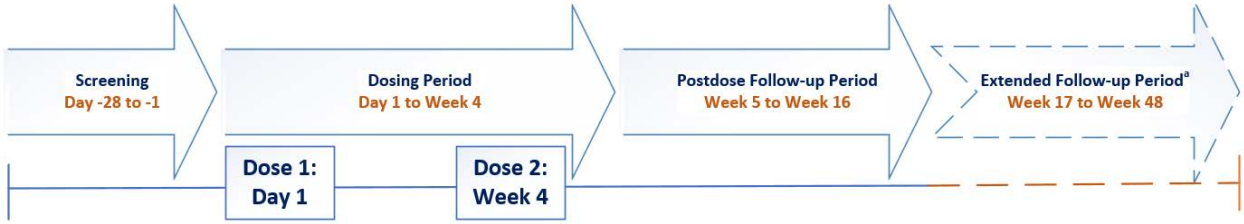
This is a randomized, double-blind, placebo-controlled study of VIR-2218 administered subcutaneously to healthy adult subjects and non-cirrhotic adult subjects with chronic HBV infection who are on NUC therapy. The study is designed to evaluate the safety, tolerability, PK, and antiviral activity of VIR-2218. Part A is planned to be conducted at 1 clinical investigative site; Parts B and C are planned to be conducted at multiple clinical investigative sites in the Asia-Pacific region. The study designs for Part A SAD and Part B/C MAD are presented in Figure 1 and Figure 2, respectively, and the cohort dosing schedule is provided in Appendix 6.

Figure 1. SAD Study Design for Part A



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

Figure 2. MAD Study Design for Part B/C



[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.

4.1.1. Part A Single Ascending Dose Phase in Healthy Adult Subjects

Healthy adult subjects will be enrolled in 1 of 4 planned ascending dose cohorts. At the start of each cohort, 2 sentinel subjects will be randomized 1:1 to VIR-2218 or placebo. These subjects will be dosed concurrently and monitored for 24 hours; if the investigator has no safety concerns, the remainder of the subjects in the same cohort will be dosed. Vital signs, symptom-directed physical examination(s), and AEs will be reviewed by the investigator prior to dosing any additional subjects. The remaining subjects will be randomized 5:1 to receive a single dose of VIR-2218 or placebo.

Subject screening will occur no more than 4 weeks prior to the Day 1 visit. Eligible subjects will be confined to the clinical investigative site on Day −1 to determine continued eligibility and for predose assessments. Subjects in each cohort will be randomized to receive VIR-2218 or placebo within 48 hours prior to study drug administration. Subjects will receive a single dose of study drug on Day 1 (VIR-2218 or placebo). Subjects will be discharged from the clinical investigative site after all assessments are completed on Day 2.

Subjects will return to the clinical investigative site on an outpatient basis for safety, tolerability, and PK monitoring at specified timepoints through the last Post-dose Follow-up Visit (Week 12).

Based on review of the accumulated, available data in Part A, the SRC may recommend dosing of 2 optional cohorts. In addition to the optional cohorts, up to 8 "floater" subjects for Part A may be added to any cohort, as determined and approved by the SRC (see Section 4.5.2 and Appendix 6 for further information).

Fasting is not required for any study procedure/assessment.

4.1.2. Part B/C Multiple Ascending Dose Phase in Non-Cirrhotic Adult Subjects with Chronic HBV Infection on Nucleoside/Nucleotide Therapy

Non-cirrhotic adult subjects with chronic HBV infection on NUC therapy for ≥ 6 months will be enrolled in the Part B/C cohorts. Part B will enroll HBeAg-negative subjects. Part C will enroll HBeAg-positive subjects. Eligible subjects should have HBV DNA < 90 IU/mL. Each cohort in Part B/C will be composed of 4 subjects randomized 3:1 to VIR-2218 or placebo, respectively. There are 3 planned and 2 optional cohorts in Part B. There are 1 planned and 2 optional cohorts in Part C.

Subjects enrolled in Part B/C of the study will remain outpatient. Subject screening will occur no more than 4 weeks prior to the Day 1 visit. Eligible subjects will undergo further assessments on Day 1 to qualify for study drug administration on Day 1. 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.

Subjects in each cohort will be randomized 3:1 to receive VIR-2218 or placebo within 48 hours 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.

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Subjects will return to the clinical investigative site on an outpatient basis for safety, tolerability, PK, and antiviral activity monitoring at specified timepoints through the last Post-dose Follow-up Visit (Week 16). 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.

Based on review of the accumulated, available data in Parts A, B, and C, the SRC may recommend dosing of optional cohorts following the same stratification. In addition to the optional cohorts, a combined total of up to 16 "floater" subjects for Part B/C may be added to any cohort, as determined and approved by the SRC (see Section 4.5.5 and Appendix 6 for further information).

