A Phase 2 Multicenter, Randomized, Open-label Study to Investigate the Safety and Efficacy of BRII-835 (VIR-2218) and BRII-179 (VBI-2601) Combination Therapy for the Treatment of Chronic Hepatitis B Virus (HBV) Infection

NCT04749368

Protocol Amendment 1.1 (Version 2.1)

17 November 2021

Title

Protocol Title: A Phase 2 Multicenter, Randomized, Open-label Study to Investigate the Safety and Efficacy of BRII-835 (VIR-2218) and BRII-179 (VBI-2601) Combination Therapy for the Treatment of Chronic Hepatitis B Virus (HBV) Infection

Protocol Number: BRII-179-835-001

Compound: BRII-835 (VIR-2218); BRII-179 (VBI-2601)

Study Phase: II

Short Title: Study to Investigate the Safety and Efficacy of BRII-835 and BRII-179 Combination Therapy Treating Chronic HBV Infection

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Protocol Version: Amendment 1.1 (Version 2.1)

Approval Date: 17 November 2021

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Date (dd-mmm-yyyy)

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INVESTIGATOR AGREEMENT PAGE

For protocol number BRII-179-835-001

I confirm agreement to conduct the study in compliance with the protocol, *International Conference on Harmonisation Good Clinical Practices (ICH GCP)* as well as applicable local regulatory and ethical requirements.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout study.

Investigator Name: _____

_____ _____

Investigator Signature **Date** (dd/mm/yyyy)

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 1.1 (Version 2.1)	17 November 2021
Amendment 1 (Version 2.0)	04 March 2021
Original Protocol (Version 1.0)	21 October 2020

Amendment 1.1 (Version 2.1) 17 November 2021

Overall Rationale for the Amendment

All changes from this amendment are clarifications and non-substantial.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA)	Added footnote to specify sample collection for PBMC analysis.	Changes clarified that blood samples for PBMC isolation would be collected in the planned (defined in Section 5.1 Number of Participants) participants only.
Section 1.3.1	Applied the existing footnote g to symptom-directed physical exam.	Change clarified that weight would be collected during symptom-directed physical exam.
Section 4.1.1 Planned Cohorts and Dosing	Added clarifications to the duration of BRII-835 dosing period in each cohort.	Changes clarified that BRII-835 dosing period would be from Day 1 to Week 32.
Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Corrected wording for AE collection time period.	Changes clarified that medical occurrences beginning during the screening period that are deemed not related to the screening activities will be reported as medical history.
Section 9.4.2 Primary Endpoints	Clarified the definition of TEAEs.	Changes clarified that any AEs occurred or worsened following the first administration of study drug will be flagged as treatment emergent.

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ABBREVIATIONS

AAV	adeno-associated virus
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
anti-HBe	hepatitis B e-antigen antibody
anti-HBs	antibodies to hepatitis B surface antigen
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	events of clinical interest
EPO	erythropoietin
ET	early termination
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBcrAg	hepatitis B core-related antigen
HBeAg	hepatitis B e-antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
ICF	informed consent form
IFN-α	interferon-alpha
IM	intramuscular
IU	international units
kPa	kilopascal
Kg	kilogram
LLOQ	lower limit of quantification
m	meter
µg	microgram
ml	milliliter
mRNA	messenger RNA
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NrtI	nucleos(t)ide reverse transcriptase inhibitors
ULN	upper limit of normal
PBMC	peripheral blood mononuclear cell
PEG-IFN-α	pegylated interferon-alpha
pgRNA	pregenomic RNA
PK	pharmacokinetic
RNA	ribonucleic acid
siRNA	small interfering RNA
SC	subcutaneous
SoA	schedule of activities
SAE	serious adverse event
SRC	Safety Review Committee

WOCBP	women of child-bearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2 Multicenter, Randomized, Open-label Study to Investigate the Safety and Efficacy of BRII-835 (VIR-2218) and BRII-179 (VBI-2601) Combination Therapy for the Treatment of Chronic Hepatitis B Virus (HBV) Infection

Short Title: Study to Investigate the Safety and Efficacy of BRII-835 and BRII-179 Combination Therapy Treating Chronic HBV Infection

Rationale:

Combination therapies with differential mechanisms of actions on HBV is an encouraging strategy to achieve higher rates of HBsAg loss and ideally HBV surface antibody seroconversion. The present study will evaluate the efficacy and safety of a small interfering RNA (siRNA) (BRII-835 [VIR-2218]) in combination with a recombinant protein immunotherapeutic (BRII-179 [VBI-2601]) in participants with chronic HBV infection without cirrhosis receiving nucleos(t)ide reverse transcriptase inhibitors (NrtI) background therapy.

BRII-835 (VIR-2218) is an siRNA targeting a region of the HBV genome that is common to all HBV viral transcripts. siRNA can have multiple antiviral effects, including degradation of the pregenomic RNA (pgRNA), thus inhibiting viral replication, and degradation of all viral messenger RNA (mRNA) transcripts, thereby preventing expression of viral proteins. This may result in the return of a functional immune response directed against HBV, either alone or in combination with other therapies. Additionally, it is postulated that the recombinant protein immunotherapeutic, BRII-179 (VBI-2601), may break immunological tolerance and restore and/or augment adaptive T cell and antibody responses to the surface antigens. These responses together have the potential to achieve a functional cure of chronic HBV infection.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate safety, efficacy, and dose regimens of combination BRII-835 (VIR-2218) and BRII-179 (VBI-2601) therapy	• Percentage of participants with sustained HBsAg loss (defined as undetectable HBsAg for at least 24 weeks) during the 48-week follow-up period after NrtI withdrawal • Number of participants with adverse events (AEs) and serious adverse events (SAEs) (up to Week 96) • Number of participants with abnormalities in clinical laboratory tests (up to Week 96)
Secondary	

To assess the antiviral activity of combination BRII-835 (VIR-2218) and BRII-179 (VBI-2601) therapy	• Percentage of participants meeting the NrtI withdrawal criteria at Week 44 • Percentage of participants with HBsAg loss with or without anti-HBs seroconversion at Week 72 • Percentage of participants with HBsAg loss at any timepoint • Percentage of participants with HBsAg seroconversion at any timepoint • Change from baseline in serum HBsAg at Week 72 • Percentage of participants with Hepatitis B e-antigen (HBeAg) loss and/or Hepatitis B e-antigen antibody (anti-HBe) seroconversion at Week 44 in those that are HBeAg positive at screening • Time to achieve HBsAg seroclearance • Time to achieve HBsAg seroconversion • Time to achieve HBeAg seroconversion
To characterize the PK and to evaluate anti-drug antibody (ADA) to BRII-835 (VIR-2218)	• Evaluation of plasma exposure of BRII-835 (VIR-2218) and its metabolites • Evaluation of ADA to BRII-835 (VIR-2218)
To assess effect on HBV specific immunological markers	• Changes from baseline in serum appearance and/or titer of anti-HBs, CCI [redacted] at any timepoint.
Exploratory	
To assess effect on other HBV specific immunological responses	• Change from baseline in HBV specific cellular immunity at any timepoint • Change from baseline in CCI [redacted]
To assess other antiviral activity of the combination therapy	• Percentage of participants with HBsAg loss with or without anti-HBs seroconversion at 24 and 48 weeks after NrtI withdrawal • Percentage of participants with HBsAg loss with or without anti-HBs seroconversion at Week 72 in those continuing NrtI therapy • Frequency of virologic and clinical relapse 48 weeks after NrtI withdrawal. Virologic relapse is defined as > 1 log increase from baseline in HBV DNA levels measured at 2 consecutive study visits; clinical relapse is defined as virologic relapse AND ALT > 2x ULN.

	• Percentage of participants requiring NrtI retreatment within 48 weeks after NrtI withdrawal • Percentage of participants with undetectable HBV-DNA (HBV DNA < LLOQ and Target Not Detected) 24 and 48 weeks after NrtI withdrawal • Assessment of the effect on other markers of HBV infection including but not limited to CCI [redacted]

Overall Design

This is an open label, randomized, parallel-group study of combination treatment BRII-835 (VIR-2218) administered subcutaneously (SC) and BRII-179 (VBI-2601) administered intramuscularly (IM) to evaluate the safety and efficacy in non-cirrhotic; virologically suppressed adult participants with chronic HBV infection receiving NrtI as background therapy. Efficacy (including HBsAg loss) and safety (including AEs/SAEs, laboratory assessments and physical examination) will be assessed throughout the study.

The study will include three cohorts evaluating different dose regimens of BRII-835 (VIR-2218) and/or BRII-179 (VBI-2601) with or without IFN-α in combination with NrtI for treatment of chronic HBV infection. Eligible participants will be stratified by their HBeAg status at screening. Eligible participants will be randomized 1:2:2 to Cohort A, B, or C. The study design schema can be found in Section 1.2.

Estimated total duration for each participant will include the following: screening (up to 6 weeks), dosing period (32 weeks [Cohort A], 40 weeks [Cohort B and Cohort C]), and follow-up period (40 weeks [Cohort A], 32 weeks [Cohort B and Cohort C]). Eligible participants that meet NrtI withdrawal criteria at Week 44 may enter a NrtI discontinuation monitoring period (48 weeks) from Week 48.

Number of Participants:

A total of 10 evaluable adult participants are planned for Cohort A. 20 evaluable adult participants are planned for both Cohort B and C, respectively. Up to 60 floater participants may be enrolled as expansion to the existing cohort(s).

Intervention Groups and Duration:

Eligible participants will receive the study intervention, BRII-835 (VIR-2218) alone or BRII-835 (VIR-2218) and BRII-179 (VBI-2601) as combination treatment, per the following dose regimens:

- **Cohort A:** Each participant will receive 9 doses of BRII-835 (VIR-2218) 100 mg administered SC every 4 weeks, from Day 1 to Week 32.

- **Cohort B:** Each participant will receive 9 doses of BRII-835 (VIR-2218) 100 mg administered SC every 4 weeks, from Day 1 to Week 32; and will receive 9 doses of BRII-179 (VBI-2601) 40 µg with IFN-α 3 MIU administered IM every 4 weeks, from Week 8 to Week 40.

