

Official Title: A Phase 1, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of VIR-3434

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CLINICAL STUDY PROTOCOL

Study Title A Phase 1, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of VIR-3434

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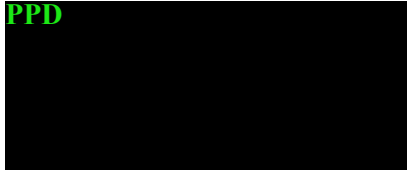
Investigational Product VIR-3434

Indication Chronic Hepatitis B Virus (HBV) Infection

IND Number Not Applicable

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Vir Study Director PPD 

Protocol Version & Date Amendment 4 20 January 2022

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1. PROTOCOL SYNOPSIS

Study Title A Phase 1, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of VIR-3434	
Sponsor Vir Biotechnology, Inc. 499 Illinois Street, Suite 500 San Francisco, CA 94158, USA	
Protocol Number VIR-3434-1002	IND Number Not Applicable
Investigational Product VIR-3434	EudraCT Number 2019-003837-40
Indication Chronic Hepatitis B Virus (HBV) Infection	Clinicaltrials.gov ID NCT04423393
Study Phase 1	
Clinical Investigative Site(s) Planned Part A: 1 clinical investigative site Parts B, C, and D: Multiple clinical investigative sites	
Study Objectives Part A The primary objective is as follows: <ul style="list-style-type: none">To evaluate the safety and tolerability of VIR-3434 in healthy adult subjects The secondary objectives are as follows: <ul style="list-style-type: none">To characterize the serum pharmacokinetics (PK) of VIR-3434 in healthy adult subjectsTo evaluate the immunogenicity (induction of anti-drug antibody [ADA]) of VIR-3434 in healthy adult subjects Parts B, C, and D The primary objective is as follows: <ul style="list-style-type: none">To evaluate the safety and tolerability of VIR-3434 in adult subjects with chronic HBV infection without cirrhosis The secondary objectives are as follows: <ul style="list-style-type: none">To characterize the serum PK of VIR-3434 in adult subjects with chronic HBV infection without cirrhosisTo assess the antiviral activity of VIR3434 in adult subjects with chronic HBV infection without cirrhosis	

- To evaluate the immunogenicity (induction of ADA) of VIR-3434 in adult subjects with chronic HBV infection without cirrhosis

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Criteria for Evaluation

Part A Endpoints

The primary endpoints of this study are as follows:

- Number of subjects with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Number of subjects with clinical laboratory abnormalities

The secondary endpoints of this study are as follows:

- VIR-3434 serum PK parameters, for example: C_{max} , C_{last} , T_{max} , T_{last} , AUC_{inf} , AUC_{last} , $\%AUC_{exp}$, $t_{1/2}$, λ_z , V_z (IV only), CL (IV only), V_z/F (SC only), and CL/F (SC only)
- Incidence and titers (if applicable) of ADA to VIR-3434

Parts B, C, and D Endpoints

The primary endpoints of this study are as follows:

- Number of subjects with TEAEs and SAEs
- Number of subjects with clinical laboratory abnormalities

The secondary endpoints of this study are as follows:

- VIR-3434 serum PK parameters, for example: C_{max} , C_{last} , T_{max} , T_{last} , AUC_{inf} , AUC_{last} , $\%AUC_{exp}$, $t_{1/2}$, λ_z , V_z/F , and CL/F.
- Incidence and titers (if applicable) of ADA to VIR-3434
- Maximum reduction of serum HBsAg from baseline (Day 1 predose)
- Part D only: maximum change of HBV DNA from baseline (Day 1 predose)

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Number of Subjects Planned

Part A: Up to 40 healthy adult subjects

Part B: Up to 56 adult subjects with chronic HBV infection without cirrhosis on nucleos(t)ide reverse transcriptase inhibitor (NRTI) therapy who are HBeAg-negative and who have HBsAg < 3,000 IU/mL

Part C: Up to 24 adult subjects with chronic HBV infection without cirrhosis on NRTI therapy who are HBeAg-negative or HBeAg-positive and who have HBsAg \geq 3,000 IU/mL

Part D: Up to 24 adult subjects with chronic HBV infection without cirrhosis who are HBeAg-negative or HBeAg-positive with any HBsAg level and HBV DNA \geq 1,000 IU/mL

Diagnosis and Main Criteria for Inclusion

Refer to Section 6 for full list of eligibility criteria.

Part A

Healthy adult subjects age 18 to 55 years who weigh \geq 40 kg to \leq 125 kg. Refer to Section 6 for detailed inclusion and exclusion criteria.

Part B/C

Subjects age 18 to 65 years who weigh \geq 40 kg to \leq 125 kg with chronic HBV infection without cirrhosis on NRTI therapy. Refer to Section 6 for detailed inclusion and exclusion criteria.

Part D

Subjects age 18 to 65 years who weigh \geq 40 kg to \leq 125 kg with chronic HBV infection without cirrhosis who are not on NRTI therapy. Refer to Section 6 for detailed inclusion and exclusion criteria.

Duration of Study Participation

Part A: Subjects will receive a single dose of study drug. The estimated total time on study, inclusive of screening and follow-up, for each subject is up to 28 weeks.

Parts B, C, and D: Subjects will receive a single dose of study drug. The estimated total time on study, inclusive of screening and follow-up, for each subject is up to 46 weeks.

Duration of Follow-Up

Part A: All subjects will be followed for 24 weeks after study drug administration.

Parts B, C, and D: All subjects will be followed for 8 weeks after study drug administration. Subjects with > 2-fold HBsAg reduction at Week 8 will undergo extended follow-up for up to 40 weeks total or until the reduction in HBsAg is < 2-fold relative to baseline at 2 consecutive collections, whichever occurs first. The extended follow-up may be discontinued at the Sponsor's discretion based on emerging data.

Study Design

This study is designed to evaluate the safety, tolerability, PK, and antiviral activity of VIR-3434.

A Safety Review Committee (SRC) will perform ongoing reviews of safety, tolerability, and antiviral activity data (Parts B and C only) at specified timepoints based on available data collected throughout the study. While the primary data that will be reviewed by the SRC for dose escalations and enrollment

of optional cohorts is listed throughout the protocol, additional relevant data from other cohorts may also be reviewed by the SRC to inform decisions. Details are provided in the SRC charter.

The study will be conducted in 4 Parts:

- **Part A:** Randomized, double-blind, placebo-controlled, single ascending dose (SAD) study of VIR-3434 administered via subcutaneous (SC) injection or intravenous (IV) infusion to healthy adult subjects
- **Part B:** Randomized, double-blind, placebo-controlled, SAD study of VIR-3434 administered via SC injection to adult subjects with chronic HBV infection without cirrhosis who are on NRTI therapy, are HBeAg-negative, and have HBsAg < 3,000 IU/mL
- **Part C:** Optional, randomized, double-blind, placebo-controlled, SAD study of VIR-3434 administered via SC injection to adult subjects with chronic HBV infection without cirrhosis who are on NRTI therapy, are HBeAg-negative or HBeAg positive, and who have HBsAg \geq 3,000 IU/mL
- **Part D:** Optional, randomized, double-blind, placebo-controlled, SAD study of VIR-3434 administered via SC injection to adult subjects with chronic HBV infection without cirrhosis who are not on NRTI therapy, have HBV DNA \geq 1,000 IU/mL, are HBeAg-negative or HBeAg positive, and have any HBsAg level

Part A

Three sequential cohorts are planned for Part A evaluating 90 mg, up to 300 mg, and up to 900 mg administered by SC injection. The SRC will review available clinical and laboratory safety data up to 2 weeks post-dose for all available subjects within a cohort prior to dose escalation. Two optional cohorts in Part A may be added evaluating up to 900 mg and 3,000 mg administered by IV infusion. Enrollment of these optional cohorts may occur following SRC review of available Week 2 data from all available subjects in Cohort 3a (up to 900 mg SC).

While all of the SC cohorts (Cohort 1a, 2a, and 3a) in Part A are planned to be enrolled sequentially, cohorts may be enrolled in parallel if the additional cohort(s) examine a dose level that is at or below a dose level that has previously been found to have an acceptable safety and tolerability profile in a prior cohort in Part A.

In each cohort, 2 sentinel subjects will be randomized 1:1 to receive VIR-3434 or placebo. These subjects will be dosed and monitored for at least 24 hours in an inpatient setting; 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 receive VIR-3434 or placebo.

The maximum dose escalation factor in Part A will not exceed 5-fold.

Part B

The first cohort in Part B (Cohort 1b) will be enrolled after SRC review of available Week 2 data from all available subjects in Cohort 1a (90 mg SC).

Five cohorts are planned for Part B evaluating 6 mg (Cohort 1b), 18 mg (Cohort 2b), up to 75 mg (Cohort 3b), up to 300 mg (Cohort 4b), and up to 900 mg (Cohort 5b) administered by SC injection. The SRC will review available clinical and laboratory safety data and antiviral activity data up to 4 weeks post-dose for all available subjects within the prior cohort prior to dose escalation.

Two optional cohorts in Part B may be added following the same dosing schedule. The optional cohorts may be dosed at a lower, equivalent, or intermediate dose level relative to the dose levels explored in the planned Part B cohorts, or after cohort 5b at a dose level not exceeding 900 mg. The maximum dose level for the optional cohorts in Part B will not exceed the highest single dose found to

have an acceptable safety and tolerability profile in Part A. The optional cohorts may be enrolled at any time within the Part B planned cohorts based on the approval of the SRC.

While all of the cohorts in Part B are planned to be enrolled sequentially, cohorts may be enrolled in parallel if the additional cohort(s) examine a dose level that is at or below a dose level that has previously been found to have an acceptable safety and tolerability profile in a prior cohort in Part A and Part B.

In each cohort, 2 sentinel subjects will be randomized 1:1 to receive VIR-3434 or placebo by SC injection. These subjects will be dosed and monitored through at least 72 hours post-dose; if the investigator(s) have no safety concerns, the remainder of the subjects in the same cohort will be dosed. The remaining subjects will be randomized 5:1 to receive VIR-3434 or placebo by SC injection.

The maximum dose escalation factor in Part B will not exceed 5-fold.

Part C

Part C is optional and may be conducted if VIR-3434 is found to have an acceptable safety and tolerability profile in HBeAg-negative subjects with HBsAg levels < 3,000 IU/mL in Part B. For cohorts in Part C, HBeAg-negative and HBeAg-positive subjects with HBsAg \geq 3,000 IU/mL will be enrolled. The first cohort in Part C may be enrolled after SRC review of available data for all subjects in Part B through the Week 4 visit for the cohort of subjects in Part B who are receiving a matching or higher dose relative to the proposed starting dose level in Part C.

Three optional cohorts may be enrolled in Part C. Each cohort may evaluate up to 900 mg administered by SC injection and the dose utilized in Part C cohorts will not exceed the highest dose level in Part B that was found to have an acceptable safety and tolerability profile by the SRC. Cohorts may be enrolled in parallel.

In each cohort, 2 sentinel subjects will be randomized 1:1 to receive VIR-3434 or placebo by SC injection. These subjects will be dosed and monitored through at least 72 hours post-dose; if the investigator(s) have no safety concerns, the remainder of the subjects in the same cohort will be dosed. The remaining subjects will be randomized 5:1 to receive VIR-3434 or placebo by SC injection.

Part D

Part D is optional and may be conducted if VIR-3434 is found to have an acceptable safety and tolerability profile in HBeAg-negative subjects with HBsAg levels < 3,000 IU/mL in Part B. For cohorts in Part D, HBeAg-negative and HBeAg-positive subjects with HBV DNA \geq 1,000 IU/mL and any HBsAg level will be enrolled. The first cohort in Part D may be enrolled after SRC review of available data through the Week 4 visit for the cohort of subjects in Part B who have received a matching or higher dose relative to the proposed starting dose level in Part D.

Three optional cohorts may be enrolled in Part D. Each cohort may evaluate up to 900 mg administered by SC injection and the dose utilized in Part D cohorts will not exceed the highest dose level in Part B that was found to have an acceptable safety and tolerability profile by the SRC. Cohorts may be enrolled in parallel.

In each cohort, 2 sentinel subjects will be randomized 1:1 to receive VIR-3434 or placebo by SC injection. These subjects will be dosed and monitored through at least 72 hours post-dose; if the investigator(s) have no safety concerns, the remainder of the subjects in the same cohort will be dosed. The remaining subjects will be randomized 5:1 to receive VIR-3434 or placebo by SC injection.

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, physical examination, vital signs, 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. Subjects may be admitted into the clinical investigative site on Day -1 or 1.

Dosing Day (Day 1)

- Eligible subjects will be randomized to receive VIR-3434 or placebo within 48 hours prior to study drug administration on Day 1.
- Eligible subjects will receive a single dose of study drug and applicable assessments will be performed on Day 1.

Follow-Up Period

- Subjects will be discharged after all study assessments are performed on Day 2. All subsequent study visits are outpatient.
- Subjects will return to the clinical investigative site for in-person assessments per the SoA including but not limited to physical examination, vital signs, laboratory testing, PK assessments, and review of AEs and concomitant medications through Week 24.

Parts B, C, and D

Screening

- Screening will be performed no more than 6 weeks prior to the Day 1 visit and will include written informed consent, determination of eligibility, collection of demographics and medical history, physical examination, vital signs, 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. Subjects may be admitted into the clinical investigative site on Day -1 or 1.

Dosing Day (Day 1)

- Eligible subjects will be randomized to receive VIR-3434 or placebo within 48 hours prior to study drug administration on Day 1.
- Eligible subjects will receive a single dose of study drug and applicable assessments will be performed on Day 1.
- Patients must be monitored through at least 6 hours post-dose prior to discharge.

Follow-Up Period

- Subjects will be discharged after all study assessments are performed on Day 1. All subsequent study visits are outpatient.
- Subjects will return to the clinical investigative site for assessments per the SoA including but not limited to physical examination, vital signs, laboratory testing, PK assessments, efficacy assessments and review of AEs and concomitant medications through Week 8.

Extended Follow-Up Period

- Subjects with > 2-fold HBsAg reduction at Week 8 will return to the clinical investigative site for in-person assessments per the SoA through Week 40 or until the reduction in HBsAg is < 2-fold

relative to baseline at 2 consecutive collections, whichever occurs first. The extended follow-up may be discontinued at the Sponsor's discretion based on emerging data.

Investigational Product, Dosage, and Mode of Administration

VIR-3434 will be supplied as a lyophilized solid to be reconstituted with Water for Injection at a concentration of 150 mg/mL and administered as a SC injection or IV infusion.