Fasting is not required for any study procedure/assessment. The assessments performed at each visit are described in Appendix 3 .

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 12 visit for Part A or the Week 16 visit for Part B/C, 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 dose escalation 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 (for Part B/C), discontinue due to an AE that does not meet study progression/escalation 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

A 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 a new cohort in Parts A, B, and C of the study in accordance with the SRC Charter. In addition, ad hoc SRC meetings may take place as needed, eg, 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, Study Progression, and Dose Escalation

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 and Appendix 3 for Cohort A and Cohort B/C, respectively.

4.5.1. Part A Study Drug Dosing, Study Progression, and Dose Escalation in Planned Cohorts

The starting dose for the first cohort in Part A is 50 mg, as described in Section 1.2.4. The SRC will review available laboratory and clinical safety data, including Week 4 data from the last available subject enrolled in the cohort to proceed to the next planned cohort in Part A. There are 4 planned cohorts in Part A: 50 mg, 100 mg, 200 mg, and 400 mg (Table 4).

4.5.2. Part A Optional Cohorts and Floater Subjects

Based on SRC review of accumulated safety and tolerability data, 2 optional cohorts may be enrolled and dosed according to the same eligibility criteria and corresponding randomization scheme to better define safety and tolerability. The maximum optional dose in Part A will not exceed the defined maximum administered single dose of 900 mg (see Appendix 6 for additional information).

In addition to the optional cohorts, up to 8 “floater” subjects in total for Part A may be added to expand any of 6 possible cohorts (planned or optional), as determined and approved by the SRC. Each expansion must include a minimum of 4 “floater” subjects, randomized 3:1 to VIR-2218 or placebo, furthermore only half of the total “floater” subjects (4 subjects in Part A) may enroll in the highest optional dose cohort.

4.5.3. Part B Study Drug Dosing, Study Progression, and Dose Escalation in Planned Cohorts

Overview*:* There are 3 planned cohorts in Part B: 50 mg, 100 mg, and 200 mg. Part B is limited to subjects with chronic HBV infection who are HBeAg-negative. Each cohort will receive a dose on Day 1, and a second dose at Week 4, such that the cumulative dose received for the planned cohorts in Part B will be 100 mg, 200 mg, and 400 mg (Table 4).

Initiation of Part B*:* 2 dose levels in Part A (1a: 50 mg and 2a: 100 mg) must be completed and cumulative safety data, inclusive of the clinical and laboratory data from Week 4 from the last subject dosed in Cohort 2a (100 mg), must be reviewed by the SRC to begin dosing Part B (1b: 50 mg).

Escalation within Part B: Escalation to a higher dose-level cohort will only occur after the SRC has reviewed clinical and laboratory data including data from the Week 6 visit of the last available subject in the ongoing cohort, and the subject has completed their Week 8 visit. The SRC may review cumulative data from subjects in Parts A, B, and C at the time of meeting. The SRC will ensure that no subject in a cohort from Part B will receive a particular dose level prior to review of Week 4 data from subjects in Part A who have received at least the same cumulative dose level.

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4.5.4. Part C Study Drug Dosing, Study Progression, and Dose Escalation in Planned Cohorts

Overview*:* There is 1 planned cohort in Part C: 200 mg (Cohort 3c). Escalations to higher dose levels may only occur in the optional cohorts (Section 4.5.5). Part C is limited to subjects with chronic HBV infection who are HBeAg-positive. This cohort will receive a dose on Day 1, and a second dose at Week 4, such that the cumulative dose received will be 400 mg (Table 4).

Initiation of Part C*:* The planned Cohort 3c will initiate at the same time as Cohort 3b (200 mg, given as 2 doses, 4 weeks apart), after the SRC has reviewed clinical and laboratory data including from the Week 6 visit of the last available subject in Cohort 2b. Initiation of Cohort 3c will not occur until the last available subject in Cohort 2b has completed their Week 8 visit.

4.5.5. Part B/C Optional Cohorts and Floater Subjects

Based on SRC review of accumulated safety and tolerability data, up to 2 optional dose-level cohorts may be enrolled and dosed in each study part according to the randomization scheme to better define dose response and/or safety and tolerability. Enrollment of the Part B/C optional cohorts will be according to the same Part B/C eligibility criteria as the planned cohorts.

The optional cohorts may be dosed at lower, intermediate, and/or higher dose levels than the dose levels explored in the planned Part B or C cohorts. The maximum cumulative dose level in any cohort in Part B or C will not exceed the highest single dose found to be well tolerated in Part A. For example, if a single dose of 900 mg in Part A is determined by the SRC to have an acceptable safety profile, dose levels of 450 mg (cumulative dose of 900 mg) or lower dose levels can be explored in Part B/C. The maximum administered cumulative dose in any cohort will not exceed 900 mg (Table 4).