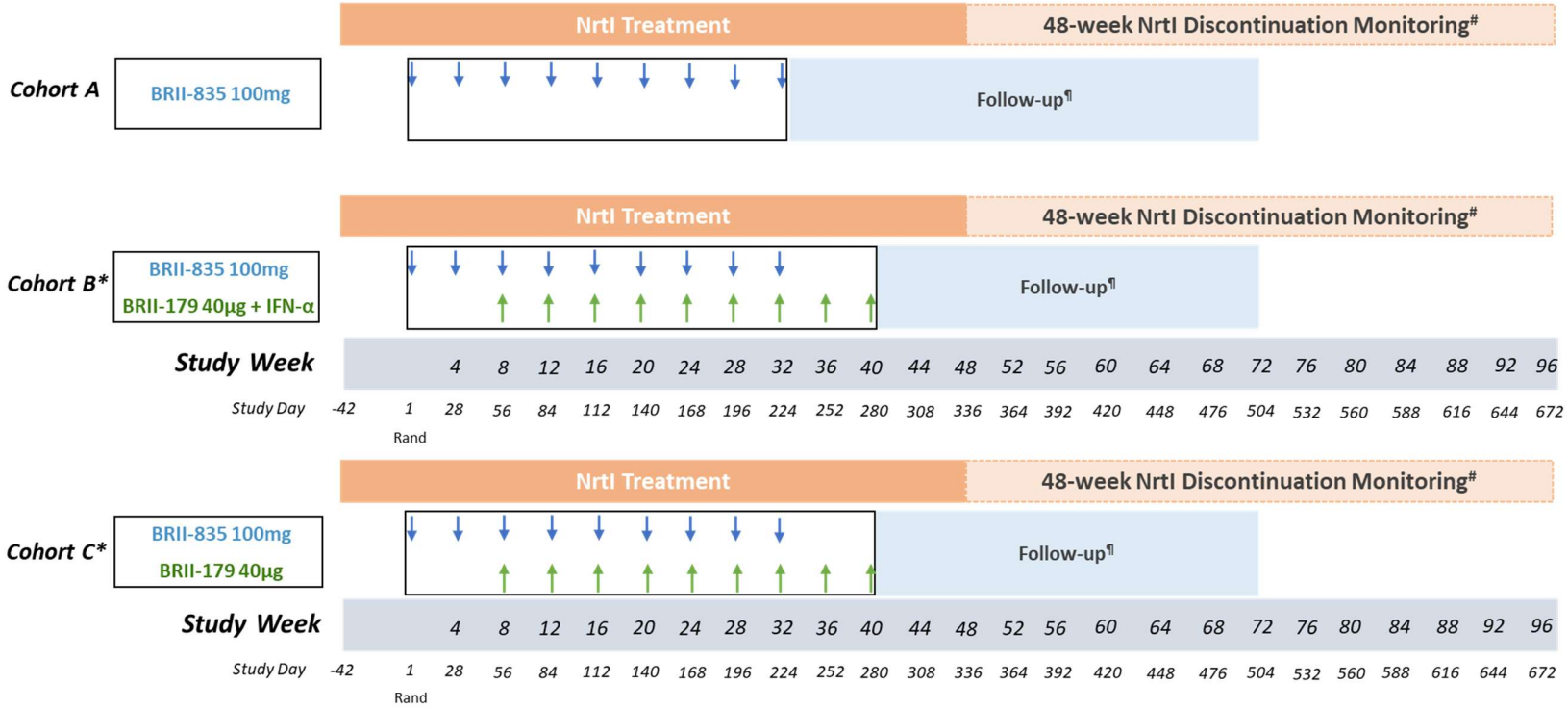
- **Cohort C:** Each participant will receive 9 doses of BRII-835 (VIR-2218) 100 mg administered SC every 4 weeks, from Day 1 to Week 32; and will receive 9 doses of BRII-179 (VBI-2601) 40 µg administered IM every 4 weeks, from Week 8 to Week 40.

Safety Review Committee

An SRC for this study will monitor participant safety and consider study-specific data as well as relevant background information about the study drugs and target population under study to inform on study discontinuation, the addition of "floaters", and adjudication of liver flare.

Disclosure Statement: This is a phase II, randomized, open-label, parallel-group study to evaluate the safety and efficacy of BRII-835 (VIR-2218) and BRII-179 (VBI-2601) combination therapy for the treatment of chronic HBV infection. All references to "Sponsor" contained herein shall refer to Brii Biosciences.

1.2. Schema



NrtI = nucleos(t)ide reverse transcriptase inhibiton; Rand = Randomization

#NrtI Discontinuation Monitoring: Participants who meet the NrtI Discontinuation Criteria at Week 44 may be eligible to discontinue from NrtI therapy and enter into the NrtI Discontinuation Monitoring Period on the first day of Week 48.

¶Participants that have NOT achieved NrtI discontinuation criteria by Week 44 will be discharged from the study after completion of all follow-up visits by Week 72.

***Floater Participants:** Up to 60 participants may be added to any existing cohort(s) as expansions of the existing cohort(s) if further data is required. The allocation of floater participants is not required to be distributed evenly.

1.3. Schedule of Activities (SoA)

1.3.1. Cohort A (32-week Dosing Period and 40-week Follow-up Period)

Study Stage	**Screen**	**Dosing Period (Cohort A)[b]**									**Follow-up Period[c, d]**			
Study Visit Week		Rand	W4	W8	W12	W16	W20	W24	W28	W32/ET	W36	W40	W44	W72/ET
Study Visit Day ± Visit Window	D -42 to -1	D1[a]	D28 ± 3	D56 ± 3	D84 ± 3	D112 ± 3	D140 ± 3	D168 ± 3	D196 ± 3	D224 ± 3	D252 ± 5	D280 ± 5	D308 ± 5	D504 ± 7
Informed consent form (ICF)	X													
Inclusion/exclusion criteria	X	X[e]												
Demography	X													
Medical history including HBV genotype[f]	X													
Full physical exam[g]	X					X				X			X	X
Symptom-directed physical exam[g]		X	X	X	X		X	X	X		X	X		
FibroScan[h]	X													
Alcohol intake assessment[i]		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[j]	X	X				X				X				
12-lead ECG[k]	X	X								X				
Participant instructed to complete diary		X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X												
Urine for drugs abuse[l]	X													
Urine pregnancy test[m]		X	X	X	X	X	X	X	X	X			X	X
Serum pregnancy test[m]	X													
Safety Laboratory Assessments[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X												
Study drug administration[o]		X	X	X	X	X	X	X	X	X				
Screening viral serology	X													
Blood sample for PK analysis[p]		X								X				
Blood sample for ADA to BRII-835 (VIR-2218)		X				X				X			X	
Blood sample for HBsAg quantitative	X	X	X	X		X		X		X		X	X	X
Blood sample for anti-HBs quantitative	X	X				X		X		X		X	X	X
Blood sample for HBV DNA quantitative[q]	X	X				X		X		X			X	X
Blood sample for HBeAg qualitative	X									X[r]			X[r]	X[r]
Blood sample for anti-HBe qualitative[r]	X									X			X	X
Blood sample for CCI [redacted]		X								X				X
Blood sample for cell mediated immunity (PBMC)[s]		X		X				X	X		X		X	
Blood sample for CCI [redacted]		X				X		X		X		X	X	X

CCI [redacted]		←----------X----------→
Exploratory analyses[u]		←----------X----------→
Adverse event assessment[v]	←----------X----------→	
Concomitant medications review	←----------X----------→	
Nrtl medication adherence review	←----------X----------→	
ECI surveillance[w]		←----------X----------→

AE = adverse event; ECG = electrocardiogram; ET = early termination; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis e-antigen; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; Nrtl = nucleoside/nucleotide reverse transcriptase inhibitor; PBMC = peripheral blood mononuclear cells
Note: When scheduled at the same timepoints, the assessments of vital signs and 12-lead ECGs must be performed before blood sample collections.

[a] Assessments performed predose unless otherwise specified.
[b] If a participant withdraws prematurely from the study prior to their Week 32 visit or during Follow-up, ET assessments should be performed.
[c] Participants that meet Nrtl discontinuation criteria (Section 4.1.4.14.1.4.1) at Week 44 from that visit's laboratory results may discontinue Nrtl and enter into Nrtl Discontinuation Monitoring Period (Section 1.3.3) as Day 1 on the first day of their Week 48.
[d] Participants that have **NOT** achieved Nrtl discontinuation criteria (Section 4.1.4.1) by the Week 44 Visit will be discharged from the study after completion of all follow-up visits at Week 72.
[e] Evaluation of inclusion and exclusion criteria related to pregnancy testing, urine drug screen, medical history and concomitant medications prior to dosing.
[f] A complete medical history will be taken at screening including HBV genotype if available. Any changes should be updated prior to dosing.
[g] Height and weight will be recorded at screening. Body mass index will be calculated based on the measurements. Only weight will be collected afterwards.
[h] Not required if FibroScan available from 6 months before screening or liver biopsy available 1 year before screening that confirm absence of Metavir F3 fibrosis or F4 cirrhosis.
[i] Participants' alcohol intake will be recorded while on study.
[j] Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) should be measured after the participant has rested comfortably for approximately 10 minutes. On Day 1, vital signs should be measured within 2 hours predose and 4 hours (±30 minutes) post-dose. On all other visit days, vital signs are only required to be recorded once during the visit.
[k] 12-lead safety ECGs should be measured in the supine position after the participant has rested comfortably for 10 minutes.
[l] Drugs of abuse included in the screen are described in the inclusion/exclusion criteria. Screening results for drugs of abuse must be reviewed prior to dosing.
[m] Women of childbearing potential are required to have pregnancy tests. Negative pregnancy test must be confirmed prior to study drug administration. Urine pregnancy test results from local laboratory are acceptable.
[n] Safety laboratory assessment parameters are described in Section 10.2.
[o] Study drug BRII-835 will be administered via SC injection at Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, and Week 32.
[p] Blood samples for PK analysis will be collected at the timepoints listed in Section 8.2.9.
[q] If a participant experiences ALT flare (as defined by ALT > 2x ULN) or HBV DNA ≥ 500 IU/mL, additional HBV DNA quantitation sample(s) may be collected.
[r] Only for participants with positive baseline HBeAg.
[s] Blood sample for PBMC isolation will be collected in the planned (defined in Section 5.1 Number of Participants) participants only.
[t] Blood sample for CCI [redacted] sequencing will be collected once at Day 1. If a participant experiences HBV DNA ≥ 500 IU/mL at any visit, collect blood sample for HBV DNA sequencing at the next scheduled visit. HBV genome will be sequenced if HBV breakthrough is confirmed as defined by HBV DNA ≥ 500 IU/mL at two consecutive visits.
[u] Serum CCI [redacted] will be assessed using spare serum collected for serology testing. Details for sample collection, processing, and analysis will be provided in the Laboratory Manual.