- Cohort 1a: VIR-3434, single dose of 90 mg administered by SC injection
- Cohort 2a: VIR-3434, single dose of up to 300 mg administered by SC injection
- Cohort 3a: VIR-3434, single dose of up to 900 mg administered by SC injection
- Cohort 4a (optional): VIR-3434, single dose of up to 900 mg administered by IV infusion
- Cohort 5a (optional): VIR-3434, single dose of up to 3,000 mg administered by IV infusion
- Cohort 1b: VIR-3434, single dose of 6 mg administered by SC injection
- Cohort 2b: VIR-3434, single dose of 18 mg administered by SC injection
- Cohort 3b: VIR-3434, single dose of up to 75 mg administered by SC injection
- Cohort 4b: VIR-3434, single dose of up to 300 mg administered by SC injection
- Cohort 5b: VIR-3434, single dose of up to 900 mg administered by SC injection
- Cohort 6b (optional): VIR-3434, single dose of up to 900 mg administered by SC injection
- Cohort 7b (optional): VIR-3434, single dose of up to 900 mg administered by SC injection
- Cohort 1c (optional): VIR-3434, single dose of up to 900 mg administered by SC injection
- Cohort 2c (optional): VIR-3434, single dose of up to 900 mg administered by SC injection
- Cohort 3c (optional): VIR-3434, single dose of up to 900 mg administered by SC injection
- Cohort 1d (optional): VIR-3434, single dose of up to 900 mg administered by SC injection
- Cohort 2d (optional): VIR-3434, single dose of up to 900 mg administered by SC injection
- Cohort 3d (optional): VIR-3434, single dose of up to 900 mg administered by SC injection

Reference Therapy, Dosage, and Mode of Administration:

Subjects randomized to placebo will be administered sterile, preservative-free normal saline 0.9% solution by SC injection (Parts A, B, C, and D) or IV infusion (Part A only).

Statistical Methods

Statistical analyses will be primarily descriptive. All study data will be presented by subject data listings. For all Study Parts, summary tables will present results by cohort for VIR-3434 and placebo, where the placebo subjects will be combined across dose cohorts by route of administration for each Part.

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. Further details will be provided in the Statistical Analysis Plan.

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirement, including archiving of essential documents.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	anti-drug antibodies
ADCC	antibody dependent cellular cytotoxicity
ADCP	antibody dependent cellular phagocytosis
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
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
CL _{cr}	creatinine clearance
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EF	end of follow-up
ET	end of treatment
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
GNA	glycol nucleic acid
HBcrAg	hepatitis B core-related antigen
HBeAg	hepatitis B e-antigen

HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HED	human equivalent dose
Hgb	hemoglobin
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IgM	immunoglobulin M
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
LDH	lactate dehydrogenase
LLN	lower limit of normal
LLOQ	lower limit of quantitation
LLT	Lower-Level Term
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibodies
NOAEL	no observed adverse effect level
NRTI	nucleos(t)ide reverse transcriptase inhibitor
OTC	over-the-counter
PK	pharmacokinetics
PT	Preferred Term
Q1	first quartile
Q3	third quartile

RBC	red blood cell (count)
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SoA	schedule of assessments
SOC	System Organ Class
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TCR	tissue cross reactivity
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

2. INTRODUCTION

2.1. Background

VIR-3434 is a human monoclonal antibody (mAb) 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](#)). It is estimated that approximately 300 million people are living with chronic HBV infection worldwide ([Polaris 2016](#)). 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 ([Stanaway 2016](#)).

HBV prevalence varies geographically, with a range of less than 2% in low prevalence countries 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 via 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 is dependent 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 60% of children infected between 6 months and 5 years of age are chronically infected. Additionally, 25% of people who acquire HBV during infancy and childhood will develop primary liver cancer or cirrhosis during adulthood.

In acute resolving infections, the virus is controlled by effective innate and adaptive immune responses that include both cytotoxic T cells capable of directly killing HBV-infected hepatocytes and B cells that produce potent neutralizing antibodies against the virus ([Bertoletti 2016](#); [Li 2016](#); [Maini 2016](#)). In contrast, chronic HBV infection is associated with the inability of the immune system to suppress viral replication and circulation of subviral particles containing the HBV surface antigen (HBsAg). The massive secretion of HBsAg, as well as expression of HBV epitopes on the surface of infected hepatocytes, is thought to contribute to T and B cell dysfunction during chronic HBV infection and to impair the host's ability to clear or control the virus ([Bertoletti 2016](#); [Burton 2018](#); [Maini 2016](#)). The laboratory hallmark of chronic HBV infection is persistence of HBsAg in the blood for greater than 6 months and lack of detectable anti-HBs antibody. Chronic infection is divided into 4 stages based on HBV markers in blood [HBsAg, hepatitis B e-antigen (HBeAg)/anti-HBe antibody, HBV DNA], and liver disease based on biochemical (ALT) and 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) resolve the disease, as determined by HBsAg seroclearance.

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, HBV polymerase, PreS1/PreS2/HBsAg (large, medium, and small surface envelope glycoproteins), and HBx (HBV x 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 infectious virion, is converted into a covalently closed circular DNA (cccDNA) that 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 rcDNA to form new virions, which are secreted without causing cytotoxicity. In addition, truncated forms of HBV DNA integrate into the host genome, often in a confirmation that still allows for translation of HBsAg, which can ultimately contribute to hepatocyte transformation ([Levrero 2016](#); [Sung 2012](#); [Toh 2013](#); [Zhao 2016](#)). Infected hepatocytes secrete large amounts of subviral particles containing HBsAg that originate from cccDNA and integrated DNA and may exceed the number of secreted virions by 10,000-fold ([Seeger 2015](#)).

Currently, there are 2 standard of care treatment options for patients with chronic HBV infection: nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and pegylated interferon-alpha (PEG-IFN) ([Liang 2015](#)).

NRTIs inhibit HBV replication by interfering with the activity of the pol/reverse transcriptase (pol/RT) and promoting DNA chain termination, preventing the production of HBV DNA containing virions. Although HBV DNA suppression can be achieved with NRTIs alone, they do not directly eliminate cccDNA or integrated DNA and therefore, transcription and translation of viral proteins continues. Thus, continued HBV DNA suppression requires lifelong treatment and rarely results in HBsAg loss. Consequently, expression of viral proteins on hepatocytes, secretion of subviral particles, and immune dysfunction remain largely unaffected by NRTI therapy in the majority of patients. Additionally, while NRTI therapy reduces the incidence of HCC, it does not eliminate the increased risk of HCC due to the reservoir of cccDNA and integrated HBV forms.

In contrast to NRTIs, PEG-IFN can induce long-term viral control, but only in a small percentage of patients (< 10%) and after 48 weeks of therapy ([Konerman 2016](#)). While the exact mechanism of action of PEG-IFN treatment is unknown, interferon induces multiple innate immune mechanisms and exerts antiproliferative and antiviral effects at various points of the HBV lifecycle in vitro ([PEGASYS® Package Insert](#); [Rijckborst 2010](#)). The low response rate coupled with limited tolerability and a long treatment course preclude treatment of most patients with PEG-IFN monotherapy ([PEGASYS® Package Insert](#)). The limitations of NRTI and PEG-IFN therapy highlight the need for novel HBV therapies that are well tolerated and have a finite duration of administration.

Several investigational agents are currently under development for the treatment of chronic HBV infection. These include HBsAg targeting mAbs, small interfering RNA (siRNA) molecules, viral entry inhibitors, capsid assembly modulators, innate immune stimulators, therapeutic vaccines, checkpoint inhibitors and nucleic acid polymers. Early clinical data suggests that a combination of multiple therapeutic modalities will likely be necessary to achieve functional cure in the majority of chronic HBV patients, and further suggests that lowering HBsAg is a critical component of any combination regimen ([Revill 2019](#), [Zoulim 2015](#)). VIR-3434 is a mAb targeting HBsAg with multiple potential mechanisms of action including strong neutralizing activity and enhanced immunologic activity due to Fc domain engineering. Therefore, VIR-3434 has the potential to cure chronic HBV infection either alone or in combination with other therapeutic modalities.

2.2. VIR-3434

2.2.1. VIR-3434 Description

VIR-3434 is a half-life extended human monoclonal antibody that binds the antigenic loop present in all forms of the surface envelope protein (small, middle, and large HBsAg). VIR-3434 recognizes all known 10 HBV genotypes (A-J), potently neutralizes HBV virions (5,000x greater neutralizing ability than Hepatitis B Immune Globulin [HBIG]) and reduces serum HBsAg in preclinical animal models. VIR-3434 inhibits viral entry into hepatocytes in vitro. Additional potential effects of VIR-3434 include elimination of HBV infected hepatocytes via antibody dependent cellular cytotoxicity (ADCC)/antibody dependent cellular phagocytosis (ADCP) and induction of HBV-targeting cytotoxic T cells (vaccinal effect). The Fc domain contains mutations that have been engineered to potentially enhance these immune-stimulatory effects and lead to the aforementioned extended half-life.

See the Investigator's Brochure for additional information on VIR-3434.

2.2.2. Summary of Nonclinical Experience

Refer to the Investigator's Brochure for VIR-3434 nonclinical information.

2.2.3. Summary of Clinical Experience

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2.3. Rationale

2.3.1. Rationale for VIR-3434 for the Treatment of HBV Infection

VIR-3434 offers a novel strategy for the treatment of chronic HBV infection because it not only neutralizes HBV viral and subviral particles through the targeting of HBsAg, but also inhibits viral entry into hepatocytes. Additionally, the Fc region of VIR-3434 is engineered to increase binding affinity to the neonatal Fc receptor (FcRn) and alter the Fc-gamma receptor (FcγR) binding profile. These changes are anticipated to prolong the serum half-life and to potentially enhance ADCC/ADCP and antigen presentation, subsequently leading to the induction of de-novo T cell responses (“vaccinal effect”).

The normal serum half-life of IgG is approximately 21 days and is regulated by a balance of FcRn-mediated endocytosis and recycling versus endosomal degradation. To produce a product with sustained activity against HBV, the well characterized LS modification (M430L and N436S) ([Gaudinski 2018](#); [Ko 2014](#); [Zalevsky 2010](#)) was included in the Fc region of VIR-3434. The LS modification increases IgG1 binding to FcRn only at the acidic pH of the endosomal compartment thereby increasing IgG recycling back into circulation. Monoclonal antibodies containing the LS mutation have previously been studied in humans ([Gaudinski 2018](#)). For example, VRC01LS, a mAb against the CD4 binding site of the HIV-1 glycoprotein, was deemed safe and well tolerated at doses of 5 to 40 mg/kg IV and 5 mg/kg SC in healthy volunteers. PK analysis revealed a half-life of 71 days, more than 4-fold longer than that seen previously with the parent wild-type molecule. No anti-drug antibodies (ADAs) were detected out to 48 weeks. VIR-3434 is similarly anticipated to have an extended half-life in humans, resulting in a prolonged duration of exposure. In vitro data for VIR-3434 suggests that the LS mutation is not anticipated to interfere with the additional Fc modifications described below.

The Fc region of VIR-3434 was also engineered to include a modification which modulates binding to human FcγRs by enhancing binding to the activating receptors FcγRIIa and FcγRIIIa, while diminishing binding to the inhibitory receptor FcγRIIb. This Fc modification is designed to enhance ADCC/ADCP and antigen presentation and, as a result, promote the induction of T cell responses (“vaccinal effect”). The impact of similar modifications on mAb efficacy have been studied in a FcγR-humanized lymphoma mouse model. In this model, anti-CD20 antibodies promoted direct killing of tumor cells via engagement of FcγRIIIa on macrophages and monocytes. In addition, anti-CD20-immune complexes induced CD8+ T cell responses via FcγRIIa-dependent presentation of tumor antigens by dendritic cells. Overall, Fc-engineering of anti-CD20 antibodies to increase FcγRIIa and FcγRIIIa binding (GASDALIE mutation) had superior therapeutic activity ([DiLillo 2015](#)). Parallel reduction of binding to the inhibitory FcγRIIb has the potential to further augment this vaccinal effect ([DiLillo 2015](#)).

Available data regarding the use of HBsAg directed antibodies in the treatment of patients with chronic HBV infection suggest that these molecules have the potential to reduce HBsAg levels while maintaining an acceptable safety and tolerability profile. GC1102, a fully human anti-HBsAg mAb in development for chronic HBV infection and prevention of recurrent HBV following liver transplantation, effectively lowered HBsAg by 2-3 logs and was well tolerated in a Phase 1 study in patients with chronic HBV infection, with no evidence of serious sequelae such as immune complex disease (Lee 2018). HBV-AB^{XTL} (HepeX-B), a mixture of two human anti-HBsAg mAbs, was administered to 27 untreated patients with levels of HBsAg ranging from approximately 20 to 85,000 IU/mL. HBV-AB^{XTL} was found to have a favorable safety and tolerability profile at doses up to 80 mg administered weekly for 4 doses, and no signs of immune complex disease or hepatotoxicity were reported. Substantial reductions in HBsAg and HBV DNA were observed following administration of HBV-AB^{XTL} (Galun 2002). Similarly, no adverse events were reported in two studies of chronic HBV patients receiving high doses of Hepatitis B Immune Globulin (HBIG) to prevent re-infection following liver transplantation (Reed 1973; Tsuge 2016).

Clinical data from the oncology setting suggests that Fc engineering designed to enhance ADCC/ADCP and antigen presentation may improve efficacy without compromising safety or tolerability (Im 2019). Margetuximab is a modified version of trastuzumab that is currently in clinical development for the treatment of HER2-positive carcinomas. Similar to VIR-3434, margetuximab contains modifications designed to enhance ADCC/ADCP and antigen presentation. Margetuximab was well tolerated in a first-in-human (FIH) Phase 1 study in patients with HER-2 positive carcinomas. Common toxicities were primarily \leq Grade 2, including no evidence of cardiotoxicity (Bang 2017), which has been observed with the non-Fc modified parent mAb, trastuzumab, in late-stage clinical trials (Ponde 2016; Riccio 2016).

Taken together, these data suggest that mAbs that are Fc engineered to prolong serum half-life and optimize immune effector cell activity have the potential to improve the efficacy of therapeutic mAbs without compromising safety. The ability to lower HBsAg is likely to be a key component of curative therapy for chronic HBV infection. VIR-3434 is predicted to decrease serum HBsAg, inhibit intrahepatic viral spread, eliminate infected hepatocytes, and stimulate HBV-specific immune responses. Therefore, VIR-3434 has the potential, alone or in combination with other therapies, to achieve a functional cure of chronic HBV infection.

2.3.2. Rationale for Dose Selection

Part A: Single Ascending Dose Study in Healthy Adult Subjects

In Part A, healthy adult subjects will receive a single dose of study drug. VIR-3434 has no endogenous targets in healthy adult subjects and thus, no dose-limiting toxicities are expected at any dose level. Sufficient margins of safety have been established and the recommended starting dose for VIR-3434 in healthy adult subjects is based on safety factors derived from the no-observed-adverse-effect-level (NOAEL) in the Good Laboratory Practice (GLP) rat repeat-dose toxicity study. For additional details, refer to the Investigator's Brochure.