Dose escalation in the optional Part B/C cohorts will occur according to the same criteria as dose escalation within Part B (Section 4.5.3.)

In addition to the optional cohorts, up to 16 "floater" subjects in total for Part B/C may be added to expand any Part B or C cohort (planned or optional), as determined and approved by the SRC. This "floater" pool is shared between Part B/C and the allocation of floater subjects does not need to be distributed evenly across parts. Subjects will be added in increments of 4 and randomized 3:1 to VIR-2218 or placebo, furthermore only half of the total "floater" subjects (8 total subjects in Part B/C) may enroll in the highest optional dose cohort.

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 dose escalation/progression will be suspended. An ad hoc SRC meeting will be held, and only following SRC approval, may dosing be resumed at the same or a higher dose level; 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, cohort dosing will be suspended or stopped:

- Part A only: If a sentinel subject experiences a VIR-2218-related Grade 3 or higher AE
- If 1 or more subjects experience a Grade 3 VIR-2218-related rash
- If 2 or more subjects experience the same VIR-2218-related Grade 3 or higher AE
- If 1 or more subjects experience a VIR-2218-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 in Part B/C

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

- Serum ALT > 10 × 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

5. SUBJECT POPULATION

5.1. Number of Subjects and Subject Selection

A total of up to 104 subjects are planned to complete this study, comprising up to 56 healthy adult subjects (Part A) and up to 48 non-cirrhotic adult subjects with chronic HBV infection on NUC therapy (Part B/C).

- **Part A Planned/Optional Dose Cohorts:** Up to 48 healthy subjects
    - **Part A "Floater" Subjects**: Up to 8 "floater" subjects may be added
- **Part B Planned/Optional Dose Cohorts:** Up to 20 non-cirrhotic adult subjects with chronic HBV infection that are HBeAg-negative on NUC therapy
- **Part C Planned/Optional Dose Cohorts:** Up to 12 non-cirrhotic adult subjects with chronic HBV infection that are HBeAg-positive on NUC therapy
    - **Part B/C "Floater" Subjects**: Up to 16 "floater" subjects may be added

5.2. Part A Inclusion Criteria

Each subject must meet all the following inclusion criteria at screening to be eligible for enrollment in the study:

1. Age 18 (or age of legal consent, whichever is older) to 55 years
2. 12-lead electrocardiogram (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 age > 50 years with no menses for at least 2 years. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test 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 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 to not donate sperm for the 12 weeks following study drug administration. Refer to Section 6.6 for more information on highly effective methods of contraception.
5. Agrees not to donate blood during the duration of the study

6. Willing to comply with the study requirements and able to provide written informed consent
7. Body mass index (BMI) ≥ 18.0 kg/m^2 and ≤ 32 kg/m^2
8. Agree to not increase physical activity for 4 weeks after study drug administration

5.3. Part A 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 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 study drug administration
3. Receipt of a vaccine 14 days prior to Day 1
4. 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
5. Systolic blood pressure > 140 mmHg and a diastolic blood pressure of > 90 mmHg after approximately 10 minutes resting at screening
6. Subject has the following laboratory parameters at screening:
   a. ALT, AST, creatinine or total bilirubin above the upper limit of normal (ULN)
   b. hemoglobin (Hgb), absolute neutrophil count (ANC), platelets, or albumin below the lower limit of normal (LLN)
   c. white blood cells (WBC), potassium (K), or sodium (Na) above the ULN or below the LLN

   Study laboratory tests may be repeated once (eg, for values thought to be erroneous) with Sponsor medical monitor approval.
7. 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.
8. Laboratory evidence of active infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or HBV
9. 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
10. 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.

11. Known hypersensitivity or contraindication to an siRNA or GalNAc
12. History of intolerance to SC injection
13. 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
14. Donated more than 500 mL of blood within 90 days before study drug administration
15. Creatinine clearance (CL_{cr}) < 90 mL/min as calculated by the Cockcroft-Gault formula at screening
16. 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 1 medication (two active components in one medication is permitted) for > 6 months. Asthma must be well controlled, requiring, on average, use of a rescue bronchodilator no more than twice per week.
17. Use of over-the-counter (OTC) medication or herbal remedy within 14 days before study drug (≤ 2g/day of paracetamol (acetaminophen), ≤ 3g/day of aspirin or < 1.2 g/day of ibuprofen is permitted) and throughout the study.