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

[w] Participant will be monitored for clinical laboratory events of clinical interest (ECI) and additional assessments may be performed if indicated. ECI for this study include ALT > 3x ULN, if Day 1 predose ALT ≤ ULN; ALT > 2x baseline, if Day 1 predose ALT > ULN. See Section 8.2.8.

1.3.2. Cohort B/C (40-week Dosing Period and 32-week Follow-up Period)

Study Stage	**Screen**	**Dosing Period (Cohort B)[b]**											**Follow-up Period[c, d]**			
Study Visit Week		Rand	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40/ET	W44	W48	W52	W72/ET
Study Visit Day ± Visit Window	D -42 to -1	D1[a]	D28 ± 3	D56 ± 3	D84 ± 3	D112 ± 3	D140 ± 3	D168 ± 3	D196 ± 3	D224 ± 3	D252 ± 3	D280 ± 3	D308 ± 5	D336 ± 5	D364 ± 5	D504 ± 7
Informed consent form (ICF)	X															
Inclusion/exclusion criteria	X	X[e]														
Demography	X															
Medical history including HBV genotype[f]	X															
Full physical exam[g]	X						X					X			X	X
Symptom-directed physical exam[g]		X	X	X	X	X		X	X	X	X		X	X		
FibroScan[h]	X															
Alcohol intake assessment[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[j]	X	X					X					X				
12-lead ECG[k]	X	X										X				
Participant instructed to complete diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X														
Urine for drugs abuse[l]	X															
Urine pregnancy test[m]		X	X	X	X	X	X	X	X	X	X	X			X	X
Serum pregnancy test[m]	X															
Safety Laboratory Assessments[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X														
Study drug administration[o]		X	X	X	X	X	X	X	X	X	X	X				
Screening viral serology	X															
Blood sample for PK analysis[p]		X								X						
Blood sample for ADA to BRII-835		X				X				X			X			
Blood sample for HBsAg quantitative	X	X	X	X		X		X		X		X	X		X	X
Blood sample for anti-HBs quantitative	X	X				X		X		X		X	X		X	X
Blood sample for HBV DNA quantitative[q]	X	X				X		X		X			X		X	X
Blood sample for HBeAg qualitative	X									X[r]			X[r]			X[r]
Blood sample for anti-HBe qualitative[r]	X									X			X			X
Blood sample for CCI [redacted]		X								X						X
Blood sample for cell mediated immunity (PBMC)[s]		X		X				X	X		X		X			
Blood sample for CCI [redacted]		X				X		X		X		X	X		X	X

CCI [redacted]		←----------X----------→
Exploratory analyses[u]		←----------X----------→
Adverse event assessment[v]	←----------X----------→	
Concomitant medications review	←----------X----------→	
Nrtl medication adherence review	←----------X----------→	
ECI surveillance[w]		←----------X----------→

AE = adverse event; ECG = electrocardiogram; ET = early termination; CCI [redacted]; HBeAg = hepatitis e-antigen; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; Nrtl = nucleoside/nucleotide reverse transcriptase inhibitor; PBMC = peripheral blood mononuclear cells
Note: When scheduled at the same timepoints, the assessments of vital signs and 12-lead ECGs must be performed before blood sample collections.

a Assessments performed predose unless otherwise specified.
b If a participant withdraws prematurely from the study prior to their Week 40 visit or during Follow-up, ET assessments should be performed.
c Participants that meet Nrtl discontinuation criteria (Section 4.1.4.1) at Week 44 from that visit's laboratory results may discontinue Nrtl and enter into Nrtl Discontinuation Monitoring Period (Section 1.3.3) on the first day of Week 48.
d Participants that have **NOT** achieved Nrtl discontinuation criteria (Section 4.1.4.1) by the Week 44 Visit will be discharged from the study after completion of all follow-up visits at Week 72.
e Evaluation of inclusion and exclusion criteria related to pregnancy testing, urine drug screen, medical history and concomitant medications prior to dosing.
f A complete medical history will be taken at screening including HBV genotype if available. Any changes should be updated prior to dosing.
g Height and weight will be recorded at screening. Body mass index will be calculated based on the measurements. Only weight will be collected afterwards.
h Not required if FibroScan available from 6 months before screening or liver biopsy available 1 year before screening that confirm absence of Metavir F3 fibrosis or F4 cirrhosis.
i Participants' alcohol intake will be recorded while on study.
j Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) should be measured after the participant has rested comfortably for approximately 10 minutes. On Day 1, vital signs should be measured within 2 hours predose and 4 hours (±30 minutes) post-dose. On all other visit days, vital signs are only required to be recorded once during the visit.
k 12-lead safety ECGs should be measured in the supine position after the participant has rested comfortably for 10 minutes.
l Drugs of abuse included in the screen are described in the inclusion/exclusion criteria. Screening results for drugs of abuse must be reviewed prior to dosing.
m Women of childbearing potential are required to have pregnancy tests. Negative pregnancy test must be confirmed prior to study drug administration. Urine pregnancy test results from local laboratory are acceptable.
n Safety laboratory assessment parameters are described in Section 10.2. Thyroid panel will only be collected at screening, Week 20, Week 32, and Week 72.
o Study drug BRII-835 will be administered via SC injection at Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, and Week 32. Study drug BRII-179 with IFN-α (Cohort B) or without IFN-α (Cohort C) will be administered via IM injection starting from Week 8 and every 4 weeks for 9 doses.
p Blood samples for PK analysis will be collected at the timepoints listed in Section 8.2.9.
q If a participant experiences ALT flare (as defined by ALT > 2x ULN) or HBV DNA ≥ 500 IU/mL, additional HBV DNA quantitation sample(s) may be collected
r Only for patients with positive baseline HBeAg.
s Blood sample for PBMC isolation will be collected in the planned (defined in Section 5.1 Number of Participants) participants only.
t Blood sample for CCI [redacted] will be collected once at Day 1. If a participant experiences HBV DNA ≥ 500 IU/mL at any visit, collect blood sample for HBV DNA sequencing at the next scheduled visit. HBV genome will be sequenced if HBV breakthrough is confirmed as defined by HBV DNA ≥ 500 IU/mL at two consecutive visits.
u Serum CCI [redacted] will be assessed using spare serum collected for serology testing. Details for sample collection, processing, and analysis will be provided in the Laboratory Manual.

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

[w] Participant will be monitored for clinical laboratory events of clinical interest (ECI) and additional assessments may be performed if indicated. ECI for this study include ALT > 3x ULN, if Day 1 predose ALT ≤ ULN; ALT > 2x baseline, if Day 1 predose ALT > ULN. See Section 8.2.8.

1.3.3. NrtI Discontinuation Monitoring Period

Study Stage	NrtI Discontinuation Monitoring Period[b,c]									
Study Visit Week		W4	W8	W12	W16	W20	W24	W32	W40	W48/ET
Study Visit Day ± Visit Window	D1[a]	D28 ± 3	D56 ± 3	D84 ± 3	D112 ± 7	D140 ± 7	D168 ± 7	D224 ± 7	D280 ± 7	D336 ± 7
Safety Laboratory Assessments[d]	X	X	X	X	X	X	X	X	X	X
Symptom-directed physical exam	X	X	X	X	X	X	X	X	X	X
Fibroscan										X
Pregnancy test		X	X							
Blood sample for HBsAg quantitative	X		X		X		X	X	X	X
Blood sample for anti-HBs quantitative	X		X		X		X	X	X	X
Blood sample for HBV DNA quantitative	X	X	X	X	X	X	X	X	X	X
Blood sample for [redacted]	X		X		X		X	X	X	X
Blood sample for cell mediated immunity (PBMC)[e]		X						X		
Blood sample for HBV sequence analysis[f]	X	X	X	X	X	X	X	X	X	X
Exploratory analyses[g]	←----------X----------→									
Concomitant medications	←----------X----------→									
Adverse event assessment	←----------X----------→									
NrtI retreatment surveillance[h]	←----------X----------→									
ECI surveillance[i]	←----------X----------→									

AE = adverse event; ECG = electrocardiogram; ECI = events of clinical interest; ET = early termination; [redacted]; HBeAg = hepatitis e-antigen; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; NrtI = nucleoside/nucleotide; PBMC = peripheral blood mononuclear cells

[a] All timepoints are relative to the day of NrtI discontinuation (D1) which is the first day the NrtI withdrawal eligible participant discontinuing their NrtI therapy.

[b] All participants who discontinue NrtI therapy will be followed through 48 weeks, even if NrtI retreatment occurs. If a participant withdraws prematurely from the study prior to the W48 visit, ET assessments should be performed.

[c] NrtI retreatment guidelines are provided in Section 4.1.4.1.

[d] Safety laboratory assessments are limited to liver function tests for participants from Cohort A. Participants from Cohort B or Cohort C will receive full safety laboratory assessments for Day 1 and Week 4 visits and liver function tests afterwards.

[e] Blood sample for PBMC isolation will be collected in the planned (defined in Section 5.1 Number of Participants) participants only.

[f] HBV sequence analysis may be performed if a participant experiences viral breakthrough (including but not limited to HBV DNA breakthrough) or is otherwise indicated.

[g] Samples collected for serology testing will be used to perform exploratory analyses [redacted]. Details for sample collection, processing, and analysis will be provided in the Laboratory Manual.