Consistent with currently recommended practice for dosing mAbs (Bai 2012) and to reduce the potential for dose calculation errors associated with weight-based dosing, a fixed dosing approach will be used.

Based on findings of VIR-3434 GLP toxicity studies and PK predictions, and to support clinically relevant dosing scenarios in patients with chronic HBV infection, a broad dose range is proposed for the Phase 1 study. In Part A, doses of 90 mg up to 900 mg will be administered by SC injection, and 900 mg up to 3,000 mg will be administered by IV infusion. The associated stepwise escalation factors are approximately 3- to 4-fold. Specifically, this dose range was chosen to ensure a safe starting dose, to assess the safety of VIR-3434 across a range of exposures that are expected to provide a safety margin for clinically relevant doses, and to provide PK data for further clinical development. See Section 5.3.1 for further details. Additionally, details on the dose escalation plan for Part A can be found in Table 1. The planned SC dose levels for Part A were designed to evaluate the safety profile of doses that will be explored in subjects with chronic HBV infection in Parts B and C. The optional IV dose cohorts in Part A are designed to assess the safety profile of exposures that are predicted to be consistent with possible treatment regimens including VIR-3434 to be evaluated later in clinical development, as appropriate.

Results from a non-GLP PK study in cynomolgus monkeys (PK-3434-0109) was used to develop a linear two-compartment PK model which was further scaled to human using allometry. Human VIR-3434 serum clearance and volume of distribution were predicted to be approximately 65.7 mL/day and 2.43 L, respectively, in the central compartment and 612.7 mL/day and 2.85 L, respectively, in the peripheral compartment. Based on these estimations, terminal elimination half-life of VIR-3434 in humans was predicted to be approximately 58 days. These parameters were used to simulate human PK profiles over the proposed Part A dose range of 90 to 900 mg administered by SC injection and 900 mg and 3,000 mg administered by IV infusion. Additional information is provided in the Investigator’s Brochure.

Table 1: Part A Dose Escalation Plan

Study Part	Cohort	Active:Placebo	Dose (Route)	Frequency of Administration
A	1a	6:2	90 mg (SC)	Once
	2a	6:2	Up to 300 mg (SC)	Once
	3a	6:2	Up to 900 mg (SC)	Once
	4a (Optional)	6:2	Up to 900 mg (IV)	Once
	5a (Optional)	6:2	Up to 3,000 mg (IV)	Once

IV = intravenous; SC = subcutaneous.

Part B: Single Ascending Dose Study in Subjects with Chronic HBV Infection

In Part B, subjects with chronic HBV infection will receive a single dose of study drug. The presence of the therapeutic target of VIR-3434, HBsAg, in subjects with chronic HBV infection alters the potential risks of VIR-3434 administration. Potential risks include immune complex disease due to the formation of antigen-antibody complexes and hepatotoxicity due to elimination of infected hepatocytes via ADCC/ADCP and/or a “vaccinal effect”. To minimize risks to subjects, Part B will be conducted in subjects who are on NRTIs and have HBV DNA < 100 IU/mL at screening, and who have good hepatic reserve and low levels of hepatic inflammation, as determined by lack of significant fibrosis/cirrhosis and ALT $\leq 2 \times$ ULN.

Available non-clinical toxicology and PK/PD data, as well as experience with molecules having similar characteristics, were taken into account when selecting the starting dose and dose escalation scheme for VIR-3434 in subjects with chronic HBV infection. The proposed starting dose of 6 mg (approximately 0.1 mg/kg) is supported by the following rationale:

1. The Minimal Anticipated Biological Effect Level (MABEL) for VIR-3434: The MABEL for VIR-3434 is defined as the dose level predicted to result in a mean serum HBsAg decline that is of minimal clinical consequence. The value chosen, 0.3-log_{10} , represents the mean decline in HBsAg that is associated with 48 weeks of NRTI therapy, a well-tolerated therapy that is considered ineffective in lowering HBsAg to a clinically relevant extent (Marcellin 2016). The effect of VIR-3434 on lowering serum HBsAg was evaluated in a mouse model of chronic HBV infection (AAV-HBV mouse model, see Investigator's Brochure for more details), and translational PK/PD modeling was applied to predict the pharmacologic activity of VIR-3434 in humans at doses up to 15 mg/kg. Assuming a conservative baseline HBsAg level of 50 IU/mL (Jang 2011), a dose of 0.1 mg/kg (6 mg) is predicted to result in a mean serum HBsAg decline of approximately 0.3-log_{10} . This HBsAg decline corresponds to a pharmacologic activity level of <20% relative to the maximum pharmacologic activity (HBsAg decline) predicted to be achieved with 15 mg/kg. This pharmacologic activity level is below the lower bound of the 20-80% pharmacologic activity range determined by the United States (US) Food and Drug Administration (FDA) to result in acceptable toxicities for immune activating antibodies (Saber 2016).
2. A starting dose of 6 mg (approximately 0.1 mg/kg) is 15-fold lower than the proposed starting dose in Part A and is therefore supported by safety margins relative to the NOAEL of the GLP rat toxicology study. For additional information, please refer to the Investigator's Brochure.
3. Prior experience with molecules possessing similar characteristics as VIR-3434:
 - a. GC1102: a fully human anti-HBsAg mAb in development for the treatment of chronic HBV infection that has been administered to 53 patients with low levels of HBsAg ($\leq 1,000$ IU/mL HBsAg). GC1102 was found to have a favorable safety and tolerability profile at doses up to approximately 1.2 mg/kg administered weekly for 4 doses, with no AEs related to immune complex disease or hepatotoxicity reported (Lee 2019).
 - b. HBV-AB^{XTL} (HepeX-B): a mixture of two human anti-HBsAg mAbs that was administered to 27 patients with levels of HBsAg ranging from approximately 20 to 85,000 IU/mL. HBV-AB^{XTL} was found to have a favorable safety and tolerability profile at doses up to 80 mg administered weekly for 4 doses, and no signs of immune complex disease or hepatotoxicity were reported (Galun 2002).
 - c. Margetuximab: a mAb with Fc-modifications to enhance ADCC and antigen presentation that is in clinical development for HER2-positive carcinomas. In vitro data suggests that the respective Fc modifications of VIR-3434 and Margetuximab result in similar enhancements in ADCC. Margetuximab administration to 66 patients with HER-2 positive tumors was found to be well tolerated at doses ranging from 0.1-6 mg/kg administered IV weekly and up to 18 mg/kg administered IV every

3 weeks (Bang 2017). Further development of margetuximab as a single agent or and in combination with other therapeutics is ongoing.

Five dose level cohorts are planned for Part B. Doses will increase stepwise by a factor of approximately 3 to 4-fold to a maximum planned dose of 900 mg administered by SC injection. See Section 5.3.2 for further details. Two optional cohorts may also be enrolled up to a maximum dose of 900 mg administered by SC injection. Cohort 7b may be enrolled for the purpose of, but not limited to, collection and evaluation of immune response samples at select sites when and where available. These dose levels are based on preclinical animal models and translational PK/PD modeling that predict a significant HBsAg decline for doses in the range of 2 to 15 mg/kg. Details on the dose escalation plan for Part B can be found in Table 2.

Table 2: Part B Dose Escalation Plan

Study Part	Cohort	Active:Placebo	Dose (Route)	Frequency of Administration
B	1b	6:2	6 mg (SC)	Once
	2b	6:2	18 mg (SC)	Once
	3b	6:2	Up to 75 mg (SC)	Once
	4b	6:2	Up to 300 mg (SC)	Once
	5b	6:2	Up to 900 mg (SC)	Once
	6b (Optional)	6:2	Up to 900 mg (SC)	Once
	7b (Optional)	6:2	Up to 900 mg (SC)	Once

SC = subcutaneous

Optional Part C: Single Ascending Dose Study in Subjects with Chronic HBV Infection

In Part C, which is optional, subjects with chronic HBV infection will receive a single dose of study drug to further evaluate the safety, tolerability and anti-viral activity of VIR-3434 following evaluation of HBeAg-negative subjects with HBsAg < 3,000 IU/mL in Part B. See Section 5.3.3 for further details. Part C consists of three optional dose level cohorts, with each evaluating a dose of up to 900 mg administered by SC injection. One or more of the optional cohorts in Part C may be enrolled for the purpose of, but not limited to, collection and evaluation of immune response samples at select sites when and where available.

Optional Part D: Single Ascending Dose Study in Subjects with Chronic HBV Infection who are not on NRTIs

In Part D, which is optional, subjects with chronic HBV infection who are not on NRTIs and have HBV DNA ≥ 1,000 IU/mL and any HBsAg level will receive a single dose of study drug to further evaluate the safety, tolerability and anti-viral activity of VIR-3434 following evaluation of HBeAg-negative subjects with HBsAg < 3,000 IU/mL in Part B. See Section 5.3.4 for further details. Part D consists of three optional dose level cohorts, with each evaluating a dose of up to 900 mg administered by SC injection. One or more of the optional cohorts in Part D may be enrolled for the purpose of, but not limited to, collection and evaluation of immune response samples at select sites when and where available.

2.4. Overall Risk/Benefit Assessment

Data on the safety profile of VIR-3434 are limited, as there has been no prior human use; thus, there are no known safety risks associated with VIR-3434. Because the antigenic target is not present on human tissues, and because the nonclinical safety studies have not identified any VIR-3434 related safety concerns of relevance, the potential risks for healthy adult subjects are based on the common safety risks observed with the mAb class of therapeutics and are not specific to VIR-3434: anaphylaxis and other serious allergic reactions and injection/infusion-related reactions. The risk of developing such conditions after dosing with VIR-3434 specifically is unknown.

Part A of the study will gather important information on the safety and tolerability of VIR-3434 as well as relevant data on the PK profile and the generation of anti-drug antibodies (ADAs). VIR-3434 is not expected to offer benefit to healthy subjects enrolled in Part A of this study. Subjects will be monitored for important potential risks, and routine pharmacovigilance and risk minimization activities will be performed.

The potential benefits of VIR-3434 in subjects with chronic HBV infection over the current standard of care are the following:

- Reduction in serum HBsAg and HBV DNA, inhibition of intrahepatic spread of HBV, elimination of infected hepatocytes, and stimulation of adaptive immune responses against HBV, which have the potential to lead to functional cure
- A pangenotypic therapy for HBV infection that is well-tolerated and administered SC for a finite duration of time

In addition to the aforementioned risks of anaphylaxis, other serious allergic reactions, and injection/infusion-related reactions, potential risks associated with the administration of VIR-3434 to subjects with chronic HBV infection include immune complex disease and hepatotoxicity due to the elimination of infected hepatocytes via ADCC/ADCP and/or cytotoxic T-cells induced via a vaccinal effect. The study design of Parts B, C, and D includes several elements to mitigate these risks:

- Part B will enroll subjects with serum HBsAg < 3,000 IU/mL, to mitigate the risk for immune complex disease and hepatotoxicity. Additionally, Part B safety data will be reviewed by the SRC prior to enrolling subjects with potentially higher baseline HBsAg values in the optional Parts C and D of the study.
- Parts B and C will enroll subjects who are on NRTIs and have HBV DNA < 100 IU/mL at screening and have good hepatic reserve and a low level of hepatic inflammation at baseline as determined by the following attributes: ALT or AST $\leq 2 \times$ ULN, no history of hepatic decompensation, and lack of significant fibrosis and cirrhosis.
- Part D, which will enroll subjects who are not on NRTIs and have HBV DNA $\geq 1,000$ IU/mL and any HBsAg level, will be initiated only following SRC review of available safety data through the Week 4 visit for the cohort of subjects in Part B who are receiving a matching or higher dose.
- Two sentinel subjects will be randomized 1:1 to VIR-3434 or placebo and dosed. These sentinel subjects will be monitored through at least 72 hours post-dose and if the

investigator(s) have no safety concerns, the remaining 6 subjects in the same cohort will be dosed 5:1 (5 active and 1 placebo).

- Dose escalation will occur after SRC review of available safety data up to 4 weeks after dose administration to account for the anticipated timing of potential immune complex disease and hepatotoxicity due to the elimination of infected hepatocytes via ADCC/ADCP and/or cytotoxic T-cells induced via a vaccinal effect.
- Safety monitoring, including liver function tests, urinalysis, renal function, vital signs, and physical examination findings, is designed to detect evidence of VIR-3434-associated immune adverse events.

The risk/benefit assessment for subjects with chronic HBV is based on the balance between potential safety issues associated with the presence of antigen (HBsAg) and the anticipated benefits of a treatment modality designed to effectively reduce HBsAg, an immune tolerogen, and lead to clearance of infected hepatocytes. There is no approved therapy that reduces serum HBsAg in a substantial proportion of patients. If serum HBsAg can be effectively reduced in combination with clearance of infected hepatocytes, the anticipated safety profile of VIR-3434 would offer a favorable risk-benefit profile in patients with chronic HBV infection enrolled in Parts B, C, and D of the study.

3. OBJECTIVES

3.1. Part A Objectives

The primary objective is as follows:

- To evaluate the safety and tolerability of VIR-3434 in healthy adult subjects

The secondary objectives are as follows:

- To characterize the serum PK of VIR-3434 in healthy adult subjects
- To evaluate the immunogenicity of VIR-3434 (induction of anti-drug antibody [ADA]) in healthy adult subjects

3.2. Parts B, C, and D Objectives

The primary objective is as follows:

- To evaluate the safety and tolerability of VIR-3434 in adult subjects with chronic HBV infection without cirrhosis

The secondary objectives are as follows:

- To characterize the serum PK of VIR-3434 in adult subjects with chronic HBV infection without cirrhosis
- To assess the antiviral activity of VIR-3434 in adult subjects with chronic HBV infection without cirrhosis
- To evaluate the immunogenicity (induction of ADA) of VIR-3434 in adult subjects with chronic HBV infection without cirrhosis

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4. ENDPOINTS

4.1. Part A Endpoints

The primary endpoints are as follows:

- Number of subjects with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Number of subjects with clinical laboratory abnormalities

The secondary endpoints are as follows:

- VIR-3434 serum PK parameters, for example: C_{max} , C_{last} , T_{max} , T_{last} , AUC_{inf} , AUC_{last} , $\%AUC_{exp}$, $t_{1/2}$, λ_z , V_z (IV only), CL (IV only), V_z/F (SC only), and CL/F (SC only).
- Incidence and titers (if applicable) of ADA to VIR-3434

4.2. Parts B, C, and D Endpoints

The primary endpoints are as follows:

- Number of subjects with TEAEs and SAEs
- Number of subjects with clinical laboratory abnormalities

The secondary endpoints are as follows:

- VIR-3434 serum PK parameters, for example: C_{max} , C_{last} , T_{max} , T_{last} , AUC_{inf} , AUC_{last} , $\%AUC_{exp}$, $t_{1/2}$, λ_z , V_z/F , and CL/F.
- Incidence and titers (if applicable) of ADA to VIR-3434
- Maximum reduction of serum HBsAg from baseline (Day 1 predose)
- Part D only: maximum change of HBV DNA from baseline (Day 1 predose)

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5. INVESTIGATIONAL PLAN

5.1. Overall Study Design

This is a phase 1, randomized, double-blind, placebo-controlled study of VIR-3434 administered by subcutaneous (SC) injection or intravenous (IV) infusion to healthy adult subjects and adult subjects with chronic HBV infection without cirrhosis. The study is designed to evaluate the safety, tolerability, PK, and antiviral activity of VIR-3434. Investigators, designated study staff, and subjects are blinded to treatment allocation. The Sponsor is not blinded.