5.4. Part B/C Inclusion Criteria

Each subject must meet all the following inclusion criteria at screening to be eligible for enrollment in the study:

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 age > 50 years with no menses for at least 2 years at the time of screening. 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. BMI ≥ 18.0 kg/m^2 and ≤ 32 kg/m^2
8. Chronic HBV infection as defined by a positive serum HBsAg for ≥ 6 months
9. On NUC therapy for at least 6 months without an interruption of 7 or more consecutive days
10. HBsAg > 150 IU/mL (by central laboratory)
11. HBV DNA < 90 IU/mL (by central laboratory)
12. Serum ALT and AST ≤ 2 × ULN (by central laboratory)
13. Agrees not to increase physical activity for 4 weeks after each study drug administration

5.5. Part B/C Exclusion Criteria

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 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 7.2.9 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, total bilirubin, INR or prothrombin time above the ULN
   b. hemoglobin, ANC, platelets, or albumin below the LLN
   c. WBC, potassium, or sodium above the ULN or below the LLN
   d. serum ALT or AST > 2 × ULN

   Study laboratory tests may be repeated once (eg, for values thought to be erroneous) with Sponsor 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 study drug 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 HIV, 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. CL_{cr} < 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 trial 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 subcutaneous 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.

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 healthy subjects and 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/per 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)[a]
1a	50	0.25	50	1	1	0.25
2a	100	0.50	100	1	1	0.50
3a	200	1.0	200	1	1	1.0
4a	400	2.0	400	2	2	2.0
Optional 5a	≤ 900	≤ 4.5	≤ 900	3	3	≤ 4.5
Optional 6a	≤ 900	≤ 4.5	≤ 900	3	3	≤ 4.5
1b	50	0.25	100	1	2	0.50
2b	100	0.50	200	1	2	1.0
3b	200	1.0	400	1	2	2.0
Optional 4b	≤ 300	≤ 1.5	≤ 600	1	2	≤ 3
Optional 5b	≤ 450	≤ 2.25	≤ 900	2	4	≤ 4.5
3c	200	1.0	400	1	2	2.0
Optional 4c	≤ 300	≤ 1.5	≤ 600	1	2	≤ 3
Optional 5c	≤ 450	≤ 2.25	≤ 900	2	4	≤ 4.5

a Injection volume per site will not exceed 1.5mL

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

For Part A, B, and C 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

- Prescription drugs necessary to treat hypertension. Hypertension must be well controlled (on a stable dose of no more than 2 medications **or** 1 medication with two active components for > 6 months)

- 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.

6.4.2. Prohibited Concomitant Medications

For Part A, B, and C the following medications/treatments are prohibited:

- Any OTC medications or herbal remedy within 14 days before of study drug administration 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 NUC therapy for Part B/C subjects

6.5. NUC Therapy

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

- Tenofovir (at recommended dose for the given formulation)

- 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 (eg, 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 no menses for 24 months in subjects > 50 years of age.

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 Study Assessments is provided in Appendix 2 for Part A and Appendix 3 for Part B/C. 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 (Part B/C only) and HBV genotype history (if available; Part B/C only), 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 Part B/C, assessments of antiviral activity will include: HBsAg, HBeAg, CCI, anti-HBs, anti-HBe, HBV DNA, CCI, and assessment of HBV and NUC resistance if indicated. HBV genome will be sequenced and analyzed for mutations that can confer resistance to VIR-2218 and NUCs in subjects with confirmed HBV breakthrough as defined by HBV DNA ≥ 500 IU/mL measured at 2 consecutive study visits. 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 are as follows:

- Part A: Active infection with HIV infection, HCV infection, and HBV infection.
- Part B/C: 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 and urine samples will be collected to assess concentrations of VIR-2218 and metabolites, as applicable. Detailed schedules of timepoints for the collection of samples for VIR-2218 PK analysis for Part A of the study are provided in Appendix 4. Timepoints for the collection of samples for VIR-2218 PK analysis for Part B/C of the study are provided in Appendix 5.

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 first, before the physical examinations, blood sample collections, and urine collections.

7.2.5. Electrocardiogram

Safety ECGs: 12-lead safety ECGs will be recorded and reviewed on-site by the investigator as outlined in Appendix 2 and Appendix 3. Specified collection timepoints for each visit are provided in Appendix 4 and Appendix 5.

Cardiodynamic ECG evaluation (Part A only): (12-lead ECGs extracted from continuous Holter recordings): Up to 10 replicate ECGs may be extracted by the central ECG core laboratory at

timepoints provided in Appendix 4 and Appendix 5. Subjects will be resting supine for at least 10 minutes prior to and 5 minutes after each nominal time point. 12-lead ECGs will be extracted from the 5-minute time window following the nominal time point. When scheduled at the same time points, the assessments of vital signs and 12-lead ECGs should be performed first, before the physical examinations, blood sample collections, and urine collections.

In Part A, the 12-lead Holter and ECG equipment will be supplied and supported by the central ECG core laboratory. All cardiodynamic ECG data will be collected using a Global Instrumentation M12R ECG continuous 12-lead digital recorder. The continuous 12-lead digital ECG data will be stored onto SD memory cards. ECGs to be used in the analyses may be selected by pre-determined time points as defined in Appendix 4 and Appendix 5, and cardiodynamic ECGs will be stored and may be read by the central ECG core laboratory.