[h] Investigator should monitor participant for NrtI retreatment criteria. See Section 4.1.4.2.

[i] Participant will be monitored for clinical laboratory events of clinical interest (ECI) and additional assessments may be performed if indicated. ECI for this study include ALT > 3x ULN, if Day 1 predose ALT ≤ ULN; ALT > 2x baseline, if Day 1 predose ALT > ULN. See Section 8.2.8.

2. INTRODUCTION

2.1. Background

Chronic HBV infection remains an important global public health problem that leads to serious sequelae over time, including cirrhosis, liver failure, and hepatocellular carcinoma (Trepo, 2014). An estimated 290 million people are living with chronic HBV infection worldwide, and almost 800,000 people die annually due to associated sequelae (Stanaway, 2016).

Human HBV is a deoxyribonucleic acid (DNA) virus in the Hepadnaviridae family, with 10 HBV genotypes (A to J). The distribution of these genotypes varies geographically, with A and D being more common in Northern Europe, North America, and Western and Central Asia; and B and C being more common in Southeast Asia and China. HBV genotypes may influence disease progression rates and treatment response (Kramvis, 2014).

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

Current treatment options for chronic HBV infection are limited. One option is long-term Nucleoside reverse transcriptase inhibitors (NrtI) therapy, for example tenofovir (tenofovir disoproxil fumarate or tenofovir alafenamide) or entecavir (Lok, 2016). However, NrtI therapy does not result in a cure of HBV infection. The viral DNA is not cleared from the infected cell, and viral protein production, in particular the production of HBsAg, typically continues at high levels as measured in blood (Scaglione, 2012). These high levels of HBsAg subviral particles are proposed to mediate HBV-specific immune dysfunction by decoying and exhausting host cellular and humoral adaptive immune responses. Therefore, reduction or clearance of HBsAg from blood is considered central to achieving a functional cure (sustained loss of HBsAg in blood with or without seroconversion to the surface antigen antibody) and is considered an optimal outcome of treatment (Block, 2013). An alternative treatment option is a finite course of Pegylated Interferon α (PEG-IFN-α) therapy which can induce a functional cure, but only in a small percentage of patients (< 10%) (Konerman, 2016). Unfortunately, PEG-IFN-α therapy carries considerable risk of dose-limiting adverse events (AEs) which may be severe and/or serious, and discontinuation rates are significant (Perrillo, 2009).

The failure of NrtI therapy to produce a functional cure and the limitations of PEG-IFN-α therapy highlight the clinical need for effective, well-tolerated HBV therapies of finite duration.

To address this unmet need, Brii Biosciences in partnership with Vir Biotechnology, Inc. and VBI Vaccines Inc., is developing BRII-835 (VIR-2218) and BRII-179 (VBI-2601) for the treatment of chronic HBV infection. By enabling sequence-specific RNA cleavage and degradation, BRII-835 (VIR-2218) can have multiple antiviral effects, including inhibiting viral replication, translation, and secretion of HBsAg. Meanwhile, it is postulated that BRII-179 (VBI-2601) may break immunological tolerance and restore and/or augment adaptive T cell and antibody responses to the surface antigens. Thus, BRII-835 (VIR-2218) and BRII-179 (VBI-2601) as combination treatment have the potential to achieve a functional cure of chronic HBV infection.

2.2. Study Rationale

2.2.1. Rationale for BRII-835 (VIR-2218) for Treatment of Chronic HBV Infection

BRII-835 (VIR-2218) is an siRNA targeting a region of the HBV genome that is common to all HBV viral transcripts. The siRNA is chemically modified using Enhanced Stabilization Chemistry Plus (ESC+) consisting of 2'-fluoro (2'F), 2'-O-methoxy (2'OMe) ribose sugar modifications, phosphorothioate backbone modifications, glycol nucleic acid (GNA) modification, and conjugation to a triantennary N-acetyl-galactosamine ligand (GalNAc) at the 3' end of the sense strand, to facilitate delivery to hepatocytes through the asialoglycoprotein receptor (ASGPR). VIR-2218 is pharmacologically active against HBV genotypes A through J.

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

2.2.2. Rationale for BRII-179 (VBI-2601) with or without IFN-α for Treatment of Chronic HBV Infection

BRII-179 (VBI-2601) is a recombinant protein immunotherapeutic consisting of three HBsAg forms: small, middle and large proteins that form the HBV envelope. Large S protein contains the N-terminal preS1 and preS2 domains and the adjacent small S protein. The middle S protein contains preS2 and the adjacent small S protein.

It was hypothesized that high levels of circulating HBsAg lead to immune tolerance of HBV and contributed to chronic HBV infection. The preS1 domain contains several relatively conserved B and T helper cell epitopes (Milich, 1985; Milich, 1986), expressed at a much lower level than HBsAg, hence it may be more efficacious than recombinant small HBV envelope-based vaccines for breaking tolerance in chronic HBV patients (Bian, 2017). Therefore, BRII-179 (VBI-2601) utilizes preS1, preS2, and S protein components as the immunogen in a therapeutic application of preS1/S2 containing HBsAg. To have an effective T cell response, BRII-179 (VBI-2601) differs from Sci-B-Vac® and most of the recombinant envelope vaccines in using aluminium phosphate

as an adjuvant rather than aluminum hydroxide. Aluminum phosphate as adjuvant results in enhanced antigen specific Th1 T cell responses in preclinical studies. It also has been safely used as an adjuvant in several commercially available vaccines.

To further enhance the ability of BRII-179 (VBI-2601) to induce Th1 response, IFN-α has been selected and will be tested as an additional adjuvant. IFN-α is a cytokine with many antiviral activities and has been approved for treating chronic HBV infection.

The combination of HBV vaccines with IFN-α as an adjuvant rather than as a therapy has been explored in uninfected subjects. Improved antibody titers could be observed in immunocompromised or non-responder populations but not in healthy subjects (Grob, 1984; Goldwater, 1994; Rizza, 2008; Miquilena-Colina, 2009). In a recent study in an AAV-HBV mouse model of persistent HBV infection, BRII-179 demonstrated its ability to break the immune tolerance and to induce antigen specific immune responses. These BRII-179 induced HBV antigen specific immune responses were further enhanced by admixture with IFN-α.

In this study, IFN-α will be evaluated as a co-adjuvant to BRII-179 (VBI-2601) by co-administering as a single intramuscular injection. Based on the known mechanisms of action, there is no expected risk for pharmacodynamic drug-drug interactions or overlapping toxicities between IFN-α and BRII-179 (VBI-2601).

2.3. Benefit/Risk Assessment

This study will provide information on the safety, efficacy, and dose regimens of BRII-835 (VIR-2218) and BRII-179 (VBI-2601) combination therapy, which has the potential to functionally cure chronic HBV infection.

The safety profile of BRII-835 (VIR-2218) has been investigated in healthy adult participants and adult participants with chronic HBV infection without cirrhosis. Single dose of BRII-835 (VIR-2218) up to 600 mg in healthy adult volunteers and two doses of up to 200 mg administered every 4 weeks in participants with chronic HBV infection were well tolerated and exhibited safety profiles supportive of continued clinical development. PK simulations predict that liver concentrations resulting from the proposed BRII-835 (VIR-2218) regimens will not substantially exceed those associated with administration of a single 600 mg dose. Therefore, the safety profile of BRII-835 (VIR-2218) supports exploration of the proposed treatment regimens of BRII-835 (VIR-2218) 100 mg every 4 weeks for 9 doses.

In both HBeAg-negative and HBeAg-positive adult subjects with chronic HBV infection, dose levels of BRII-835 (VIR-2218) up to two 200 mg doses administered every four weeks were associated with substantial reductions in HBsAg but did not lead to HBsAg clearance or anti-HBs seroconversion. The proposed nine dose regimens for BRII-835 (VIR-2218) was designed to provide a greater magnitude and duration of HBsAg suppression than those that have been studied, i.e., two doses administered every four weeks, in order to maximize the probability of a favorable response.

Two dose levels of BRII-179 (VBI-2601), 20 µg and 40 µg, with or without IFN-α as an adjuvant, administered every 4 weeks for a total of 4 doses, have been evaluated in adult

participants with chronic HBV infection. Favorable safety and tolerability profiles were observed at both dose levels. Sci-B-Vac®, which contains the immunogenic compositions of BRII-179 (VBI-2601), was well tolerated in a study in CHB subjects at 20 μg, administered up to 8 doses, (Hoa, 2009). The significant reduction in IFN-α dose (approximately $1/10^{th}$ that used to treat chronic HBV infection) and dosing frequency administered as an adjuvant is anticipated to have an improved safety profile over therapeutic dosage.

In summary, the proposed combination therapy may reduce HBsAg effectively and induce HBV-specific immunity which may lead to the functional cure of chronic HBV infection. The safety profiles of BRII-835 (VIR-2218) and BRII-179 (VBI-2601) are supportive of the overall risk/benefit profile for the proposed dose regimens and treating durations.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of BRII-835 (VIR-2218) and BRII-179 (VBI-2601) may be found in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives

The primary objective is:

- To evaluate safety, efficacy, and dose regimens of combination BRII-835 (VIR-2218) and BRII-179 (VBI-2601) therapy.

The secondary objectives are:

- To assess the antiviral activity of combination BRII-835 (VIR-2218) and BRII-179 (VBI-2601) therapy.
- To characterize the PK and to evaluate anti-drug antibody ADA of BRII-835 (VIR-2218).
- To assess effect on HBV specific immunological markers.