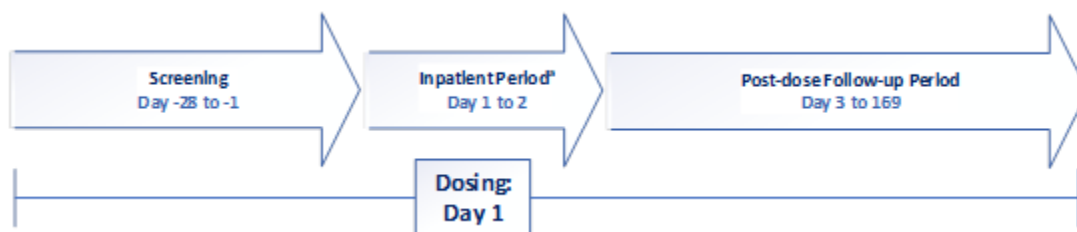
The study will be conducted in up to 4 Parts:

- **Part A:** Randomized, double-blind, placebo-controlled, SAD study of VIR-3434 in healthy adult subjects
- **Part B:** Randomized, double-blind, placebo-controlled, SAD study of VIR-3434 in adult subjects with chronic HBV infection without cirrhosis who are on NRTI therapy, are HBeAg-negative, and who have HBsAg < 3,000 IU/mL
- **Part C (Optional):** Randomized, double-blind, placebo-controlled, SAD study of VIR-3434 in adult subjects with chronic HBV infection without cirrhosis who are on NRTI therapy, are HBeAg-positive or HBeAg-negative, and who have HBsAg \geq 3,000 IU/mL
- **Part D (Optional):** Randomized, double-blind, placebo-controlled, SAD study of VIR-3434 administered via SC injection to adult subjects with chronic HBV infection without cirrhosis who are not on NRTI therapy, have HBV DNA \geq 1,000 IU/mL, are HBeAg-negative or HBeAg positive, and have any HBsAg level

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 globally. The study designs for Part A and Parts B, C, and D are presented in Figure 1 and Figure 2, respectively, and the cohort dosing schedule is provided in Appendix 7.

A Safety Review Committee (SRC) will perform ongoing reviews of available safety, tolerability, and antiviral activity data collected throughout the study with the primary purpose of protecting the safety of subjects. While the primary data that will be reviewed by the SRC for dose escalations and enrollment of optional cohorts is listed throughout the protocol, additional relevant data from other cohorts may also be reviewed by the SRC as indicated to inform decisions. Details are provided in the SRC charter.

Figure 1: SAD Study Design for Part A



*Subject discharge will occur after all assessments are completed on Day 2

Figure 2: SAD Study Design for Parts B, C, and D



5.1.1. Part A: SAD Phase in Healthy Adult Subjects

Healthy adult subjects will be enrolled in 1 of 5 cohorts (3 planned, 2 optional) in Part A. Subject screening will occur no more than 4 weeks prior to the Day 1 visit. Eligible subjects may be admitted into the clinical investigative site on Day -1 or 1. Prior to study drug administration on Day 1, subject eligibility will be confirmed. Any changes to medical history will also be evaluated and recorded. Eligible subjects in each cohort will be randomized to receive VIR-3434 or placebo within 48 hours prior to study drug administration. Subjects will receive a single dose of study drug on Day 1 (VIR-3434 or placebo).

At the start of each cohort, 2 sentinel subjects will be randomized 1:1 to VIR-3434 or placebo. These subjects will be dosed and monitored for at least 24 hours in an inpatient setting. Vital signs, ECG, symptom-directed physical examination(s), and AEs will be reviewed by the investigator; if the investigator has no safety concerns, the remainder of the subjects in the same cohort will be dosed. The remaining subjects in the cohort will be randomized 5:1 to receive a single dose of VIR-3434 or placebo. All subjects will be closely monitored following dose administration. In the event of an acute immune reaction (such as anaphylaxis or cytokine release syndrome), recommended therapeutic and supportive measures can be found in [Appendix 8](#).

Subjects will be discharged from the clinical investigative site after all study assessments are performed on Day 2. Subjects will return to the clinical investigative site for assessments per the schedule of assessments through the last post-dose follow-up visit (Week 24; [Appendix 2](#)).

5.1.2. Part B: SAD Phase in Adult Subjects with Chronic HBV Infection without Cirrhosis who are on NRTI Therapy and who have HBsAg < 3,000 IU/mL

Adult subjects with HBeAg-negative chronic HBV infection without cirrhosis and with HBsAg < 3,000 IU/mL on NRTI therapy for ≥ 2 months will be enrolled in 1 of 7 cohorts (5 planned, 2 optional) in Part B. Subject screening will occur no more than 6 weeks prior to the Day 1 visit. Subjects may be admitted into the clinical investigative site on Day -1 or 1. Prior to study drug administration on Day 1, subject eligibility will be confirmed. Any changes to medical history will also be evaluated and recorded. Eligible subjects in each cohort will be randomized to receive VIR-3434 or placebo within 48 hours prior to study drug administration on Day 1.

At the start of each cohort, 2 sentinel subjects will be randomized 1:1 to VIR-3434 or placebo. These subjects will be dosed and monitored through at least 72 hours post-dose; if the investigator(s) have 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 in the cohort will be randomized 5:1 to receive a single dose of VIR-3434 or placebo. All subjects will be closely

monitored following dose administration. In the event of an acute immune reaction (such as anaphylaxis or cytokine release syndrome) recommended therapeutic and supportive measures can be found in [Appendix 8](#).

Patients must be monitored through at least 6 hours post-dose prior to discharge. Subjects will be discharged after all study assessments are performed on Day 1. All subjects will return to the clinical investigative site per the schedule of assessments ([Appendix 3](#)) through the final required follow-up day (Week 8). In the event of suspected immune complex disease, recommended therapeutic and supportive measures can be found in [Appendix 8](#). Subjects with > 2-fold HBsAg reduction at Week 8 will be followed for an additional 32 weeks or until the reduction in HBsAg is < 2-fold relative to baseline at 2 consecutive collections, whichever occurs first. During this extended follow-up period, subjects will return to the clinical investigative site for assessments per the schedule of assessments ([Appendix 3](#)). Extended follow-up may be discontinued for any subject at Sponsor's discretion based on emerging data.

5.1.3. Part C: Optional SAD Phase in Adult Subjects with Chronic HBV Infection without Cirrhosis who are on NRTI Therapy and who have HBsAg \geq 3,000 IU/mL

Part C is optional. Adult subjects with chronic HBV infection without cirrhosis who are on NRTI therapy for \geq 2 months may be enrolled in 1 of 3 optional cohorts in Part C. For cohorts in Part C, HBeAg-negative and HBeAg-positive subjects with HBsAg \geq 3,000 IU/mL will be enrolled. Subject screening will occur no more than 6 weeks prior to the Day 1 visit. Subjects may be admitted into the clinical investigative site on Day -1 or 1. Prior to study drug administration on Day 1, subject eligibility will be confirmed. Any changes to medical history will also be evaluated and recorded. Eligible subjects in each cohort will be randomized to receive VIR-3434 or placebo within 48 hours prior to study drug administration on Day 1.

At the start of each cohort, 2 sentinel subjects will be randomized 1:1 to VIR-3434 or placebo. These subjects will be dosed and monitored through at least 72 hours post-dose; if the investigator(s) have 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 in the cohort will be randomized 5:1 to receive a single dose of VIR-3434 or placebo. All subjects will be closely monitored following dose administration. In the event of an acute immune reaction (such as anaphylaxis or cytokine release syndrome) recommended therapeutic and supportive measures can be found in [Appendix 8](#).

Patients must be monitored through at least 6 hours post-dose prior to discharge. Subjects will be discharged after all study assessments are performed on Day 1. All subjects will return to the clinical investigative site per the schedule of assessments ([Appendix 3](#)) through the final required follow-up day (Week 8). In the event of suspected immune complex disease, recommended therapeutic and supportive measures can be found in [Appendix 8](#). Subjects with > 2-fold HBsAg reduction at Week 8 will be followed for an additional 32 weeks or until the reduction in HBsAg is < 2-fold relative to baseline at 2 consecutive collections, whichever occurs first. During this extended follow-up period, subjects will return to the clinical investigative site for assessments per the schedule of assessments ([Appendix 3](#)). Extended follow-up may be discontinued for any subject at Sponsor's discretion based on emerging data.

5.1.4. Part D: Optional SAD Phase in Adult Subjects with Chronic HBV Infection without Cirrhosis who are not on NRTI Therapy

Part D is optional. Adult subjects with chronic HBV infection without cirrhosis who are not on NRTI therapy may be enrolled in 1 of 3 optional cohorts in Part D. For cohorts in Part D, HBeAg-negative and HBeAg-positive subjects with HBV DNA $\geq 1,000$ IU/mL may be enrolled. Subject screening will occur no more than 6 weeks prior to the Day 1 visit. Prior to study drug administration on Day 1, subject eligibility will be confirmed. Any changes to medical history will also be evaluated and recorded. Eligible subjects in each cohort will be randomized to receive VIR-3434 or placebo within 48 hours prior to study drug administration on Day 1.

At the start of each cohort, 2 sentinel subjects will be randomized 1:1 to VIR-3434 or placebo. These subjects will be dosed and monitored through at least 72 hours post-dose; if the investigator(s) have 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 in the cohort will be randomized 5:1 to receive a single dose of VIR-3434 or placebo. All subjects will be closely monitored following dose administration. In the event of an acute immune reaction (such as anaphylaxis or cytokine release syndrome) recommended therapeutic and supportive measures can be found in [Appendix 8](#).

Patients must be monitored through at least 6 hours post-dose prior to discharge. Subjects will be discharged after all study assessments are performed on Day 1. All subjects will return to the clinical investigative site per the schedule of assessments ([Appendix 3](#)) through the final required follow-up day (Week 8). In the event of suspected immune complex disease, recommended therapeutic and supportive measures can be found in [Appendix 8](#). Subjects with > 2 -fold HBsAg reduction at Week 8 will be followed for an additional 32 weeks or until the reduction in HBsAg is < 2 -fold relative to baseline at 2 consecutive collections, whichever occurs first. During this extended follow-up period, subjects will return to the clinical investigative site for assessments per the schedule of assessments ([Appendix 3](#)). Extended follow-up may be discontinued for any subject at Sponsor's discretion based on emerging data.

5.2. Safety Review Committee

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

The SRC will undertake safety data review prior to initiation of dosing a new cohort in 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 cohort stopping criterion being reached ([Section 5.6](#)).

While decisions to suspend dosing will be made according to predetermined stopping rules ([Section 5.6](#)), the SRC may also recommend discontinuation of the study to the Sponsor. The SRC membership composition and data review requirements are described in detail in the SRC Charter.

5.3. Study Drug Dosing, Study Progression, and Dose Escalation

Progression rules for cohorts are based on the absence of substantial safety signals. Standard toxicity grading according to the current Common Terminology Criteria for Adverse Events (CTCAE v 5.0) will be used to grade AEs. The decision to permit enrollment of an optional cohort will be made by the SRC based on a review of available safety, tolerability, and antiviral activity data (Parts B, C, and D only).

For cohorts in which a maximum dose level has been provided in lieu of an exact dose level, a final dose will be proposed by the Sponsor based on available safety and efficacy data (Parts B, C, and D only), prior to enrollment of the cohort. This dose level must be reviewed and approved by the SRC prior to enrollment of the cohort.

The maximum dose escalation factor in Study Parts A and B will not exceed 5-fold.

5.3.1. Part A Study Drug Dosing, Study Progression, and Dose Escalation

Overview: There are 3 planned cohorts in Part A: 90 mg SC (Cohort 1a), up to 300 mg SC (Cohort 2a), and up to 900 mg SC (Cohort 3a; Table 3). The SRC will review available laboratory and clinical safety data through 2 weeks post-dose from the last available subject in the current Part A cohort prior to permitting dosing in subsequent cohorts. While all of the SC cohorts (Cohort 1a, 2a, and 3a) in Part A are planned to be enrolled sequentially, cohorts may be enrolled in parallel if the additional cohort(s) is examining a dose level which is at or below a dose level that has previously been found to have an acceptable safety and tolerability profile in a prior cohort in Part A.

Optional Cohorts: Optional IV cohorts (Cohorts 4a and 5a) may be enrolled and dosed based on SRC review of available safety and tolerability data through at least 2 weeks after the last available subject is dosed within Cohort 3a. Enrollment of Cohorts 4a and 5a will be according to the same Part A eligibility criteria as the planned Part A cohorts.

Table 3: Part A Cohort Overview

Study Part	Cohort	Route	Dose Level	Active:Placebo
A	1a	SC	90 mg	6:2
A	2a	SC	up to 300 mg	6:2
A	3a	SC	up to 900 mg	6:2
A	4a (optional)	IV	up to 900 mg	6:2
A	5a (optional)	IV	up to 3,000 mg	6:2

5.3.2. Part B Study Drug Dosing, Study Progression, and Dose Escalation

Overview: There are 5 planned cohorts in Part B: 6 mg SC (Cohort 1b), 18 mg SC (Cohort 2b), up to 75 mg SC (Cohort 3b), up to 300 mg SC (Cohort 4b), and up to 900 mg SC (Cohort 5b; Table 4). Cohort 1b will be the first cohort enrolled. Prior to initiating dosing of subsequent cohorts, the SRC will review available laboratory and clinical safety data and antiviral activity data through 4 weeks post-dose from the last available subject in the current Part B cohort prior to permitting dosing in subsequent cohorts. While these cohorts are planned to be enrolled

sequentially, they may be enrolled in parallel if the additional enrolled cohort(s) is examining a dose level which is at or below a dose level that has previously been found to have an acceptable safety and tolerability profile in Part A and Part B. Doses explored in Part B cohorts will not exceed the highest dose level in Part A that was determined to have an acceptable safety and tolerability profile by the SRC.