The following principles will be followed in the central ECG core laboratory:

- ECG analysts are blinded to the subject, visit, and treatment allocation
- Baseline and on-treatment ECGs for a particular subject will be over-read on the same lead and will be analyzed by the same reader
- The primary analysis lead is lead II. If lead II is not analyzable, then primary lead of analysis will be changed to another lead for the entire subject data set.

The following is a brief description of ECG analysis methods utilized by the central ECG core laboratory.

TQT Plus ECG Extraction Technique

Ten 14-second digital 12-lead ECG tracings may be extracted from the continuous Holter recordings using the 'TQT Plus method', a computer-assisted and statistical process utilized by the central ECG core laboratory. The method enables extraction of ECGs with the lowest HR variability and noise within the protocol-specified extraction time window (eg, the HR and QT changes from beat-to-beat in the range of < 10%). At each protocol-specified timepoint, 10 ECG replicates may be extracted from a 5-minute "ECG window" (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine or semi-recumbent quiet position).

Expert-Precision QT Analysis

Expert-precision QT analysis may be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures are used to review and assess all beats and identify "high" and "low" confidence beats using several criteria, including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely).
- RR values exceeding or below certain thresholds (biologically unlikely).
- Rapid changes in QT, QTc or RR from beat to beat.

Measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates that are deemed "high confidence" are performed using COMPAS software. All low-confidence beats are reviewed manually and adjudicated using pass-fail criteria. The final QC assessment is performed by a cardiologist. The beats found acceptable by manual review are included in the analysis. The median QT, QTc, and RR value from each extracted replicate is calculated, and then the mean of all available medians from a nominal timepoint is used as the subject's reportable value at that timepoint.

T-wave morphology categories are presented in Table 5. Categorical T-wave morphology analysis and the measurement of PR and QRS intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) is electronically marked.

In addition to the T-wave categorical analysis, the presence of abnormal U-waves is noted.

Table 5. T-Wave Morphology Categories (Assessed Manually)

Category	Description
Normal T-wave	Any T-wave not meeting any criterion below
Flat T-waves	T amplitude < 1 mm (either positive or negative) including flat isoelectric line
Notched T-wave (+)	Presence of notch(es) of at least 0.05 mV amplitude on ascending or descending arm of the positive T-wave
Biphasic	T-wave that contains a second component with an opposite phase that is at least 0.1 mV deep (both positive and negative/positive and polyphasic T-waves included)
Normal T-wave (-)	T amplitude that is negative, without biphasic T-wave or notches
Notched T-wave (-)	Presence of notch(es) of at least 0.05 mV amplitude on descending or ascending arm of the negative T-wave

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 age > 50 years with no menses for at least 2 years at the time of screening. Pregnancy tests will be performed for WOCBP only. Pregnancy testing will be performed per the schedule of assessments (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 6. 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 6. 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[a]	• 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 only)	• Urine pregnancy test
Serology	
• Hepatitis B, C, and Delta	• Human immunodeficiency virus I and II

[a] Only required if ALT and/or AST is elevated 2 × higher than predose Day 1 baseline value

7.2.8. FibroScan

To exclude the presence of cirrhosis, subjects in Part B/C 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 CRF (Case Report Form).
- Unless associated with signs or symptoms, laboratory abnormalities (eg, 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; ie, 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 (eg, 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 (eg, 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 (eg, 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 (eg, anemia), not the laboratory result (ie, 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 Vir

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.

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. Vir may request that certain AEs be followed beyond the protocol-defined follow-up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (ie, 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 Vir.

- For fatal or life-threatening events, copies of hospital case reports, discharge summaries, autopsy reports, and other documents should be submitted by email or fax when requested and applicable. Transmission of such documents should occur without personal 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 eCRF and the event description section of the SAE form.

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

PPD

8.4. Vir 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.

Reporting Other Special Situations

All other special situations must be reported to PPD [redacted] 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 [redacted]

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. 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 (eg, 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.

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

PK parameters of VIR2218 and possible metabolites will be computed using standard noncompartmental methods. Parameters may include, but not be limited to, plasma: 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; urine: fraction eliminated in the urine and renal clearance, and will be listed and summarized using descriptive statistics. 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

For Part B/C, selected data relating to the antiviral activity of VIR2218, 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 104 subjects (up to 56 healthy subjects and up to 48 subjects with chronic HBV infection) are planned to complete the study. The 104 subjects includes “floater” subjects (up to 8 healthy subjects and up to 16 subjects with chronic HBV infection) that may be added as part of expansion of an existing cohort or cohorts based on SRC recommendations if further data are necessary.