The exploratory objectives are:

- To assess effect on other HBV specific immunological responses.
- To assess other antiviral activity of the combination therapy

3.2. Endpoints

3.2.1. Primary Endpoints

- Percentage of participants with sustained HBsAg loss (defined as undetectable HBsAg for at least 24 weeks) during the 48-week follow-up period after NrtI withdrawal
- Number of participants with Adverse Events (AE) and Serious Adverse Events (SAE) (up to Week 96)
- Number of participants with abnormalities in clinical laboratory tests (up to Week 96)

3.2.2. Secondary Endpoints

- Percentage of participants meeting the NrtI withdrawal criteria at Week 44
- Percentage of participants with HBsAg loss with or without anti-HBs seroconversion at Week 72
- Percentage of participants with HBsAg loss at any timepoint
- Percentage of participants with HBsAg seroconversion at any timepoint

- Change from baseline in serum HBsAg at Week 72
- Percentage of participants with Hepatitis B e-antigen (HBeAg) loss and/or Hepatitis B e-antigen antibody (anti-HBe) seroconversion at Week 44 in those that are HBeAg positive at screening
- Time to achieve HBsAg seroclearance
- Time to achieve HBsAg seroconversion
- Time to achieve HBeAg seroconversion
- Evaluation of plasma exposure of BRII-835 (VIR-2218) and its metabolites.
- Evaluation of ADA to BRII-835 (VIR-2218)
- Change from baseline in serum appearance and/or titer of anti-HBs, CCI [redacted] at any timepoint

3.2.3. Exploratory Endpoints

- Change from baseline in HBV specific cellular immunity at any timepoint
- CCI [redacted]
- Percentage of participants with HBsAg loss with or without anti-HBs seroconversion 24 and 48 weeks after NrtI withdrawal
- Percentage of participants with HBsAg loss with or without anti-HBs seroconversion at Week 72 in those continuing NrtI therapy
- Frequency of virologic and clinical relapse 48 weeks after NrtI withdrawal. Virologic relapse is defined as > 1 log increase from baseline in HBV DNA levels measured at 2 consecutive study visits; clinical relapse is defined as virologic relapse AND ALT > 2x ULN.
- Percentage of participants requiring NrtI retreatment within 48 weeks after NrtI withdrawal
- Percentage of participants with undetectable HBV-DNA (HBV DNA < LLOQ and Target Not Detected) 24 and 48 weeks after NrtI withdrawal
- Assessment of the effect on other markers of HBV infection including but not limited to CCI [redacted]

4. STUDY DESIGN

4.1. Overall Design

This is an open label, randomized, parallel-group study of combination treatment BRII-835 (VIR-2218) administered subcutaneously (SC) and BRII-179 (VBI-2601) administered intramuscularly (IM) to evaluate the safety and efficacy in non-cirrhotic; virologically suppressed adult participants with chronic HBV infection receiving NrtI as background therapy. Efficacy (including HBsAg loss) and safety (including AEs/SAEs, laboratory assessments and physical examination) will be assessed throughout the study.

The study will include three cohorts evaluating different dose regimens of BRII-835 (VIR-2218) and/or BRII-179 (VBI-2601) with or without IFN-α in combination with NrtI for treatment of chronic HBV infection. Eligible participants will be stratified by their HBeAg status at screening. Eligible participants will be randomized 1:2:2 to Cohort A, B, or C. A total of 10 evaluable adult participants are planned for Cohort A. 20 evaluable adult participants are planned for both Cohort B and C, respectively. Up to 60 floater participants may be enrolled as expansion to the existing cohort(s). The study design schema can be found in Section 1.2.

4.1.1. Planned Cohorts and Dosing

Eligible participants will receive the study intervention, BRII-835 (VIR-2218) alone or BRII-835 (VIR-2218) and BRII-179 (VBI-2601) as combination treatment, per the following dose regimens:

- **Cohort A:** Each participant will receive 9 doses of BRII-835 (VIR-2218) 100 mg administered SC every 4 weeks, from Day 1 to Week 32.
- **Cohort B:** Each participant will receive 9 doses of BRII-835 (VIR-2218) 100 mg administered SC every 4 weeks, from Day 1 to Week 32; and will receive 9 doses of BRII-179 (VBI-2601) 40 µg with IFN-α 3 MIU administered IM every 4 weeks, from Week 8 to Week 40.
- **Cohort C:** Each participant will receive 9 doses of BRII-835 (VIR-2218) 100 mg administered SC every 4 weeks, from Day 1 to Week 32; and will receive 9 doses of BRII-179 (VBI-2601) 40 µg administered IM every 4 weeks, from Week 8 to Week 40.

All participants will be followed per the SoAs (Section 1.3) for the safety, tolerability, and antiviral activity after completion of study intervention. Participants will be assessed by the investigator for their eligibility of NrtI discontinuation at Week 44. Participants that meet NrtI withdrawal criteria may enter a 48-week NrtI discontinuation monitoring period for additional follow-up of the efficacy and safety of study intervention. Participants that do not meet NrtI withdrawal criteria will be followed until Week 72.

Estimated total duration for each participant will include the following: screening (up to 6 weeks), dosing period (32 weeks [Cohort A], 40 weeks [Cohort B and Cohort C]), and follow-up period (40 weeks [Cohort A], 32 weeks [Cohort B and Cohort C]). Eligible

participants that meet NrtI withdrawal criteria at Week 44 may enter a 48-week NrtI discontinuation monitoring period from Week 48. Study assessments and procedures for each cohort are further described in Section 8.1.

4.1.2. Floater Participants

Based on SRC review of accumulated safety and efficacy data from planned cohorts, up to 60 floater participants may be added to expand any existing cohort(s) to further evaluate safety, efficacy, and dose regimens of combination therapy. The allocation of floater participants is not required to be distributed evenly.

4.1.3. Safety Review Committee

An SRC for this study will monitor participant safety and consider study-specific data as well as relevant background information about the study drugs and target population under study to inform on study discontinuation, the addition of "floaters", and adjudication of liver flare. Ad hoc SRC meetings may take place as needed and/or in the event an unexpected safety concern is identified.

The SRC charter outlining the member composition and operating procedures will be developed before the study starts. Each data element, triggers for data review, and guidelines for monitoring will be clearly defined.

4.1.4. NrtI Discontinuation

4.1.4.1. NrtI Discontinuation Criteria

The investigator will evaluate whether participants are eligible for discontinuation of NrtI therapy and will consider NrtI discontinuation in participants meeting the following criteria:

- HBeAg negative (HBeAg loss for participant with positive HBeAg at screening) AND
- HBsAg loss AND
- Alanine aminotransferase (ALT) < 2x Upper Limit of Normal (ULN) AND
- HBV DNA < Lower Limit of Quantification (LLOQ)

Participants who are eligible to discontinue from NrtI therapy may enter NrtI Discontinuation Period on the first day of Week 48. Participants who discontinue from their NrtI therapy will be followed in the NrtI Discontinuation Monitoring Period for an additional 48 weeks from the day of NrtI discontinuation. Participants discontinuing NrtI therapy will complete assessments of NrtI Discontinuation Monitoring Period (Section 1.3.3).

4.1.4.2. NrtI Retreatment

It is recommended that the Investigator should consider retreatment with NrtI therapy during the NrtI Discontinuation Monitoring Period if participants meet the following criteria at the same visit (based on Papatheodoridis, 2020):

- ALT > 15x ULN
- ALT 10-15x ULN: retreatment may be implemented at investigator's discretion
- ALT 5-15x ULN with elevated total bilirubin > 2 mg/dL (predominantly direct) and/or prolongation of prothrombin time (PT) ⩾ 3 seconds
- ALT 2-5x ULN and HBV DNA >2000 IU/mL persisting for ≥ 12 consecutive weeks
- ALT > 3x ULN and HBV DNA > 100 000 IU/mL at the same visit

Participants who are retreated with NrtI therapy should continue to be followed per the SoA Section 1.3.3 for the duration of the 48-week NrtI Discontinuation Monitoring Period.

4.2. Scientific Rationale for Study Design

This Phase II, open-label, randomized, parallel-group study will investigate the safety and efficacy of BRII-835 (VIR-2218) and BRII-179 (VBI-2601) combination therapy. The study design will provide an opportunity to determine the safety profile as well as the ability to meet NrtI discontinuation criteria with the proposed dose regimens of BRII-835 (VIR-2218) and BRII-179 (VBI-2601).

The expectation that all patients will adhere to long-term or lifelong noncurative treatment with NrtI is not realistic, and there is a strong patient preference for finite therapy options. New therapeutic strategies and novel drugs like BRII-835 (VIR-2218) and BRII-179 (VBI-2601) are anticipated to increase the likelihood of achieving functional cure. In addition, there is increasing evidence that low levels of quantitative HBsAg may improve the potential for HBsAg loss, and this is most evident in patients who lose HBsAg after stopping long-term NrtI therapy. Recently, it was observed that patients with decreasing HBsAg and a lower HBsAg level < 100 IU/mL at the end of treatment were able to maintain control of HBV after discontinuation of long-term NrtI therapy (Chang, 2015; Yao 2017; Jeng, 2018; Papatheodoridi, 2020).

Viral rebound may occur shortly after NrtI withdrawal in some cases, which requires close monitoring during study participation in order to control ALT flares. The HBV viral relapse after NrtI withdrawal may induce the host immune response and potentially a long-term immune control against the viral infection. Sustained HBsAg loss and/or virological response were observed in HBeAg-negative patients stopping NrtI therapy in prospective cohort studies (van Bömmel, 2017) as well as in a randomized controlled study (Berg, 2017). This study design allows the potential benefit from immune responses resulting from decreased viral antigen exposure after long-term NrtI cessation.

Surrogate endpoints of HBV functional cure measure biochemical, virological, and histological outcomes. Based on current knowledge, the best surrogate of HBV functional cure is HBsAg loss confirmed on 2 occasions at least 6 months apart without requirement for anti-HBs seroconversion plus undetectable HBV DNA (Cornberg, 2020). The incidence of sustained HBsAg loss and undetectable HBV DNA will be used as part of the secondary endpoints to assess the potential of combination therapy of BRII-835 (VIR-2218) and BRII-179 (VBI-2601) to induce functional cure.

The target population of this study is HBeAg-negative or HBeAg-positive non-cirrhotic patients with chronic HBV infection that has been virologically suppressed with NrtI therapy. This represents a patient population with acceptable heterogeneity who may have a higher likelihood of HBsAg loss.

4.3. Justification for Dose

Three cohorts are planned for this study to evaluate different dose regimens of BRII-835 (VIR-2218) and BRII-179 (VBI-2601), i.e. BRII-835 (VIR-2218) alone; BRII-835 (VIR-2218) in combination with BRII-179 (VBI-2601) with IFN-α as adjuvant; and BRII-835 (VIR-2218) in combination with BRII-179 (VBI-2601) without IFN-α as adjuvant.