Initiation of Part B: Cohort 1b will be initiated after review of available safety data, inclusive of available Week 2 laboratory and clinical safety data, from Cohort 1a.

Optional Cohorts: Upon SRC review of available clinical and laboratory safety data and antiviral activity data, optional Cohort 6b and/or optional Cohort 7b may be enrolled and dosed at a lower, equivalent, or intermediate dose level relative to the dose levels explored in the planned Part B cohorts, or after cohort 5b at a dose level not exceeding 900 mg. The maximum dose level for the optional cohorts in Part B will also not exceed the highest single dose found to have an acceptable safety and tolerability profile in Part A. The optional cohorts may be enrolled at any time within the Part B planned cohorts based on the approval of the SRC. Enrollment of the Part B optional cohorts will be according to the same Part B eligibility criteria as the planned cohorts.

Table 4: Part B Cohort Overview

Study Part	Cohort	Route	Dose Level	Active:Placebo
B	1b	SC	6 mg	6:2
B	2b	SC	18 mg	6:2
B	3b	SC	up to 75 mg	6:2
B	4b	SC	up to 300 mg	6:2
B	5b	SC	up to 900 mg	6:2
B	6b (optional)	SC	up to 900 mg	6:2
B	7b (optional)	SC	up to 900 mg	6:2

5.3.3. Part C Study Drug Dosing, Study Progression, and Dose Escalation

Overview: Part C is optional and may be conducted if VIR-3434 is found to have an acceptable safety and tolerability profile in HBeAg-negative subjects with HBsAg levels < 3,000 IU/mL in Part B. For cohorts in Part C, HBeAg-negative and HBeAg-positive subjects with HBsAg \geq 3,000 IU/mL will be enrolled.

There are 3 optional cohorts in Part C each evaluating up to 900 mg SC (Table 5). Cohort 1c will be the first cohort to initiate enrollment. Doses explored in Part C cohorts will not exceed the highest dose level in Part B that was determined to be safe by the SRC. Part C cohorts may be enrolled in parallel.

Initiation of Part C: Cohort 1c may be initiated after SRC review of available data for all subjects in Part A and Part B through the Week 4 visit for the cohort of subjects in Part B who are receiving a matching or higher dose.

Table 5: Part C Cohort Overview

Study Part	Cohort	Route	Dose Level	Active:Placebo
C	1c (optional)	SC	up to 900 mg	6:2
C	2c (optional)	SC	up to 900 mg	6:2
C	3c (optional)	SC	up to 900 mg	6:2

5.3.4. Part D Study Drug Dosing, Study Progression, and Dose Escalation

Overview: Part D is optional and may be conducted if VIR-3434 is found to have an acceptable safety and tolerability profile in HB ϵ Ag-negative subjects with HBsAg levels < 3,000 IU/mL in Part B.

There are 3 optional cohorts in Part D each evaluating up to 900 mg SC (Table 6). Cohort 1d will be the first cohort to initiate enrollment. Doses explored in Part D cohorts will not exceed the highest dose level in Part B that was determined to be safe by the SRC. Part D cohorts may be enrolled in parallel.

Initiation of Part D: Cohort 1d may be initiated after SRC review of available data through the Week 4 visit for the cohort of subjects in Part B who are receiving a matching or higher dose relative to the proposed starting dose level in Part D.

Table 6: Part D Cohort Overview

Study Part	Cohort	Route	Dose Level	Active:Placebo
D	1d (optional)	SC	up to 900 mg	6:2
D	2d (optional)	SC	up to 900 mg	6:2
D	3d (optional)	SC	up to 900 mg	6:2

5.4. Withdrawal and Early Terminations

Subjects who discontinue from study participation prematurely will be followed for safety, and under certain circumstances, subjects who discontinue study treatment (as described in Section 5.5) may be replaced. If a subject discontinues from the study post-dose but before completion of the Week 24 and Week 8 visits for Part A and Parts B/C/D respectively, an End of Treatment (ET) visit should be performed. Additionally, for Parts B, C, and D, if a subject discontinues from the study post-Week 8 but before completion of the Week 40 visit, an End of Follow Up (EF) visit should be performed.

5.5. Replacement of Subjects

Subjects who do not receive the full planned dose or discontinue due to an AE that does not meet cohort stopping criteria (Section 5.6) may be replaced with confirmation by the SRC. Subjects who discontinue from the study for non-safety-related reasons or for reasons other than those requiring SRC confirmation (listed above) may be replaced following discussion between the Sponsor Medical Monitor (or designee) and the investigator.

The replacement subject will be assigned a unique subject 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.

5.6. 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.

5.6.1. Cohort Stopping Rules

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

- Any safety finding assessed as related to study drug that, in the opinion of the sponsor or the investigator, warrants suspension of further dosing of subjects until more fully assessed
- If a sentinel subject experiences a study drug-related Grade 3 or higher AE
- If 2 or more subjects experience the same study drug-related Grade 3 or higher AE
- If 1 or more subjects experience a study drug-related serious adverse event (SAE)
- If 1 or more subjects experience a Grade 3 or higher study drug-related AE of anaphylaxis, cytokine release syndrome, or immune complex disease
- If 1 or more subjects experience a serum ALT > 10 x ULN
- If 1 or more subjects experience a serum ALT or AST > 3 × baseline value with a concomitant total bilirubin > 2 × ULN or INR > 1.5
- If 1 or more subjects experience clinical manifestations of hepatic decompensation

If 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.

5.7. End of Study

The end of this study will be last subject's last observation.

6. SUBJECT POPULATION

6.1. Number of Subjects and Subject Selection

A total of up to 144 subjects are planned to complete this study, comprising up to 40 healthy adult subjects (Part A), up to 56 adult subjects with chronic HBV infection without cirrhosis on NRTI therapy who are HBeAg-negative and who have HBsAg < 3,000 IU/mL (Part B), up to 24 adult subjects with chronic HBV infection without cirrhosis on NRTI therapy who have HBsAg ≥ 3,000 IU/mL (Part C), and up to 24 adult subjects with chronic HBV infection without cirrhosis who are not on NRTI therapy, have HBV DNA ≥ 1,000 IU/mL and any HBsAg level, and are HBeAg-negative or HBeAg positive (Part D).

6.2. 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. Weight ≥ 40 kg to ≤ 125 kg
3. In good health, determined from medical history (e.g. chronic conditions such as hypertension, hyperlipidemia, gastroesophageal reflux disease, asthma, anxiety and depression must be well controlled), and no clinically significant findings from physical examination, 12-lead ECG, vital signs, and laboratory values.
4. Female subjects must have a negative pregnancy test or confirmation of postmenopausal status. Post-menopausal status is defined as 12 months with no menses without an alternative medical cause. Women of child-bearing potential (WOCBP) must have a negative blood 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 (Section 6.6) 14 days before study drug administration through 24 weeks after study drug administration.
5. 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 24 weeks post-dose of study drug: vasectomy with documentation of azoospermia, or male condom use plus partner use of 1 of the contraceptive options listed for contraception for WOCBP (Section 6.6). Male subjects must also agree not to donate sperm from the time of study drug administration through 24 weeks after study drug administration.
6. Agrees not to donate blood during the duration of the study
7. Willing to comply with the study requirements and able to provide written informed consent.

6.3. Part A Exclusion Criteria

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

1. History of allergic reactions to monoclonal antibodies or antibody fragments
2. History of anaphylaxis
3. History of clinically significant cardiovascular disease, peripheral vascular disease, cardiopulmonary disease, or diabetes
4. History of bone marrow or solid organ transplantation
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. Any clinically significant acute condition such as fever ($> 38^{\circ}\text{C}$) or acute respiratory illness within 7 days of study drug administration
7. Systolic blood pressure > 140 mmHg and/or a diastolic blood pressure of > 90 mmHg at screening
8. Laboratory evidence of active infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or HBV
9. Creatinine clearance (CLcr) < 90 mL/min as calculated by the Cockcroft-Gault formula at screening
10. Subject has the following laboratory parameters at screening by laboratory testing:
 - a. alanine and aspartate aminotransferases (ALT and AST), total bilirubin, or INR above the upper limit of normal (ULN)
 - b. hemoglobin, platelets, or albumin below the LLN
 - c. white blood cell count (WBC) or potassium above the ULN or below the LLN

Screening study laboratory tests may be repeated once (eg, for values thought to be erroneous) with Sponsor approval.

11. Regular consumption of more than 10 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]), or more than 2 units of alcohol per day
12. History or clinical evidence of alcohol or drug abuse, with the exception of cannabis use, within the 12 months before screening or a positive drug screen at screening or prior to dosing unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved by the investigator.
13. Lack of peripheral venous access or history of poor venous access
14. Not on a stable dose and regimen of any medication(s) (prescription or OTC) that the subject is taking regularly (i.e. medications for chronic conditions such as hypertension, high cholesterol, or depression must be unchanged in dose or type for at least 6 months)

15. Use of any of the following systemic medications within 14 days before study drug administration and throughout the study:
 - a. Paracetamol (acetaminophen) ≥ 2 g/day, aspirin > 3 g/day or ibuprofen ≥ 1.2 g/day
 - b. Tricyclic antidepressants
 - c. Valproate
 - d. Phenytoin
 - e. Amiodarone
 - f. Anabolic steroids
 - g. Allopurinol
 - h. Amoxicillin-clavulanate
 - i. Minocycline
 - j. Nitrofurantoin
 - k. Sulfamethoxazole/trimethoprim
 - l. Erythromycin
 - m. Isoniazid
 - n. Rifampin
 - o. Azole antifungals
 - p. Steroids (prednisone equivalent of > 5 mg/day) or other immunosuppressive agents
(Note: corticosteroid administration for the treatment of immune-mediated AEs is allowed.)
16. Use of herbal remedies within 28 days before study drug administration and throughout the duration of the study
17. Received an investigational agent within 90 days or 5 half-lives (if known), whichever is longer, 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.
18. Donated more than 500 mL of blood within 90 days before study drug administration
19. Any illness or medical condition that would make the subject unsuitable for enrollment or could interfere with the subject's participation in or completion of the study

6.4. Parts B, C, and D 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
2. Weight ≥ 40 kg to ≤ 125 kg
3. Chronic HBV infection as defined by the following criteria:
Positive serum HBsAg, HBV DNA, or HBeAg on 2 occasions at least 6 months apart based on previous or current laboratory documentation (any combination of these tests performed 6 months apart is acceptable)
4. Parts B and C only: On NRTI therapy for at least 2 months at the time of screening

5. Parts B and C only: HBV DNA < 100 IU/mL at screening
6. Part D only: HBV DNA \geq 1,000 IU/mL at screening
7. HBsAg > the lower limit of detection
8. Part B only: HBsAg < 3,000 IU/mL at screening
9. Part C only: HBsAg \geq 3,000 IU/mL at screening
10. Part B only: HBeAg-negative at screening
11. Negative anti-HBs at screening
12. Besides chronic infection with HBV, must be in good health, determined from medical history (e.g. chronic conditions such as hypertension, hyperlipidemia, gastroesophageal reflux disease, asthma, anxiety and depression must be well controlled), and no clinically significant findings from physical examination, 12-lead ECG, vital signs, and laboratory values.
13. Female subjects must have a negative pregnancy test or confirmation of postmenopausal status. Post-menopausal status is defined as 12 months with no menses without an alternative medical cause. WOCBP must have a negative blood 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 (Section 6.6) 14 days before study drug administration through 40 weeks after study drug administration. Female subjects must also agree to refrain from egg donation and in vitro fertilization from the time of study drug administration through 40 weeks after study drug administration.
14. 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 through 40 weeks after study drug administration: documentation of azoospermia or vasectomy, or male condom use plus partner use of 1 of the contraceptive options listed for contraception for WOCBP (Section 6.6). Male subjects must also agree to not donate sperm from the time of first study drug administration through 40 weeks after the dose of study drug.
15. Willing to comply with the study requirements and able to provide written informed consent

6.5. Parts B, C, and D Exclusion Criteria

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

1. 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.
2. Parts B and C only: Serum ALT or AST > 2 \times ULN at screening
3. Part D only: Serum ALT or AST > 5 \times ULN at screening

4. History of clinically significant chronic liver disease from any cause other than chronic HBV infection (subjects with positive HCV serology and negative HCV RT-PCR are permitted)
5. History of hepatic decompensation, including ascites, hepatic encephalopathy and/or esophageal or gastric varices
6. History of immune complex disease
7. History of HBV-related extrahepatic disease, including but not limited to HBV-related rash, arthritis, or glomerulonephritis
8. History of systemic lupus erythematosus (SLE) or other autoimmune disorder
9. History of allergic reactions, hypersensitivity, or intolerance to monoclonal antibodies, antibody fragments, or any excipients of VIR-3434
10. History of anaphylaxis
11. History of clinically significant cardiovascular disease, peripheral vascular disease, cardiopulmonary disease, or diabetes
12. 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
13. History of a seizure disorder
14. History of malignancy within 5 years (treated squamous or non-invasive basal cell skin cancers are permitted) or subject is under evaluation for malignancy
15. History of bone marrow or solid organ transplant
16. Any clinically significant acute condition such as fever ($> 38^{\circ}\text{C}$) or acute respiratory illness within 7 days of study drug administration
17. Systolic blood pressure > 140 mmHg and/or a diastolic blood pressure of > 90 mmHg at screening
18. Co-infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis D virus (HDV). Subjects who are HCV antibody or HDV antibody positive, but have a documented negative HCV RNA or HDV RNA, respectively, are eligible.
19. CLcr < 60 mL/min as calculated by the Cockcroft-Gault formula at screening
20. Subject has the following laboratory parameters at screening by laboratory testing:
 - a. total bilirubin or INR above the upper limit of normal (ULN)
 - b. hemoglobin, platelets, or albumin below the LLN
 - c. potassium above the ULN or below the LLN
 - d. WBC above the ULN or below the LLN (Subjects with benign ethnic neutropenia, defined as an absolute neutrophil count below the LLN and $> 1,200$ cells/microliter at screening, may be enrolled as long as there is no history of recurrent, severe, or atypical infections, no presence of other related or clinically relevant abnormalities, and no alternative cause for the neutropenia)

- Screening study laboratory tests may be repeated once (eg, for values thought to be erroneous) with Sponsor medical monitor approval.
21. Regular consumption of more than 10 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]), or more than 2 units of alcohol per day
 22. History or clinical evidence of alcohol or drug abuse, with the exception of cannabis use, within the 12 months before screening or a positive drug screen at screening unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved by the investigator.
 23. Not on a stable dose and regimen of any systemic medication(s) (prescription or OTC) that the subject is taking regularly (i.e., medications for chronic conditions such as hypertension, high cholesterol, or depression must be unchanged in dose or type for at least 3 months)
 24. Use of any of the following systemic medications within 14 days before study drug administration and throughout the study:
 - a. Paracetamol (acetaminophen) \geq 2g/day, aspirin $>$ 3g/day or ibuprofen \geq 1.2 g/day
 - b. Tricyclic antidepressants
 - c. Valproate
 - d. Phenytoin
 - e. Amiodarone
 - f. Anabolic steroids
 - g. Allopurinol
 - h. Amoxicillin-clavulanate
 - i. Minocycline
 - j. Nitrofurantoin
 - k. Sulfamethoxazole/trimethoprim
 - l. Erythromycin
 - m. Isoniazid
 - n. Rifampin
 - o. Azole antifungals
 - p. Steroids (prednisone equivalent of $>$ 5 mg/day) or other immunosuppressive agents (Note: corticosteroid administration for the treatment of immune-mediated AEs is allowed.)
 25. Use of herbal remedies within 28 days before study drug administration and throughout the duration of the study.
 26. Received an investigational agent within 90 days or 5 half-lives (if known), whichever is longer, 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.
 27. Prior receipt of an oligonucleotide drug (eg, siRNA, antisense oligonucleotide) with activity against HBV

28. Any illness or medical condition other than chronic HBV infection that makes the subject unsuitable for participation in the study
29. Part D only: Receipt of NRTI therapy, interferon, or any other antiviral therapy with activity against HBV within 6 months prior to screening
30. Part D only: In the opinion of the investigator, anticipated to require to antiviral therapy for chronic HBV infection at any time during the screening period or within 8 weeks after study drug administration

6.6. Women of Childbearing Potential Definition and Contraception 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 through 40 weeks after 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-3434 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 40 weeks after 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 from heterosexual contact, 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 through 40 weeks after study drug administration.
- Barrier method in combination with hormonal contraceptive, as described above

Post-menopausal status is defined as 12 months with no menses without an alternative medical cause.