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 trial.

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 trial 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 contact 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.

11. REFERENCES

1. Allweiss L, Dandri M. The Role of cccDNA in HBV Maintenance. *Viruses.* 2017;9: 156. doi: 10.3390/v9060156

2. Burton AR, Pallett LJ, McCoy L, Suveizdyte K, Amin OE, Froghi F, Davidson BR, Gill US, Kennedy PTF, Blair PA, Mauri C, Pelletier N, and Maini MK Dysfunctional surface antigen-specific memory B cells accumulate in chronic hepatitis B infection. EASL International Liver Congress, Paris, France 2018

3. Bertoletti A, Ferrari C. Adaptive immunity in HBV infection. *Journal of Hepatology*. 2016; 64(1): S71 - S83. doi: 10.1016/j.jhep.2016.01.026

4. Hepatitis B Fact sheet. World Health Organization Website. http://www.who.int/mediacentre /*factsheets/fs204/en/. Updated July 2017.*

5. Konerman MA, Lok AS. Interferon Treatment for Hepatitis B.*Clinics in Liver Disease*. 2016;20(4): 645-665. doi: 10.1016/j.cld.2016.06.002

6. Levrero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. *Journal of Hepatology*. 2016;64(1): S84 - S101. doi: 10.1016/j.jhep.2016.02.021

7. Li Y, Si L, Zhai Y, et al. Genome-wide association study identifies 8p21.3 associated with persistent hepatitis B virus infection among Chinese. *Nature Communications*. 2016;7:11664. doi:10.1038/ncomms11664.

8. Liang TJ, Block TM, McMahon BJ, et al. Present and Future Therapies of Hepatitis B: From Discovery to Cure. *Hepatology*. 2015;62(6):1893-1908. doi:10.1002/hep.28025.

9. Lucifora J, Protzer U. Attacking hepatis B virus cccDNA—The holy grail to hepatitis B cure. *Journal of Hepatology.* 2016;64(1): S41-S48. doi: 10.1016/j.jhep.2016.02.009

10. Maini MK, Gehring AJ. The role of innate immunity in the immunopathology and treatment of HBV infection. *Journal of Hepatology.* 2016;64(1): S60-S70. 10.1016/j.jhep.2016.01.028

11. Protzer U, Maini MK, Knoelle PA. Living in the liver: hepatic infections. *Nature Reviews Immunology*. 2012;12: 201-213. doi:10.1038/nri3169

12. Schweitzer A, Horn J, Mikolajczyk RT, Kraus G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a *systematic revie*w of data published between 1965 and 2013. *The Lancet.* 2015;387(10003):1546-1555. doi: 10.1016/S0140-6736(15)61412-X

13. Seeger C, Mason WS. Molecular biology of hepatitis B virus infection. *Virology*. 2015; 479-480:672-686. doi: 10.1016/j.virol.2015.02.031.

14. Stanaway JD, Flaxman AD, Naghavi M, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Lancet (London, England)*. 2016;388(10049):1081-1088. doi:10.1016/S0140-6736(16)30579-7.

15. Tong S, Revill P. Overview of viral replication and genetic variability. *Journal of hepatology*. 2016;64(1):S4-S16. doi:10.1016/j.jhep.2016.01.027.

16. Trepo C. A brief history of hepatitis milestones. *Liver International.* 2014;34(1):29-37.doi: 10.1111/liv.12409

12. APPENDICES

Appendix 1. Investigator Signature Page

VIR BIOTECHNOLOGY, INC
499 ILLINOIS STREET SUITE 500
SAN FRANCISCO, CA 94158

STUDY ACKNOWLEDGMENT

A Phase 1/2, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of VIR-2218

VIR-2218-1001, Protocol Amendment 2, 27 March 2019

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

PPD [redacted]	
Vir Study Director and Medical Monitor	*{See Appended Electronic Signature Page}*
Printed Name	**Signature and Date**

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Vir Biotechnology, Inc. I will discuss this material with them to ensure they are fully informed about the drugs and the study.

Principal Investigator Printed Name	**Signature**
	Date

Appendix 2. Part A Schedule of Study Assessments for SAD Cohorts in Healthy Adult Subjects

Part A											
Study Stage		**Inpatient[a]**			**Outpatient (Post-dose Follow-up Period)**						
	Screening										
Study Visit Week						**W1**	**W2**	**W3**	**W4**	**W8**	**W12**
Study Visit Day±Visit Window	**D −28 to −2**	**D −1**	**D1[b]**	**D2**	**D3**	**D8±2**	**D15±2**	**D22±2**	**D29±2**	**D57±7**	**D85±7/ET**
Informed consent	X										
Demography	X										
Medical history[c]	X										
Inclusion/exclusion criteria	X	X[d]									
Full physical examination[e]	X										X
Symptom-directed physical examination		X	X	X		X	X	X	X	X	
Alcohol assessment[f]		X				X	X	X	X	X	X
Body weight	X										
Height and BMI	X										
Vital signs[g]	X	X	X	X		X	X	X	X	X	X
Safety ECGs[h]	X		X	X		X					
Cardiodynamic ECG evaluation[i]			X	X							
Pregnancy test[j]	X	X							X	X	X
Screening viral serology[k]	X										
Laboratory assessments[l]	X		X	X	X	X	X	X	X	X	X
Urinalysis[l]	X		X	X							