It is believed that high levels of HBsAg have negative impact on immune profile and may tolerize or delete HBV specific T cells in CHB patients (Kondo, 2013; Ferrari, 2015; Lebosse, 2017; Wang, 2013). Reductions of HBsAg by therapeutic intervention have resulted in the ability of HBV vaccines to break tolerance and achieve functional cure in recombinant AAV/HBV infection murine models. In one study an antibody to HBsAg was used to transiently reduce circulating levels of HBsAg, HBsAg levels returned to baseline when antibody treatment ceased; but addition of a vaccine regimen while HBsAg levels were reduced resulted in sustained suppression of HBsAg after discontinuation of antibody treatment (Zhu, 2016). Another study used siRNA to reduce HBsAg levels prior to vaccination and the combination of siRNA and vaccine achieved functional cure, but either treatment by itself did not (Michler, 2018). These studies provide basis to treat chronic HBV patients for functional cure with a combination of BRII-179 and an agent such as BRII-835 (VIR-2218), an siRNA directed against HBV to lower HBsAg.

4.3.1.1. Dose Selection Consideration for BRII-835

Available safety, tolerability, PK, and antiviral activity data from the ongoing study VIR-2218-1001, as well as currently available nonclinical data were considered when selecting dose levels for BRII-835 (VIR-2218) in combination with BRII-179 in subjects with chronic HBV infection.

The plasma PK parameters for BRII-835 (VIR-2218) from healthy adult subjects in the part A of the study VIR-2218-1001 are summarized in **Table 1**. Available PK data from the chronic HBV patients in the Parts B-C (**Table 2**) of the study VIR-2218-1001 were similar to that observed in the healthy subjects in the part A. Due to the short $t_{½}$ of BRII-835 (VIR-2218) and PK sampling schedule limitations in HBV subjects, limited PK parameters were reportable.

Table 1 Summary of Key Plasma BRII-835 (VIR-2218) PK Parameters Following Single SC Dose in Healthy Subjects for The Part A of Study VIR-2218-1001

Parameter	BRII-835 (VIR-2218) 50 mg (N=6)	BRII-835 (VIR-2218) 100 mg (N=5)[a]	BRII-835 (VIR-2218) 200 mg (N=6)	BRII-835 (VIR-2218) 400 mg (N=6)[a,b]	BRII-835 (VIR-2218) 600 mg (N=6)	BRII-835 (VIR-2218) 900 mg (N=6)
AUC_{0-12}, h*ng/mL	1200 (25.1)	3230 (32.7)	5470 (28.0)	18100 (24.2)	17500 (30.8)	44100 (17.9)
AUC_{last}, h*ng/mL	1270 (21.2)	3740 (31.8)	6630 (17.6)	23500 (11.5)	27900 (27.0)	58800 (15.4)
AUC_{∞}, h*ng/mL	1480 (8.0)	4730 (19.2)	6600 (13.6)[c]	24000 (10.2)	29600 (28.5)	60000 (14.9)
C_{max}, ng/mL	155 (42.1)	355 (32.9)	711 (29.2)	2110 (34.3)	1830 (33.5)	5010 (12.6)
$t_{1/2}$, h	2.45 (2.35, 3.26)	3.64 (3.49, 4.95)	4.38 (4.22, 6.11)[c]	3.54 (2.49, 5.51)	5.28 (5.12, 5.62)	4.55 (3.25, 4.69)

AUC = area under curve; AUC_{0-12} = AUC from time 0 to 12 h; AUC_{last} = AUC from time of dosing to last measurable time point; C_{max} = maximum concentration;
Time parameters expressed as median (quartile [Q]1, Q3), all other data are arithmetic mean (% coefficient of variation [CV]);
When n < 3, CV is not presented; due to short VIR-2218 $t_{1/2}$ and PK sampling schedule limitations, terminal phase was not adequately characterized for metabolite; therefore, apparent clearance and $t_{1/2}$ have not been reported.
[a] Excludes 1 subject who received partial dose; [b]Includes PK from 1 replacement subject; [c] Excludes 1subject in summary due to $\%AUC_{Extrap} > 20\%$.

Table 2 Summary of Key Plasma BRII-835 (VIR-2218) PK Parameters By Dosing Day Following Two SC Dose in Chronic HBV Subjects for The Part B/C of Study VIR-2218-1001

Parameter	BRII-835 (VIR-2218) 20 mg (N=3)	BRII-835 (VIR-2218) 50 mg (N=9)	BRII-835 (VIR-2218) 100 mg (N=6)	BRII-835 (VIR-2218) 200 mg (N=6)
Dosing Day: Day 1				
AUC_{0-12}, h*ng/mL	NC	763 (25.2)	2010 (35.5)	7450 (35.7)
AUC_{last}, h*ng/mL	360 (55.3)	1000 (28.4)	2700 (34.9)	9570 (25.1)
C_{max}, ng/mL	73.5 (NC)[a]	118 (52.1)[b]	235 (33.6)	826 (40.7)
Dosing Day: Day 29				
AUC_{0-12}, h*ng/mL	NC	794 (23.2)	1710 (34.7)	7300 (42.6)
AUC_{last}, h*ng/mL	339 (50.4)	910 (35.8)	2550 (25.0)	9580 (33.9)
C_{max}, ng/mL	51.8 (40.7)	115 (33.2)[c]	256 (65.2)	807 (46.3)

AUC = area under curve; AUC_{0-12} = AUC from time 0 to 12 h; AUC_{last} = AUC from time of dosing to last measurable time point; BLQ = below limit of quantitation; C_{max} = maximum concentration; NC = not calculable
Data are arithmetic mean (% coefficient of variation [CV])
When n < 3, CV is not presented
[a] Measurable in 2/3 subjects; [b] Measurable in 7/9 subjects; [c] Measurable in 8/9 subjects.

BRII-835 (VIR-2218) was absorbed after SC injection with median T_{max} of 4 to 7 hours. Consistent with rapid GalNAc-mediated liver uptake (Nair 2017), BRII-835 (VIR-2218) was not measurable in plasma after 48 hours for any subject (LLOQ of 10 ng/mL). Median apparent elimination half-life ($t_{1/2}$) of BRII-835 (VIR-2218) in plasma was 2 to 5 hours. Following a single SC injection, BRII-835 (VIR-2218) AUC_{last} and C_{max} exposures increase with dose and were slightly greater than dose-proportional across all doses. Consistent with substantial hepatic uptake for GalNAc-siRNA (Janas 2018), no accumulation of BRII-835 (VIR-2218) in plasma was evident following a second dose of BRII-835 (VIR-2218) administered 4 weeks apart in subjects with chronic HBV infection.

Despite rapid elimination of BRII-835 (VIR-2218) from plasma, prolonged presence is anticipated in the liver, based on tissue PK of BRII-835 (VIR-2218) in nonclinical species and data from other GalNAc-conjugated siRNA molecules (Janas 2018). In contrast to the short-lived plasma concentrations of VIR-2218, prolonged reduction of HBsAg was observed in HBV subjects following 2 doses of BRII-835 (VIR-2218). Preliminary PK/pharmacodynamic (PD) modeling was conducted to assess the relationship between BRII-835 (VIR-2218) PK in plasma and HBsAg reduction as the antiviral activity marker.

Since no direct measurement of liver PK was available from subjects, liver PK characteristics were inferred using a PK/PD model describing observed plasma

BRII-835 (VIR-2218) concentration and HBsAg data. A sequential PK/PD modeling approach was applied to first estimate PK parameters of BRII-835 (VIR-2218) in plasma, then an effect compartment representing the site of drug action in liver was used to link the plasma PK and HBsAg reduction observed over time in an indirect response PK/PD model. The PK/PD model described the observed BRII-835 (VIR-2218) plasma PK and HBsAg data well and predicted a $t_{½}$ of approximately 80 days in the liver.

The predicted liver $t_{½}$ of BRII-835 (VIR-2218) of 80 days was used to estimate BRII-835 (VIR-2218) liver tissue exposure in humans (**Table 3**). The median liver exposure for the proposed BRII-835 (VIR-2218) dose regimen of 100 mg every 4-week for a total of 9 doses (100 mg Q4W x9) are estimated to not exceed the projected liver exposure of the highest dose at which the safety and tolerability of BRII-835 (VIR-2218) have been demonstrated (single dose of 900 mg).

The liver exposure projections, in addition to the safety and tolerability findings of BRII-835 (VIR-2218) in healthy volunteers in Part A and in subjects with chronic HBV infection from study Part B/C of VIR-2218-1001, support the proposed BRII-835 (VIR-2218) dose regimen in the combination study.

Table 3 Estimated Median BRII-835 (VIR-2218) Liver Tissue Exposure in Humans Based on PK/PD model

Simulated Dosing Regimen	C_{max} (µg/g)	AUC (h*µg/g)
900 mg single dose	61.1	34300 (135000) [a]
100 mg Q4W × 9	30.6	19700[b]

Q4W = every 4 weeks
[a] For single dose regimens, partial AUC_{last} up to Day 29 is presented; AUC_{inf} is also presented in parenthesis
[b] For multiple dose regimens, AUC refers to AUC_{last} during the 28-day dosing interval following 2 or 6 doses of VIR-2218

Emerging PK and antiviral activity data from the ongoing study were used to develop a mechanistic BRII-835 (VIR-2218) PK/PD model to further elucidate the relationship between clinically observed HBsAg reduction and the anticipated prolonged BRII-835 (VIR-2218) exposure in the liver, the target organ. Supported by the initial analysis from the PK/PD model, with the anticipated long liver residence of BRII-835 (VIR-2218) and observed durable HBsAg reduction in the ongoing studies in subjects with chronic HBV infection, the proposed dosing regimen of 100 mg Q4W for a total of 9 doses BRII-835 (VIR-2218) have the potential to achieve significant and durable reduction of immunosuppressive antigens such as HBsAg that could enable effective immune restoration and activation by immune boosting with BRII-179(VBI-2601) treatment and ultimately lead to the HBV functional cure.