Female subjects must also agree to refrain from egg donation and in vitro fertilization from the time of study drug administration through 40 weeks after study drug administration.

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 through 40 weeks after study drug administration.

- Documentation of azoospermia or vasectomy
- 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 through 40 weeks after study drug administration.

7. STUDY DRUG

7.1. Randomization, Blinding, and Treatment Codes

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

This is a double-blind study. Investigators, designated study staff, and subjects are blinded to treatment allocation. The Sponsor is not blinded.

7.1.1. Unblinding

An individual cohort will be unblinded when all subjects enrolled in the cohort complete the Week 8 visit. The Sponsor will communicate treatment assignments to investigators, and investigators will share treatment assignment with the subject. Additional details are provided in the Statistical Analysis Plan.

7.2. 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.

7.3. Description and Handling of VIR-3434 and Placebo

The characteristics of VIR-3434 are summarized in Table 7.

Table 7: Characteristics of VIR-3434

Dosage Form:	Solution of lyophilized solid, reconstituted with sterile water for injection, USP.
Unit Dose	Based on volume and administration method
Route of Administration	Subcutaneous injection or intravenous infusion
Physical Description	Lyophilized: White solid Reconstituted: Clear, colorless to light brown solution
Manufacturer	Wuxi Biologics

7.3.1. Formulation

VIR-3434 is provided by the sponsor as a lyophilized solid. Upon reconstitution to 150 mg/mL with sterile water for injection, USP, the drug product, as administered, contains 20 mM Histidine, 7% sucrose, 0.02% PS80 at pH 6.

Placebo is a sterile, preservative-free normal saline 0.9% solution for IV infusion or SC injection supplied by the clinical site, except where required to be supplied by the Sponsor.

Sterile Water for Injection, USP used for reconstitution of VIR-3434 will be supplied by the clinical site, except where required to be supplied by the Sponsor.

7.3.2. Packaging and Labeling

VIR-3434 primary packaging consists of a 10R glass vial, 20 mm lyophilization compatible stopper and 20 mm crimp seal. VIR-3434 secondary packaging and labeling is described in the Pharmacy Manual.

7.3.3. Storage and Handling

Study drug may be dispensed only 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 IV infusion bags and 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 each cohort. Additional details regarding the procedure for preparing study drug, the volume to be loaded into each syringe or IV infusion bag, and how syringes or IV infusion bags are to be 'blinded' are provided in the Pharmacy Manual.

No special procedures for the safe handling of VIR-3434 are required. Study drug will be stored in an 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.

7.3.4. Study Drug Disposal

Refer to the Pharmacy Manual for study drug disposal details.

7.3.5. Dosage and Administration

On the day of dosing, the pharmacist or designee will prepare the study drug per the Pharmacy Manual. Study drug will be reconstituted and prepared for SC injection in one or more syringes or IV infusion in an IV bag. A qualified clinical investigative site staff member under the supervision of the investigator or designee will administer study drug to subjects. Study drug administration should be performed in a setting where personnel and equipment are available for the management of injection or infusion reactions including anaphylaxis.

If administered by SC injection, the injection site(s) will be marked and recorded for later observation and should be documented. If a local reaction around the injection site occurs, photographs may be obtained. Subjects should be instructed to monitor for local and systemic injection site reactions, including signs and symptoms of anaphylaxis and instructed to seek emergency medical care, if needed. Oral analgesics may be used to manage mild to moderate local pain or tenderness. More extensive or severe symptoms should be evaluated by the study investigator and treated as deemed appropriate by the investigator and per local standards of care.

Refer to the Pharmacy Manual for detailed study drug preparation and administration instructions.

7.4. 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.

7.5. Concomitant Medications

7.5.1. Permitted Concomitant Medications

For all study parts, a stable dose and regimen of any medication(s) (prescription or OTC) that the subject is taking regularly (i.e., medications for chronic conditions such as hypertension, high cholesterol, or depression must be unchanged in dose or type for at least 6 months for Part A or 3 months for Parts B, C, and D) is permitted, except those listed in Section 7.5.2. Additionally, use of the following is also permitted:

- Oral, injectable, subdermal, intravaginal, or implantable contraceptives, as well as intrauterine device, and intrauterine hormone-releasing system are permitted for contraception
- Paracetamol (< 2g/day), aspirin (\leq 3g/day), or ibuprofen (< 1.2 g/day)
- Antihistamines

Investigators may initiate new prescription and non-prescription concomitant medications or treatments deemed necessary to provide adequate care for AEs or other new onset medical conditions, except those listed in Section 7.5.2.

7.5.2. Prohibited Concomitant Medications

Use of any of the following systemic medications within 14 days before study drug administration and throughout the study (unless otherwise noted) is prohibited:

- Paracetamol (acetaminophen) \geq 2 g/day, aspirin > 3 g/day or ibuprofen \geq 1.2 g/day

- Tricyclic antidepressants
- Valproate
- Phenytoin
- Amiodarone
- Anabolic steroids
- Allopurinol
- Amoxicillin-clavulanate
- Minocycline
- Nitrofurantoin
- Sulfamethoxazole/trimethoprim
- Erythromycin
- Isoniazid
- Rifampin
- Azole antifungals
- Steroids (prednisone equivalent of > 5 mg/day) or other immunosuppressive agent (Note: corticosteroid administration for the treatment of immune-mediated AEs is allowed.)
- Herbal remedies within 28 days before study drug administration and throughout the duration of the study
- Part D only: antiviral therapy for chronic HBV infection within 6 months prior to screening and through the Week 8 visit
 - If, in the opinion of the investigator, antiviral therapy for chronic HBV infection is urgently indicated at any time between screening and the Week 8 visit, antiviral therapy for chronic HBV infection may be initiated at any time
 - For patients in extended follow-up, NRTI or interferon therapy may be initiated after the Week 8 visit if clinically indicated and after discussion with the Sponsor Medical Monitor (or designee)

7.5.3. NRTI Therapy (Parts B and C)

Examples of permitted NRTI therapy include, but are not limited to, the following:

- Tenofovir disoproxil/tenofovir alafenamide
- Entecavir
- Lamivudine
- Adefovir/adefovur dipivoxil

8. STUDY PROCEDURES

The Schedule of Study Assessments is provided in [Appendix 2](#) for Part A and [Appendix 3](#) for Parts B, C, and D. Unscheduled visits are permitted at the discretion of the investigator as needed for safety assessment. Fasting is not required for any study procedure/assessment

8.1. Written Informed Consent

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

8.2. Medical History

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

8.3. Full Physical Examination

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

8.4. Symptom-directed Physical Examination

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

8.5. Weight and Height

Body weight and height will be measured.

8.6. Vital Signs

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

8.7. Electrocardiogram

12-lead safety ECGs will be recorded and reviewed on-site by the investigator at the timepoints outlined in [Appendix 2](#) and [Appendix 3](#). All ECGs should be measured in the supine position after the subject has rested comfortably for approximately 10 minutes.

8.8. Pregnancy Testing

A pregnancy test or confirmation of post-menopausal status must be confirmed for all female subjects. Post-menopausal status is defined as no menses for 12 months without an alternative medical cause. Pregnancy tests will be performed for WOCBP only. Pregnancy testing will be

performed per the SoA and any time pregnancy is suspected. A WOCBP who is known to be pregnant or who does not have a negative pregnancy test at screening is not eligible for study participation. A blood pregnancy test will be performed at screening and urine pregnancy tests will be performed thereafter. During the study, the results of these pregnancy tests must be known prior to study drug administration. A WOCBP determined to be pregnant while on study will be followed until the pregnancy outcome is known, as described in Section 9.4.2.

8.9. FibroScan

To exclude the presence of cirrhosis, subjects in Parts B, C, and D will have a FibroScan evaluation. This is not required 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.

8.10. Screening Viral Serology Parameters

Screening viral serology parameters are as follows:

- **Part A:** Active infection with HIV, HCV, and HBV
- **Parts B, C, and D:** Active infection with HIV, HCV, and hepatitis Delta virus. Subjects who have positive HCV serology result must have HCV-RT PCR reflex testing to determine eligibility.

8.11. Screening Confirmation of Chronic HBV Infection

For Parts B, C, and D, chronic HBV infection will be determined at screening and is defined as the following:

- Positive serum HBsAg, HBV DNA, or HBeAg on 2 occasions at least 6 months apart based on previous or current laboratory documentation (any combination of these tests performed 6 months apart is acceptable)

8.12. Local Tolerability

For all study parts, a local tolerability assessment will be performed per the Schedule of Assessments for subjects receiving study drug by SC injection. Injection site(s) will be marked and mapped for later observation and should be documented. Injection site(s) should be monitored for pain/tenderness, swelling, redness, bruising, and pruritus.

The timing of local tolerability assessments for Part A can be found in [Appendix 2](#). The timing of the local tolerability assessments for Parts B, C, and D can be found in [Appendix 3](#).

At the discretion of the investigator, unscheduled visits are permitted as needed for follow up of any unresolved local tolerability symptoms.

8.13. Clinical Laboratory Assessments

Clinical laboratory tests that will be performed in this study are presented in [Appendix 9](#). In the event of an unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test may 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.

8.14. Screening for Drugs of Abuse

For all parts of the study, urine will be collected for drugs of abuse screening. Panel will include amphetamines, cocaine, methadone, and opiates.

8.15. Pharmacokinetic Assessments

Blood samples will be collected to assess concentrations of VIR-3434. Timepoints for the collection of samples for VIR-3434 PK analysis for Part A of the study are provided in [Appendix 4](#) and [Appendix 5](#). Timepoints for the collection of samples for VIR-3434 PK analysis for Parts B, C, and D of the study are provided in [Appendix 6](#).

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

8.16. Immunogenicity

Blood samples will be collected for analysis of immunogenic responses to determine presence/absence and titers of anti-drug antibodies (ADA) as applicable, according to the time points defined in the Schedule of Assessments. Samples may also be characterized for neutralizing potential of anti-VIR-3434 antibody (NAb), as appropriate. Details regarding the processing, shipping, and analysis of the samples are provided in the Laboratory Manual.

8.17. Assessment of Screening Viral Parameters, Antiviral Activity, and Resistance Surveillance

During Parts B, C, and D, assessment of screening viral parameters will include: HBsAg, anti-HBs, HBeAg (qualitative), and HBV DNA.

Assessments of antiviral activity performed after screening will include: HBsAg, anti-HBs, HBeAg (qualitative; should only be collected for Parts C and D subjects who are HBeAg qualitative positive at screening), HBeAg (quantitative; should only be collected for Parts C and D subjects who are HBeAg qualitative positive at screening), anti-HBe, HBV RNA, hepatitis B core-related antigen (HBcrAg), and HBV DNA.

Resistance surveillance to monitor for the potential development of resistance to NRTIs or VIR-3434 will be conducted for all subjects who receive study drug. HBV genome sequencing will be attempted in subjects with confirmed HBV DNA breakthrough as defined by having either HBV DNA $\geq 1 \log_{10}$ IU/mL above nadir for 2 consecutive visits or ≥ 500 IU/mL measured at 2 consecutive study visits after having been < 500 IU/mL. HBV genome sequencing will also be attempted in subjects who discontinue early from the study with HBV DNA ≥ 500 IU/mL. As it will not be known at the time of visit if a subject has virologic breakthrough, samples for resistance surveillance will be collected at all study visits noted in the SOA. Samples collected for resistance surveillance may be used to perform additional viral analyses, including viral sequencing.

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

8.18. Exploratory Assessments

CCI



9. ADVERSE EVENT MANAGEMENT

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

9.1.1. Adverse Event (AE)

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.

9.1.2. Serious Adverse Event (SAE)

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-3434.

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

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

Per Section 9.1.1, 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 Section 9.1.1 and Section 9.1.2. If the laboratory abnormality is part of a clinical syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

9.2. Assessment of 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.

9.2.1. Relationship to Study Drug

Relationship (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, relationship to study drug should be categorized as No. A mere possibility of a causal relationship is not grounds for a Yes categorization.

If the relationship between the AE/SAE and the investigational product is determined to be “possible” or “probable” the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

9.2.2. Assessment of Severity

Standard toxicity grading according to the CTCAE (V5.0) will be used to grade AEs and laboratory abnormalities. Definitions of severity per CTCAE (V5.0) are presented in Table 8.

Table 8: CTCAE (V5.0) Definitions of Severity

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

ADL = activities of daily living

Source: [NCI 2017](#)

9.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Vir

AEs

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.

Following initiation of study drug, collect all AEs, regardless of cause or relationship, through the required follow-up period (through Week 24 for Part A and through Week 8 for Parts B, C, and D).

Following Week 8 in Parts B, C, and D, all SAEs and targeted AEs related to immune reactions, immune complex disease (eg, vasculitis, glomerulonephritis, serum sickness and serum sickness-like reactions, extra-hepatic manifestations of HBV), new onset hepatic disorders (eg, hepatic decompensation, hepatic necrosis), and new onset chronic diseases requiring ongoing medical management should be collected through the end of extended follow-up.