Part A											
Study Stage		**Inpatient[a]**			**Outpatient (Post-dose Follow-up Period)**						
	Screening										
Study Visit Week						**W1**	**W2**	**W3**	**W4**	**W8**	**W12**
Study Visit Day±Visit Window	**D −28 to −2**	**D −1**	**D1[b]**	**D2**	**D3**	**D8±2**	**D15±2**	**D22±2**	**D29±2**	**D57±7**	**D85±7/ET**
Urine for drugs of abuse[m]	X	X									
Randomization			X								
Study drug administration[n]			X								
Blood samples for PK analysis[o]			X	X	X	X					
Urine samples for PK analysis[o]			X		X	X					
Pooled urine[o]			X	X							
Review/record AEs[p]	X										
Concomitant medications	X										

AE = adverse event; BMI = body mass index; ECG = electrocardiogram; ET = End of Treatment; PK = pharmacokinetic; SAD = single ascending dose
Note: When scheduled at the same timepoints, the assessments of vital signs and 12-lead ECGs must be performed first, before the physical examinations, blood sample collections, and urine collections.

[a] Subjects will be admitted to the clinical investigative site on Day −1 and discharged following the completion of the Day 2 assessments. If a subject discontinues prematurely, ET assessments should be performed.
[b] Assessments performed predose unless otherwise specified.
[c] Complete medical history will be taken at screening and any changes should be updated prior to dosing.
[d] Evaluation of inclusion criteria related to urine pregnancy testing and urine drug screen.
[e] See Section 7.2.1 for assessments to be performed during a full physical examination.
[f] Subjects' alcohol intake will be recorded while on study.
[g] Vital signs (blood pressure, pulse rate, respiratory rate and temperature) should be measured 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 post-dose. On all other visit days, vital signs are only required to be recorded once during the visit.
[h] 12-lead safety ECGs will be recorded on the timepoints listed in Appendix 4 and should be measured in the supine position after the subject has rested comfortably for 10 minutes.
[i] Replicate 12-lead ECGs will be extracted at the central ECG laboratory at timepoints shown in Appendix 4. Subjects must be resting supine for at least 10 minutes prior to and 5 minutes after each nominal timepoint.
[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. Negative pregnancy test must be confirmed prior to study drug administration.

[k] See Section 7.1.3 for viral serology parameters.
[l] Clinical laboratory and urinalysis parameters are described in Section 7.2.8.
[m] 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.
[n] Study drug will be administered via SC injection as described in Section 6.2.4.
[o] Blood and urine samples for PK analysis will be collected at the timepoints listed in Appendix 4.
[p] 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 B/C Schedule of Study Assessments for MAD Cohorts in Subjects with Chronic HBV Infection

Part B/C																
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**	**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															
Laboratory assessments[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]	X[n]	X[n]
Urinalysis[m]	X	X														

Part B/C																
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**	**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**
Urine for drugs of abuse[o]	X															
Randomization		X														
Study drug administration[p]		X					X									
Blood samples for PK analysis[q]		X	X	X			X[r]	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 C only[t]		X					X				X	X	X		X	X[s]
Blood sample for anti-HBe for Part C only	X										X		X		X	X[s]
Blood sample for HBV DNA quantitation[u]	X	X					X				X	X	X	X	X	X[s]
CCI [redacted]																

Part B/C																
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**	**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 [redacted]																
Review/Record AEs[x]	X															
Concomitant Medications	X															
NUC medication adherence	X															

AE = adverse event; ECG = electrocardiogram; ET=end of treatment; CCI [redacted] HBeAg = hepatitis e-antigen; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; NUC = nucleoside/nucleotide; PK = pharmacokinetics; MAD = multiple ascending dose

Note: When scheduled at the same timepoints, the assessments of vital signs and 12-lead ECGs must be performed first, before the physical examinations, blood sample collections, and urine 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 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. For example, if Day 1 predose HBsAg is 560 IU/mL and Week 16 HBsAg is 490 IU/mL, the subject will be followed until HBsAg levels returns to ≥ 504 IU/mL. 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 criteria related to urine pregnancy testing and urine drug screen.

[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 post-dose. On all other visit days, vital signs are only required to be recorded once during the visit.