In the VIR-2218-1001 study, across all BRII-835 (VIR-2218) treated chronic HBV patients, significant HBsAg reductions were observed starting from 8 weeks post the first dose, and generally reached maximum reduction by about week 16. This observation is

consistent with reported clinical data from other siRNA treatments for HBV (Gane 2020; Yuen 2020); and serves as the basis for selecting Week 8 as the time point of BRII-179 (VBI-2601) treatment initiation.

In addition, as shown in **Table 4**, the NOAEL levels estimated from the pivotal toxicology studies provides relatively large safety margins for the proposed BRII-835 (VIR-2218) dose regimen in the combination study.

Overall, the PK and PK/PD relationships in healthy subjects and chronic HBV patients, as well as safety margin assessments based on pivotal toxicology studies support the proposed BRII-835 (VIR-2218) dose regimen of 100 mg Q4W x9 in the combination study.

Table 4 Dose Levels and Safety Margins (Animal-to-Human Exposure Ratios) at the Proposed 100 mg Clinical Dose of BRII-835 (VIR-2218) in the BRII-179-835-001 Study

	NO(A)EL mg/kg	[f]AUC_{0-24} µg*h/mL	Exposure margin (AUC_{0-24})[a]	C_{max} µg/mL	Exposure margin (C_{max})[a]
Rat: 6-month pivotal (once monthly; 7 total doses)[b]	150	317	85	40.4	114
Monkey: 9-month pivotal (once monthly; 10 total doses)[c]	300	1230	329	79.8	225
Rat: embryo-fetal development (Day 6 to 17 pc)[d]	100	196	52	29.6	83
Rabbit: embryo-fetal development (Day 7 to 19 pc)[e]	100	278	74	41.3	116

[a] Exposure margins are based on the human plasma AUC_{0-24} and C_{max} of 3.74 µg*h/mL and 0.355 µg*h/mL, respectively, after a single SC dose of 100 mg in the Phase 1 clinical study (VIR-2218-1001).
[b] Based on NOAEL from the pivotal 6-month rat (TX-2218-0003) study. AUC_{last} and C_{max} values were from last day of dosing (Day 169, sexes combined).
[c] Based on NOAEL in the pivotal 9-month monkey (TX-2218-0004) study. AUC_{last} and C_{max} values were from last day of dosing (Day 253, sexes combined).
[d] Based on NOAEL in the pivotal rat embryo fetal development study (TX-2218-0106). AUC_{last} and C_{max} values were from last day of dosing (Day 17 pc) in the rat dose range finding study (TX-2218-0102).
[e] Based on NOEL in the pivotal rabbit embryo fetal development study (TX-2218-0107). AUC_{last} and C_{max} values were from last day of dosing (Day 19 pc) in the rabbit dose range finding study (TX-2218-0103).
[f] At the NO(A)EL, AUC_{last} and AUC_{0-24} are the same timepoint t=24 hours.

4.3.1.2. Dose Selection Consideration for BRII-179

Available preliminary results including safety, tolerability, and immunomodulatory activity from the ongoing study BRII-179-001 as well as currently available nonclinical data were considered when selecting dose levels for BRII-179 in combination with BRII-835 (VIR-2218) in subjects with chronic HBV infection.

In the BRII-179-001 study, 4 monthly doses of 20 µg or 40 µg of BRII-179 (VBI-2601) admixed with or without IFN-α are being evaluated for safety and immunomodulatory activity. No SAEs were reported and treatment with BRII-179 (VBI-2601) was generally safe and well tolerated. Based on the preliminary analysis of the immunomodulatory data, comparable antibody and T cell response to HBV surface antigens were observed in approximately 30% and >=50% evaluable patients across all four cohorts at 20 µg or 40 µg of BRII-179 (VBI-2601) admixed with or without IFN-α. Antibody response to pre-S1 and/or pre-S2 antigens was only seen in cohorts admixed with IFN-α, suggesting addition of IFN-α as co-adjuvant may further enhance the restimulation of immune response to pre-S1 and pre-S2 antigens. This is consistent with the preclinical study results in AAV-HBV model that BRII-179 (VBI-2601) can break tolerance and co-formulation with IFN-α can further enhance the HBV specific humoral and cellular responses compared to BRII-179 alone.

Strategies to improve immune responses to vaccines in high risk population, such as increasing the amount of antigen in the influenza vaccine in the older population, can improve protection and have a favorable effect on morbidity and mortality (DiazGranados 2004). High dose of prophylactic HBV vaccines and increasing number of doses (6-11) have been demonstrated to provide improved and durable immune response in chronic HBV patients (Hoa 2009, Roggendorf 2019, Wong 2018). Therefore, it is postulated that reducing HBsAg level by siRNA treatment followed by the extended treatment of BRII-179, e.g. up to 9 monthly injection of 40 µg of BRII-179 admixed with or without IFN-α, in chronic HBV patients could provide desirable HBV specific humoral and T cell responses that may restore and sustain immune control of HBV infection, thereby achieving functional cure. The proposed BRII-179 dosing regimens will also facilitate further understanding of local immune modulation potential of IFN-α at the IM injection site and its impact to achieve desirable sustained HBV specific immune responses.

In addition, the pivotal chronic toxicology studies also support the proposed BRII-179 (VBI-2601) dose regimen of 40 µg Q4W x9 in the combination study.

More detailed information may be found in the Investigator's Brochure for BRII-835 (VIR-2218) and BRII-179 (VBI-2601).

Timing of BRII-179 (VBI-2601) treatment initiation in the overall BRII-835 (VIR-2218) and BRII-179 (VBI-2601) combination treatment regimen is another critical design element of the study. As demonstrated in previous nonclinical studies (Zhu, 2016; Michler, 2018), initial reductions of HBsAg by therapeutic interventions enabled follow-up HBV vaccine treatments to break tolerance and achieve functional cure in the animal HBV models. It is thus hypothesized that significant HBsAg reduction by BRII-835

(VIR-2218) treatment prior to introduction of BRII-179 (VBI-2601) in the chronic HBV patients will provide an optimal treatment window to maximize the BRII-179 (VBI-2601) potential in restoring and sustaining immune control of HBV infection, and ultimately leading to functional cure. Consistent with the reported clinical data from other HBV siRNA treatments, significant HBsAg reductions, and in some cases, maximum reductions, have been observed in BRII-835 (VIR-2218) treated chronic HBV patients approximately 8 weeks after treatment initiation. As such, the proposed timing of the BRII-179 (VBI-2601) introduction in the combination treatment is on week 8, after two Q4W doses of BRII-835 (VIR-2218).

In summary, currently available clinical safety, tolerability, PK, PD and PK/PD results from BRII-835 (VIR-2218) and BRII-179 (VBI-2601) studies, as well as safety margin assessments from the toxicology studies support the proposed combination treatment regimens for the treatment of chronic HBV infection and as a potential functional cure.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

5. STUDY POPULATION

5.1. Number of Participants

A total of 50 evaluable adult participants with virologically suppressed chronic HBV infection without cirrhosis on NrtI therapy are planned for this study. Up to 60 floater participants may be added to existing cohort(s) as expansion if further data is required.

- **Cohort A:** 10 adult participants with chronic HBV infection without cirrhosis on NrtI therapy will be enrolled in Cohort A.
- **Cohort B and C:** 20 adult participants each with chronic HBV infection without cirrhosis on NrtI therapy will be enrolled in Cohort B and Cohort C.
- **Floater participants:** up to 60 floater participants can be enrolled into any existing cohort(s).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Adherence to the criteria as specified in the protocol is essential.

5.2. Inclusion Criteria

Participants eligible to be included in the study must meet all of the following criteria. All laboratory test requirements for inclusion will be performed by central laboratory unless specified otherwise.

1. A signed and dated written Informed Consent Form (ICF) prior to study participation.
2. 12-lead ECG within normal limits; or, with no clinically significant abnormalities at screening, as determined by the clinical investigator
3. Age 18 (or age of legal consent, whichever is older) to 60 years at the time of screening.
4. Female participants must have a negative pregnancy test or confirmation of post-menopausal status. Post-menopausal status is defined as 12 months with no menses without alternative medical cause. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test (using central laboratory) at screening and a negative urine pregnancy test on Day 1, cannot be breast feeding, and must be willing to use highly effective methods of contraception 14 days before study drug administration through 12 weeks after last study drug administration. Refer to Section 10.4 for more information on highly effective methods of contraception.
5. Male participants with female partners of child-bearing potential must agree to meet 1 of the following contraception requirements from the time of study drug administration until the last follow-up visit: vasectomy with documentation of azoospermia, or male condom use plus partner use of 1 of the contraceptive options listed for contraception for WOCBP. Male participants must also agree not to donate

sperm for the 12 weeks following last study drug administration. Refer to Section 10.4 for more information on highly effective methods of contraception.

6. Agrees to not donate blood during the duration of the study.

7. Body mass index ≥ 18 kg/m^2 and ≤ 32 kg/m^2.

8. Chronic HBV infection as defined by a positive serum HBsAg for ≥ 6 months. Participant must remain on the same NrtI at Screening to the end of their study participation unless medically indicated otherwise, i.e., development of resistance.

9. Must be on NrtI therapy consisting of either entecavir, tenofovir disoproxil or tenofovir alafenamide for at least 12 months, and with HBV-DNA < LLOQ for at least 6 months before screening (local laboratory results accepted).

10. HBsAg > 150 IU/mL and < 3000 IU/mL at screening.

11. HBV DNA < LLOQ IU/mL at screening (by central laboratory).

12. Serum ALT and AST ≤ 2x ULN (by central laboratory). Study screening laboratory tests may be repeated once for values considered to be erroneous with medical monitor approval.

13. Agree to not increase physical activity from the time of screening through 4 weeks after final study drug administration.

14. Willing and able to comply with the study procedures and requirements.

5.3. Exclusion Criteria

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

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

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

3. Significant liver fibrosis or cirrhosis as defined by having either a FibroScan result of > 9kPa at screening, unless the participant has results from a FibroScan evaluation performed within 6 months prior to screening or liver biopsy performed within 1 year prior to screening that confirm the absence of Metavir F3 fibrosis or F4 cirrhosis. If a participant has had both procedures in the specified timeframes, the most recent result should be used to determine eligibility.