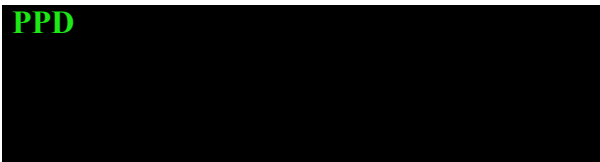
SAEs

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 and extended follow-up period (Parts B, C, and D only), must be reported as instructed. This also includes any SAEs resulting from protocol-mandated procedures performed after informed consent is signed. All SAEs should be followed up until resolution or until stable, if possible.

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:



9.4. Special Situations Reports

9.4.1. 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.

9.4.2. Instructions for Reporting Special Situations

9.4.2.1. Pregnancy Reporting

If a female subject becomes pregnant after study drug administration through 40 weeks after study drug administration, the subject will be instructed to report this to the investigator. 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. The investigator will collect follow-up information on the mother and infant and will notify the Sponsor within 24 hours of obtaining updated information regarding the pregnancy. 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 9.3. Every effort will be done to follow the infant for up to 1 year after birth.

If the partner of a male subject becomes pregnant after study drug administration through 40 weeks after study drug administration, the subject will be instructed to report this to the investigator. The partner will be asked to provide consent to be followed until the outcome of the pregnancy is known and for up to 1 year after birth (where permitted). The investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. The subject and the partner should receive any necessary counseling regarding the risk of continuing the pregnancy and the possible effects of the fetus. After obtaining consent, the investigator must report available follow-up information on the course and outcome of the pregnancy within 24 hours of learning of the information.

9.4.2.2. Reporting Other Special Situations

All other special situations must be reported to **ICON (formerly PRA)** Pharmacovigilance 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 nonrequired concomitant medications.

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.

9.5. Vir Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA 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.

10. STATISTICS

The objectives and endpoints are listed in Section 3 and Section 4 , respectively.

10.1. Analysis Sets

10.1.1. All Randomized

The all randomized analysis set includes all subjects who are randomized in the study. This is the primary analysis set for by-subject listings.

10.1.2. Safety

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

10.1.3. 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 non-missing concentration data to provide interpretable results for the specific parameters of interest for the analyte under evaluation

10.1.4. 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 non-missing data to provide interpretable results for the specific antiviral activity parameters of interest.

10.1.5. Immunogenicity

The primary analysis set for immunogenicity will be the Immunogenicity Analysis Set, which includes all subjects in the Safety Analysis Set who have at least 1 sample that has undergone testing for immunogenicity, including screening, confirmatory, or neutralizing characterization, as applicable.

10.2. Data Handling Conventions

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

10.3. 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 percentages of subjects for categorical variables.

10.4. Safety Analysis

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

If applicable, safety will be evaluated by assessment of clinical laboratory tests, physical examinations, ECGs, vital signs measurements at various time points during the study, and by the documentation of AEs.

All safety data collected on or after study drug administration up to the last scheduled visit, unless specified otherwise, will be summarized by cohort for each VIR-3434 dose and placebo.

10.4.1. 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.

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.

10.4.2. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by cohort and study visit along with corresponding change from baseline. Graded laboratory abnormalities will be defined using CTCAE Version 5.0 grading scale.

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

10.4.3. Other Safety Evaluations

Individual data for physical examination findings, prior and concomitant medications and medical history will be provided. Twelve-lead safety ECGs and vital signs measurements will be listed by subject and summarized by incidence of events/abnormalities or descriptive statistics as appropriate.

10.5. Pharmacokinetic Analysis

Part A

PK (free and total PK, as applicable) parameters of VIR-3434 will be computed using standard noncompartmental methods. Parameters may include, but not be limited to, serum: C_{max} , C_{last} , T_{max} , T_{last} , AUC_{inf} , AUC_{last} , $\%AUC_{exp}$, $t_{1/2}$, λ_z , V_z (IV only), CL (IV only), V_z/F (SC only), and CL/F (SC only) and will be listed and summarized using descriptive statistics. Other parameters may be calculated, if deemed necessary.

Parts B, C, and D

PK (free and total PK, as applicable) parameters of VIR-3434 will be computed using standard noncompartmental methods. Parameters may include, but not be limited to, serum: C_{max} , C_{last} , T_{max} , T_{last} , AUC_{inf} , AUC_{last} , $\%AUC_{exp}$, $t_{1/2}$, λ_z , V_z/F , and CL/F , and will be listed and summarized using descriptive statistics. Other parameters may be calculated, if deemed necessary

Concentration data from all sparse and intensive plasma PK samples may be pooled with data from future studies and may be used for estimation of population PK parameters.

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.

10.6. Antiviral Activity Analysis

For Parts B, C, and D, selected data relating to the antiviral activity of VIR-3434, such as HBsAg, anti-HBs, HBeAg, anti-HBe, HBV RNA, HBcrAg, 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 (defined as undetectable HBsAg measured on 2 separate, consecutive occasions, at least 2 weeks apart) will be provided by cohort and study visit.

10.7. Immunogenicity Analysis

For all study parts, immunogenicity data will be listed and summarized using descriptive statistics, including rates, titers, and neutralization data, as applicable.

Correlations between immunogenicity data and safety, efficacy, and PK data will be explored. These analyses may include graphical plots, tabular summaries, and various linear and/or nonlinear analyses. Details of immunogenicity analyses will be provided in the Statistical Analysis Plan

10.8. Sample Size

Up to 144 subjects (Part A: up to 40 subjects, Part B: up to 56 subjects, Part C: up to 24 subjects, and Part D: up to 24 subjects) are planned to complete the study. The sample size is based on practical consideration; no formal sample size calculation was conducted.

10.9. Statistical Analysis

The Statistical Analysis Plan (SAP) will be finalized prior to database lock and will include a detailed description of the statistical analyses. Prior to the final analysis, interim analyses may be conducted, and the analyses may be submitted for publication or to regulatory agencies to seek guidance for the overall clinical development program.

11. RESPONSIBILITIES

11.1. Investigator and Sponsor Responsibilities

11.1.1. 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.

11.1.2. 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.

11.1.3. 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.

11.1.4. 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.

11.1.5. 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.

11.1.6. 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.

11.1.7. 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.

11.1.8. 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 reported according to the protocol, GCP guidelines of ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the clinical investigative site to perform audits or inspections, including source data verification. The investigator should contact the Sponsor, or its designee, immediately if contact by a regulatory agency about an inspection.

11.1.9. Protocol Compliance

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

11.1.10. 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.

11.1.11. 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 11.1.3).

The investigator will submit to the Sponsor 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.

11.2. 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.

11.2.1. Study Termination

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

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APPENDIX 1. INVESTIGATOR SIGNATURE PAGE

**VIR BIOTECHNOLOGY, INC
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SAN FRANCISCO, CA 94158**

STUDY ACKNOWLEDGMENT

**A Phase 1, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability,
Pharmacokinetics, and Antiviral Activity of VIR-3434**

VIR-3434-1002, Amendment 4, 20 January 2022

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

PPD


{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 ASSESSMENTS FOR SAD COHORTS IN HEALTHY ADULT SUBJECTS

Part A											
		Inpatient ^a			Outpatient						
Study Stage	Screening	Dosing Day	Post-dose Follow-up Period								
Study Visit Week					W1	W2	W4	W8	W12	W18	W24/ET ^b
Study Visit Day±Visit Window	D -28 to -1	D1 ^c	D2	D4±1	D8±1	D15±2	D29±2	D57±7	D85±7	D127±7	D169±7
Informed consent	X										
Demography	X										
Medical history ^d	X										
Inclusion/exclusion criteria	X	X ^e									
Full physical examination ^f	X										X
Symptom-directed physical examination		X	X	X	X		X	X	X	X	
Body weight	X										
Height	X										
Vital signs ^g	X	X	X	X	X	X	X	X	X	X	X
Safety ECGs ^h	X	X	X	X	X						
Pregnancy test ⁱ	X	X					X	X	X	X	X
Screening viral serology ^j	X										
Liver Function Tests ^k	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry ^k	X	X	X	X	X	X	X	X	X	X	X

Part A											
		Inpatient ^a		Outpatient							
Study Stage	Screening	Dosing Day	Post-dose Follow-up Period								
Study Visit Week					W1	W2	W4	W8	W12	W18	W24/ET ^b
Study Visit Day±Visit Window	D -28 to -1	D1 ^c	D2	D4±1	D8±1	D15±2	D29±2	D57±7	D85±7	D127±7	D169±7
Hematology ^k	X	X	X	X	X	X	X	X	X	X	X
Coagulation Parameters ^k	X	X			X		X	X	X		X
Urinalysis ^k	X										
Urine for drugs of abuse ^l	X	X									
Randomization		X									
Study drug administration ^m		X									
Blood samples for PK analysis ⁿ		X	X	X	X	X	X	X	X	X	X
Blood samples for immunogenicity analysis ^o		X				X	X	X	X	X	X
Local tolerability ^p		X	X	X	X						
Review/record AEs ^q	X										
Concomitant medications	X										

AE = adverse event; 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 before the blood sample collections.

^a Subjects may be admitted to the clinical investigative site on Day -1 or Day 1 and will be discharged following the completion of the Day 2 assessments.

^b If a subject withdraws prematurely from the study prior to the Week 24 visit, Week 24/ET assessments should be performed.

^c Assessments performed predose unless otherwise specified.

^d Complete medical history will be taken at screening and any changes should be updated prior to dosing.

^e Prior to study drug administration on Day 1, subject eligibility will be confirmed.

^f See Section 8.3 for assessments to be performed during a full physical examination.

- ^g Vital signs (blood pressure, pulse rate, respiratory rate and temperature [oral preferred]) should be measured after the subject has rested comfortably for approximately 10 minutes. On Day 1, vital signs should be measured within 2 hours prior to dose and at 2 hours (+/- 1 hour) post-dose (SC administration only) or 2 hours (+/- 1 hour) post-end of infusion (IV administration only). On all other visit days, vital signs are only required to be recorded once during the visit.
- ^h All ECGs should be measured in the supine position after the subject has rested comfortably for approximately 10 minutes. On Day 1, 12-lead safety ECGs will be recorded predose (within 30 minutes prior to dose) and at 2 hours (+/- 1 hour) post-dose (SC administration only) or 2 hours (+/- 1 hour) post-end of infusion (IV administration only). Additionally, ECGs on Day 4 and Day 8 only need to be collected for subjects receiving study drug by SC administration.
- ⁱ WOCBP are required to have pregnancy tests. A blood pregnancy test will be performed at screening and a urine pregnancy test will be performed thereafter. The pregnancy test scheduled for Day 1 may be performed on Day -1 per local practices. Negative pregnancy test must be confirmed prior to study drug administration.
- ^j See Section 8.10 for viral serology parameters.
- ^k Clinical laboratory and urinalysis parameters are described in Appendix 9 .
- ^l Drugs of abuse included in the screen are described in Section 8.14. Collection of urine for drugs of abuse scheduled for Day 1 may be performed on Day -1 per local practices. Results for drugs of abuse must be reviewed prior to dosing. Local drugs of abuse assessment will be confirmed by central testing, but local results will be used for determination of eligibility.
- ^m Study drug will be administered via IV infusion or SC injection as described in Section 7.3.5 .
- ⁿ On Day 1, for subjects receiving study drug by SC injection, blood samples for PK analysis will be collected predose and at 1 hour, 4 hours, and 6 hours post-dose. On Day 1, for subjects receiving study drug by IV infusion, blood samples for PK analysis will be collected predose, at end of infusion, and 1, 4 and 6 hours post end of infusion.
- ^o Includes samples for ADA and neutralizing antibodies (NAb), as applicable. Additional unscheduled samples for immunogenicity analysis may be collected if an immunologic related event is suspected. Immunogenicity sampling beyond the planned follow-up period may occur based on emerging results. Further details can be found in Section 8.16 .
- ^p Local tolerability only needs to be assessed for subjects who are administered study drug by SC injection. On Day 1, local tolerability should be assessed at approximately 1 hour post-dose. At the discretion of the investigator, unscheduled visits are permitted as needed for follow up of any unresolved local tolerability symptoms.
- ^q All AEs related to screening activities must be collected starting at the time of consent; 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. Further details can be found in Section 9.3.

APPENDIX 3. PART B, C, AND D SCHEDULE OF ASSESSMENTS FOR SAD COHORTS IN SUBJECTS WITH CHRONIC HBV INFECTION WITHOUT CIRRHOSIS

Part B, C, and D														
Study Stage	Screening	Dosing Day ^a	Post-dose Follow-up Period							Extended Follow-up Period ^b				
Study Visit Week					W1		W2	W4	W8/ET ^c	W12	W16	W24	W32	W40 / EF ^d
Study Visit Day±Visit Window	D -42 to -1	D1 ^e	D2	D4+1	D8±1	D11±1	D15±2	D29±2	D57±7	D85 ±7	D113 ±7	D169 ±7	D225 ±7	D281 ±7
Informed consent	X													
Demography	X													
Medical history including HBV genotype ^f	X													
Inclusion/exclusion criteria	X	X ^g												
Full physical examination ^h	X			X					X					
Symptom-directed physical examination		X	X		X		X	X						
Body weight	X													
Height	X													
Vital signs ⁱ	X	X	X	X	X		X	X	X					
Safety ECGs ^j	X													
Pregnancy test ^k	X	X						X	X	X	X	X	X	X
FibroScan ^l	X													
Screening viral serology ^m	X													
Liver Function Tests ⁿ	X	X	X	X	X		X	X	X	X	X	X	X	X
Serum Chemistry ⁿ	X	X	X	X	X		X	X	X	X	X	X	X	X

Part B, C, and D														
Study Stage	Screening	Dosing Day ^a	Post-dose Follow-up Period							Extended Follow-up Period ^b				
Study Visit Week					W1		W2	W4	W8/ET ^c	W12	W16	W24	W32	W40 / EF ^d
Study Visit Day±Visit Window	D -42 to -1	D1 ^e	D2	D4+1	D8±1	D11±1	D15±2	D29±2	D57±7	D85 ±7	D113 ±7	D169 ±7	D225 ±7	D281 ±7
Hematology ⁿ	X	X	X	X	X		X	X	X					
Coagulation Parameters ⁿ	X	X	X	X	X		X	X	X					
Complement testing ^{n,o}		X			X		X							
Urinalysis ^{n,o}	X	X			X		X							
Urine for drugs of abuse ^p	X													
Study drug administration ^q		X												
Blood samples for PK analysis ^r		X	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for immunogenicity analysis ^s		X					X	X	X	X	X	X	X	X
Blood sample for quantitative HBsAg	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for anti-HBs	X				X		X	X	X	X	X	X	X	X
Blood sample for HBeAg qualitative	X								X ^t					X ^t
Blood sample for HBeAg quantitative ^t		X						X	X					X
Blood sample for anti-HBe		X							X					X
Blood sample for HBV RNA quantitation and HBcrAg quantitation		X						X	X	X		X	X	X

Part B, C, and D															
Study Stage	Screening	Dosing Day ^a	Post-dose Follow-up Period							Extended Follow-up Period ^b					
Study Visit Week					W1		W2	W4	W8/ET ^c	W12	W16	W24	W32	W40 / EF ^d	
Study Visit Day±Visit Window	D -42 to -1	D1 ^e	D2	D4+1	D8±1	D11±1	D15±2	D29±2	D57±7	D85 ±7	D113 ±7	D169 ±7	D225 ±7	D281 ±7	
Blood sample for HBV DNA quantitation ^u	X	X	X ^v	X ^v	X	X ^v	X	X	X	X	X ^v	X	X ^v	X	
Blood sample for analysis of peripheral immune responses ^w		X			X		X	X	X	X		X		X	
Blood sample for RNA Paxgene tube ^x		X			X		X	X	X	X		X		X	
HBV resistance surveillance ^{u,y}		X			X		X	X	X	X	X	X	X	X	
Blood sample for Fc gamma receptor genotyping and for immunoglobulin allotyping		X													
CCI															
Local tolerability ^{aa}		X	X	X	X										
Review/record AEs ^{bb}	X									X					
Concomitant medications								X							
NRTI medication adherence ^{cc}								X							

AE = adverse event; ECG = electrocardiogram; EF = end of follow-up; ET = end of treatment; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; 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 before the blood sample collections.