[i] 12-lead safety ECGs will be recorded on the timepoints listed in Appendix 5 and 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 serum pregnancy test will be performed at screening and urine pregnancy tests will be performed thereafter. 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 7.2.8.
[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 5.
[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.
CCI [redacted]
[u] If a subject experiences ALT flare (as defined by ALT > 2x ULN) additional HBV DNA quantitation sample(s) may be collected
CCI [redacted]
CCI [redacted]
[x] Al 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 4. Part A Pharmacokinetic Assessment Timepoints

Study Day/Week	Protocol Time	PK Blood	Urine PK	Pooled Urine	Cardiodynamic Extracted ECGs	Safety ECGs
Screening						X
Day 1	Predose	X[a]	X[a]		X[b]	X
	Dose			X 0-4 hours		
	30 min	X			X	
	1 hour	X			X	X
	2 hours	X			X	
	4 hours	X		X 4-8 hours	X	X
	6 hours	X			X	
	8 hours	X		X 8-12 hours	X	X
	10 hours	X			X	
	12 hours	X		X 12-24 hours	X	
Day 2	24 hours	X			X	X
Day 3	48 hours	X	X			
Week 1		X	X			X

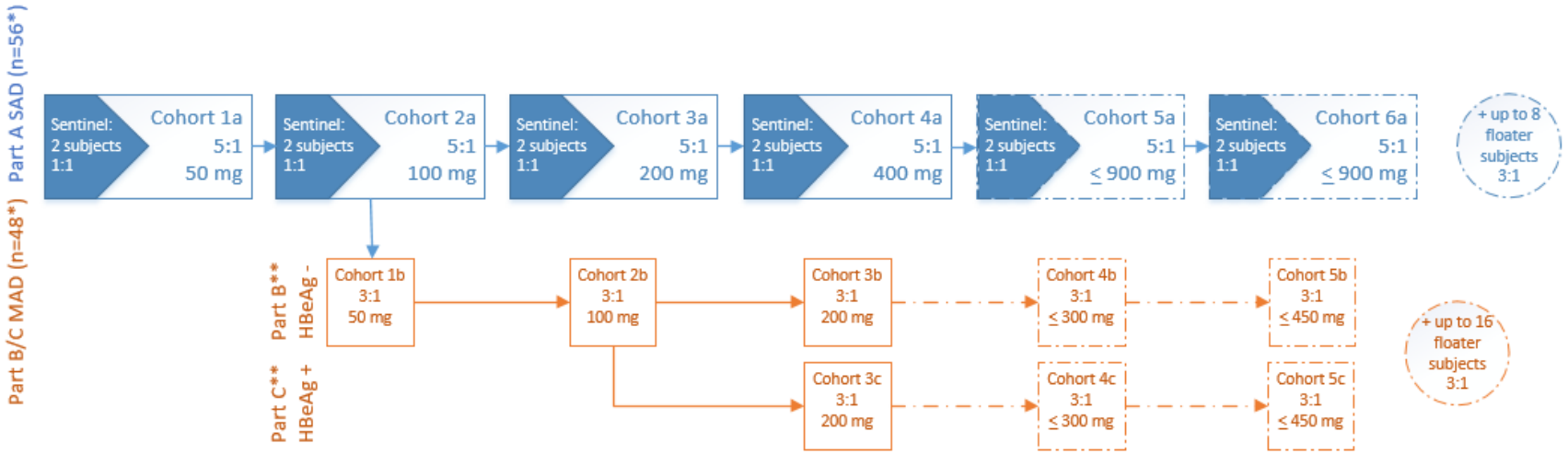
[a] At ≤ 15 minutes prior to dosing
b At 3 timepoints (-45, -30 and -15 minutes) prior to dosing

Appendix 5. Part B/C Pharmacokinetic Assessment Timepoints

Study Day/Week	Protocol Time	PK Blood	Safety ECGs
Screening			X
Day 1	Predose	X[a]	X
	Dose		
	1 hour	X	
	2 hours	X	
	4 hours	X	X
	8 hours	X	X
Day 2	24 hours	X	X
Week 1		X	
Week 4	Predose	X[a]	X
	Dose		
	1 hour	X	
	2 hours	X	
	4 hours	X	X
	8 hours	X	
	24 hours	X	
Week 5		X	

[a] At ≤ 15 minutes prior to dosing

Appendix 6. Cohort Dosing Schedule



* Up to 8 subjects for Part A and up to 16 subjects total for Parts B/C may be added as part of expansion of an existing cohort or cohorts if further data is required. The allocation of the floater subjects in Parts B/C arenot required to be distributed evenly. The total combined n for Parts B/C will not exceed 48 subjects.

** The doses designated in Parts B/C schedule are indicative of a single dose of VIR-2218 or placebo; subjects will receive up to 2 doses total.