- ^a Subjects may be admitted to the clinical investigative site on Day -1 or 1 and discharged after all study assessments are performed on Day 1. Patients must be monitored through at least 6 hours post-dose prior to discharge.
- ^b Following Week 8, subjects with > 2-fold HBsAg reduction at Week 8 should be followed for up to 40 weeks or until the reduction in HBsAg is < 2-fold relative to baseline at 2 consecutive collections, whichever occurs first. The extended follow-up may be discontinued at the Sponsor's discretion based on emerging data.
- ^c If a subject withdraws participation prematurely from the study prior to the Week 8 visit, Week 8/ET assessments should be performed.
- ^d If a subject withdraws participation prematurely from the study after the Week 8 visit and prior to the Week 40 visit, Week 40/EF assessments should be performed.
- ^e Assessments performed predose unless otherwise specified.
- ^f A complete medical history will be taken at screening. Any changes should be updated prior to dosing. HBV genotype information will also be collected, if available. For subjects with HBV DNA > 500 IU/mL, viral sequencing from the HBV resistance surveillance sample may be used to determine genotype.
- ^g Prior to study drug administration on Day 1, subject eligibility will be confirmed.
- ^h See Section 8.3 for assessments to be performed during a full physical examination.
- ⁱ Vital signs (blood pressure, pulse rate, respiratory rate and temperature [oral preferred]) should be measured after the subject has rested comfortably for approximately 10 minutes. On Day 1, vital signs should be measured within 2 hours prior to dose, at 2 hours post-dose (+/- 1 hour), and at 6 hours post-dose (+/- 1 hour). On all other visit days, vital signs are only required to be recorded once during the visit.
- ^j ECGs should be measured in the supine position after the subject has rested comfortably for approximately 10 minutes.
- ^k WOCBP are required to have pregnancy tests. A blood pregnancy test will be performed at screening and a urine pregnancy test will be performed thereafter. Negative pregnancy test must be confirmed prior to study drug administration.
- ^l 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.
- ^m See Section 8.10 for viral serology parameters.
- ⁿ Clinical laboratory and urinalysis parameters are described in Appendix 9.
- ^o Additional samples may be collected at any time post-dosing if immune-complex disease is suspected.
- ^p Drugs of abuse included in the screen are described in Section 8.14.
- ^q Study drug will be administered via SC injection as described in Section 7.3.5 .
- ^r On Day 1, blood samples for PK analysis will be collected predose and at 1 hour, 4 hours, and 6 hours post-dose. Includes samples for free and total PK assays, as applicable.
- ^s Includes samples for ADA and neutralizing antibodies (NAb), as applicable. Additional unscheduled samples for immunogenicity analysis may be collected if an immunologic related event is suspected. Immunogenicity sampling beyond the planned follow-up period may occur based on emerging results. Further details can be found in Section 8.16 .
- ^t Should only be collected for Part C and D subjects who are HBeAg qualitative positive at screening.
- ^u If a subject experiences ALT flare (as defined by >2-fold increase in ALT relative to Day 1 predose ALT), additional HBV DNA quantitation and HBV resistance surveillance sample(s) may be collected
- ^v HBV DNA samples at the Day 2 Day 4 Week 8 and Week 40 will be collected as directed

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needed for follow up of any unresolved local tolerability symptoms.

^{bb} All AEs related to screening activities must be collected starting at the time of consent; 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. All AEs will be collected through the Week 8/ET visit. Following Week 8, only targeted AEs and SAEs need to be collected through the end of the study. Further details can be found in Section 9.3 .

^{cc} For Parts B and C only; NRTIs will be continued through the end of follow-up for each subject. Subjects in Part D will not receive NRTI therapy.

**APPENDIX 4. PART A PHARMACOKINETIC TIMEPOINTS
 (SC INJECTION)**

Study Day \pm window in days (Study Week)	Protocol Time	Blood PK (serum)
Day 1	Predose	X
	Dose	
	1 hour	X
	4 hours	X
	6 hours	X
Day 2	24 hours	X
Day 4 \pm 1		X
Day 8 \pm 1 (Week 1)		X
Day 15 \pm 2 (Week 2)		X
Day 29 \pm 2 (Week 4)		X
Day 57 \pm 7 (Week 8)		X
Day 85 \pm 7 (Week 12)		X
Day 127 \pm 7 (Week 18)		X
Day 169 \pm 7 (Week 24)		X

**APPENDIX 5. PART A PHARMACOKINETIC TIMEPOINTS
 (IV INFUSION)**

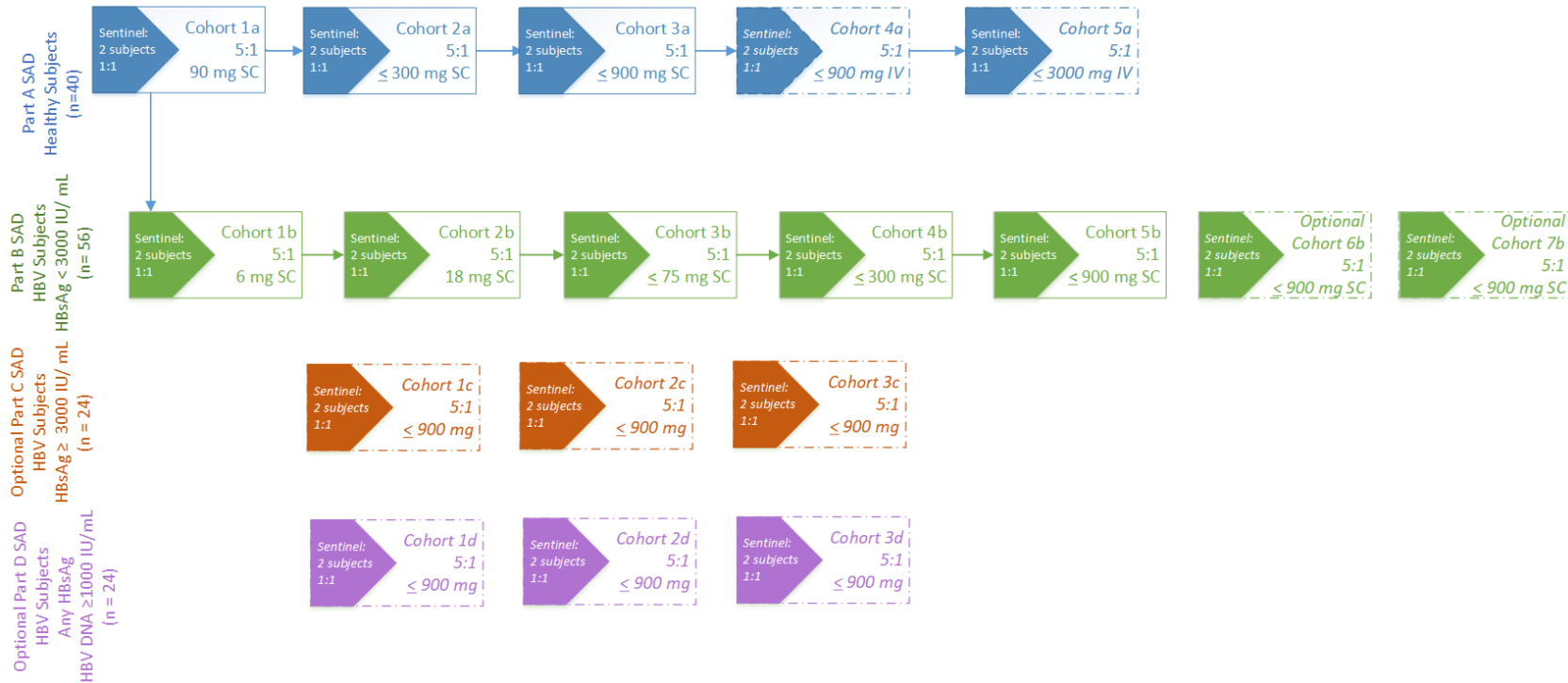
Study Day \pm window in days (Study Week)	Protocol Time	Blood PK (serum)
Day 1	Predose	X
	Dose	
	End of infusion	X
	1 hour post-end of infusion	X
	4 hours post-end of infusion	X
	6 hours post-end of infusion	X
Day 2	24 hours post-end of infusion	X
Day 4 \pm 1		X
Day 8 \pm 1 (Week 1)		X
Day 15 \pm 2 (Week 2)		X
Day 29 \pm 2 (Week 4)		X
Day 57 \pm 7 (Week 8)		X
Day 85 \pm 7 (Week 12)		X
Day 127 \pm 7 (Week 18)		X
Day 169 \pm 7 (Week 24)		X

APPENDIX 6. PARTS B, C, AND D PHARMACOKINETIC TIMEPOINTS

Study Day \pm window in days (Study Week)	Protocol Time	Blood PK (serum)
Day 1	Predose (-1 h)	X
	Dose	
	1 hour (± 5 min)	X
	4 hours (± 30 min)	X
	6 hours (± 30 min)	X
Day 2	24 hours (± 2 h)	X
Day 4 + 1		X
Day 8 \pm 1 (Week 1)		X
Day 11 \pm 1		X
Day 15 \pm 2 (Week 2)		X
Day 29 \pm 2 (Week 4)		X
Day 57 \pm 7 (Week 8)		X
Day 85 \pm 7 (Week 12)		X
Day 113 \pm 7 (Week 16)		X
Day 169 \pm 7 (Week 24)		X
Day 225 \pm 7 (Week 32)		X
Day 281 \pm 7 (Week 40)		X

APPENDIX 7. DOSING SCHEDULE

VIR-3434-1002 Cohort
Dosing Schedule



*The Part B optional cohorts may be dosed at a lower, equivalent, or intermediate dose level relative to the dose levels explored in the planned Part B cohorts, or after cohort 5b at a dose level not exceeding 900 mg.

** Parts C and D may be enrolled after SRC review of available data for all subjects in Part A and Part B through the Week 4 visit for the cohort of subjects in Part B who received a matching or higher dose relative to the proposed starting dose level in Part C and/or D.

APPENDIX 8. ANAPHYLAXIS, CYTOKINE RELEASE SYNDROME, AND IMMUNE COMPLEX DISEASE SUPPORTIVE MEASURES

The following equipment or agents may be needed in the event of a suspected anaphylactic reaction or cytokine release syndrome:

- ECG monitor
- Blood pressure monitor
- Oxygen saturation monitor
- Thermometer
- Tourniquet
- Oxygen
- Mechanical ventilator
- Renal replacement therapy
- IV infusion solutions, tubing, catheters, and tape
- Fresh-frozen plasma and/or cryoprecipitate
- Epinephrine
- Antihistamines, such as diphenhydramine
- Corticosteroids, such as hydrocortisone, prednisolone, and methylprednisolone

The following are procedures that may be followed in the event of a suspected anaphylactic reaction or cytokine release syndrome:

- Maintain an adequate airway
- Stop study drug infusion (if administering by IV infusion and reaction occurs during infusion)
- Call for additional medical assistance
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug (if administering by IV infusion and reaction occurs during infusion). Do not obstruct arterial flow in the limb.
- Ensure appropriate monitoring is in place, such as continuous ECG and pulse oximetry monitoring
- Administer epinephrine, antihistamines, corticosteroids or other medications/products as necessary based on the status of the subject and as directed by the physician
- Draw local laboratory samples as appropriate, possibly including evaluation of cytokines

The following equipment or agents that may be needed in the event of suspected immune complex disease:

- Thermometer
- Analgesic and antipyretic agents, such as non-steroidal anti-inflammatory drugs (NSAIDs)
- Antihistamines, such as diphenhydramine
- Corticosteroids, such as prednisone and methylprednisolone
- In extreme cases, equipment for plasmapheresis may be needed

The following are procedures that may be followed in the event of suspected immune complex disease:

- Though unlikely to occur acutely, stop study drug infusion (if administering by IV infusion and reaction occurs during infusion)
- Ensure temperature is appropriately monitored
- Monitor for most common manifestations, including rheumatic (arthralgias) and dermatologic (pruritic rash) findings
- Administer NSAIDs, antihistamines, corticosteroids, or other medications/products as necessary based on the status of the subject and as directed by the physician
- Draw local laboratory samples as appropriate, possibly including complete blood count, erythrocyte sedimentation rate, C-reactive protein, urinalysis, serum chemistry, and evaluation of complement
- In extreme cases, plasmapheresis may be employed

APPENDIX 9. CLINICAL LABORATORY ASSESSMENTS

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	
Liver Function Tests	
Alkaline phosphatase (ALP)	Aspartate aminotransferase (AST)
Alanine aminotransferase (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 (WOCBP only)	
Beta-human chorionic gonadotropin	Urine pregnancy test
Screening Viral Serology	
Hepatitis B, C ^b , and Delta	Human immunodeficiency virus I and II

^aOnly required if ALT and/or AST is elevated >2x the predose Day 1 baseline value

^bSubjects in Parts B, C, and D with positive HCV screening serology may have HCV RT-PCR performed to determine eligibility

Signature Page for VV-CLIN-000053 v7.0

Approval Task	PPD
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Signature Page for VV-CLIN-000053 v7.0