4. History or evidence of drug or alcohol abuse as assessed by the Investigator, within the 12 months before screening or a positive drug screen for amphetamines, cocaine, methadone or opiates at screening unless it can be explained by a prescribed

medication; the diagnosis and prescription must be approved by the investigator. Screening results must be reviewed by the investigator to confirm eligibility prior to dosing.

5. History of intolerance to SC or IM injection.

6. History of clinically significant chronic liver disease from any cause other than chronic HBV infection.

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

8. Previous vaccination with any HBV vaccine (licensed or experimental).

9. Previous treatment with IFN-α or pegylated-IFN-α.

10. Treatment by immunosuppressant (including but not limited to corticosteroids at a prednisolone equivalent dose > 20 mg/day) within 30 days before study drug administration at the Day 1 visit and throughout the duration of study participation.

11. Known history of immunological function impairment, including but not limited to:

    - Autoimmune disease (e.g., multiple sclerosis, type 1 diabetes mellitus , myasthenia gravis, Crohn's disease and other inflammatory bowel diseases, celiac disease, systemic lupus erythematosus, scleroderma, including diffuse systemic form and limited cutaneous form of systemic sclerosis or CREST syndrome, systemic sclerosis, dermatomyositis polymyositis, rheumatoid arthritis, juvenile idiopathic arthritis, autoimmune thyroiditis including Hashimoto thyroiditis, Grave's or Basedow's disease, immune thrombocytopenic purpura, autoimmune hemolytic anemia, autoimmune hepatitis, psoriasis, vitiligo, vasculitis, Guillain Barré syndrome, Addison's disease, Bell's palsy, and alopecia areata); OR

    - Primary immunodeficiency disorders (e.g., common variable immune deficiency, defective phagocytic cell function and neutropenia syndromes, and complement deficiency); OR

    - Secondary immunodeficiency disorders (e.g., resulting from acquired immunodeficiency syndrome caused by human immunodeficiency virus (HIV) infection, solid organ transplant, and splenectomy).

12. Pregnant or breastfeeding.

13. Immunization with attenuated vaccines (e.g., Mumps, Measles, Rubella) within 30 days before study drug administration at the Day 1 visit and throughout the duration of study participation.

14. Has received blood products or immunoglobulin within 90 days before study drug administration at the Day 1 visit or likely to require blood products during the study.

15. Participated in another clinical trial with an investigational drug or a biologic within 30 days or within 5 drug half-lives (whichever is longer) before study drug administration at the Day 1 visit. Participants must agree not to take part in any other study at any time during their participation in this study, inclusive of the follow-up period.

16. Has received granulocyte macrophage colony stimulating factor (GM CSF) or erythropoietin (EPO) within 30 days before study drug administration at the Day 1 visit or likely to require GM CSF/EPO during the study.

17. 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.

18. The participant has any history of cancer requiring locoregional or systemic therapy within 5 years of randomization or has current disease. Participants with completely surgically resected tumors with no evidence of disease for more than 3 years, or a history of low risk basal cell carcinoma will be accepted (low risk being defined as 1) location on the trunk of the body, arms, legs, cheeks, forehead, temples, scalp, neck, or chin, 2) < 2 cm in size, 3) nodular or superficial, 4) primary cancer that has not come back after treatment, 5) edge of the cancerous area is clear and smooth, and 6) not located in or around nerves).

19. Any skin abnormality or tattoo that would limit post treatment injection site assessment.

20. Known hypersensitivity or contraindication to BRII-179 (VBI-2601) and/or an siRNA/ GalNAc or their excipients.

21. Unwilling, or unable in the opinion of the investigator, to comply with study requirements, including the use of an adequate birth control method.

22. Active infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis Delta virus.

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

24. Renal impairment with estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73 m^2 at screening.

25. Uncontrolled diabetes mellitus as determined by the Investigator.

26. Uncontrolled hypertension (defined as an average systolic blood pressure ≥ 150 mmHg or an average diastolic blood pressure ≥ 95 mmHg based on 2 measurements after approximately 10 minutes resting at screening in participants diagnosed and treated for hypertension, and in participants without a diagnosis of hypertension).

27. Any laboratory test abnormality that is considered as clinically significant by the investigator.

28. Diagnosis of advanced stage heart failure (New York Heart Association Class III or Class IV or unstable angina).

5.4. Lifestyle Considerations

1. Alcohol consumption is limited to no more than 1 unit per day (unit: 1 glass of wine [125 mL] = 1 measure of spirits [30 mL] = one-half pint of beer [284 mL]) during the participation of this study.

2. Participants will abstain from strenuous exercise from the time of screening through 4 weeks after final study drug administration.

5.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION

The term 'study drug' is used throughout the protocol to describe any combination of products by the participant as per the protocol design. Study drug may therefore refer to the individual study drugs or the combination of those study drugs.

6.1. Study Intervention(s) Administered

6.1.1. Formulation

BRII-835 (VIR-2218) is a synthetic, chemically modified small interfering RNA (siRNA) targeting HBV RNA with a covalently attached triantennary N-acetyl-galactosamine (GalNAc) ligand that allows for specific uptake by hepatocytes. BRII-835 will be supplied as a clear, colorless to pale yellow, sterile solution for SC injection at a free acid concentration of 200 mg/mL.

BRII-179 (VBI-2601) is aluminium phosphate absorbed HBsAg Bulk Drug Substance (HBsAg spherical particles [~30 nm mean diameter] suspended in phosphate-buffered saline) and 8% Sucrose, in addition to 10 mM phosphate buffer.

Interferon-α (IFN-α), a water-soluble protein produced by recombinant DNA techniques, will be supplied to clinical sites for admix formulation with BRII-179 (VBI-2601) prior to administration on each administration day per participant.

6.1.2. Dosage and Administration

Cohort	A	B	C
Intervention Name	BRII-835 (VIR-2218)	BRII-835 (VIR-2218); BRII-179 (VBI-2601) IFN-α	BRII-835 (VIR-2218); BRII-179 (VBI-2601)
Type	Drug	Drug	Drug
Dose Formulation	Solution for Injection	Solution for Injection	Solution for Injection
Dose Level(s)	BRII-835 100 mg	BRII-835 100 mg; BRII-179 40 µg; IFN-α 3 MIU	BRII-835 100 mg; BRII-179 40 µg;
Route of Administration	Prepare 0.5 mL of BRII-835 in one syringe; administer via SC injection. Refer to the Pharmacy Manual for the details.	Prepare 0.5 mL of BRII-835 in one syringe; administer via SC injection. Prepare the admixture of required amount of BRII-179 and IFN-α in one syringe; administer via IM injection. Refer to the Pharmacy Manual for the details.	Prepare 0.5 mL of BRII-835 in one syringe; administer via SC injection. Prepare the required amount of BRII-179 in one syringe; administer via IM injection. Refer to the Pharmacy Manual for the details.
Use	Experimental	Experimental	Experimental
IMP and NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor

Packaging and Labeling	IMP will be labeled as required per country requirement.	IMP will be labeled as required per country requirement.	IMP will be labeled as required per country requirement.

On dosing days, the pharmacist or designee will prepare the required amount of study drugs into syringe(s) for injection. A qualified clinical investigative site staff member under the supervision of the investigator or designee will administer the study drug(s). The injection site(s) will be marked and mapped for later observation and should be documented. If a local reaction around the injection site occurs, photographs may be obtained. Please refer to Section 6.6 for further details.

6.2. Preparation/Handling/Storage/Accountability

1. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
2. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
3. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Randomization and Blinding

All participants will be centrally assigned to randomized study intervention using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information & directions for the IWRS will be provided to each site. The site will contact the IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form, if required.

Study intervention will be dispensed at the study visits summarized in SoA. Returned study intervention should not be re-dispensed to the participants.

This study will be conducted as an open-label study. Participants, investigators, and Sponsor personnel will be aware of treatment assignments after each participant is randomized.

6.4. Study Intervention Compliance

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

by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

All participants are required to be on NrtI therapy for at least 12 months without interruption of ≥ 7 consecutive days at the screening visit and continued throughout the study. Participants must remain on the same NrtI at screening to the end of their study participation unless medically indicated otherwise, i.e., development of resistance.

Allowed NrtI therapy must be consisting of the following:

- Entecavir
- Tenofovir disoproxil
- Tenofovir alafenamide

Any medications that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

Should subjects have a need to initiate treatment with any excluded concomitant medication, the Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the investigator must notify the Sponsor as soon as he/she is aware of the use of the excluded medication. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Permitted Medications

The following medications/treatments are permitted:

- Hormone replacement therapy.
- Oral, injectable, subdermal, intravaginal, or implantable contraceptives, as well as intrauterine device, and intrauterine hormone-releasing system are permitted for contraception.
- Inhaled or topical steroids are allowed.
- Prescription drugs necessary to treat hypertension. Hypertension must be well controlled on a stable dose of medication for > 6 months prior to study intervention administration at Day 1 visit.
- Prescription drugs necessary to treat diabetes mellitus. Diabetes mellitus must be controlled on a stable dose of medication for > 6 months prior to study intervention administration at Day 1 visit.
- Paracetamol (≤ 2 g/day), aspirin (≤ 3 g/day), or ibuprofen (< 1.2 g/day).

- Antihistamines.
- Prescription inhaler or nebulizer to treat asthma (inhaled bronchodilator or inhaled steroid). Asthma must be well controlled, defined as historical use of a rescue bronchodilator on average no more than twice per week.
- A stable dose and regimen of other medication(s) (prescription or OTC) that the participant is taking regularly (i.e. medications for chronic conditions such as high cholesterol or depression must be unchanged in dose or type for at least 6 months) is permitted.
- Licensed SARS-CoV-2 vaccines, including those approved for emergency use by local authorities, for the prophylaxis of COVID-19 are allowed. Each COVID-19 vaccine administration should be ideally with a minimum interval of 14 days before or after BRII-179 (VBI-2601) administration. However, COVID-19 vaccines may be administered within a shorter period in situations to avoid barriers or delays to COVID-19 vaccination.

6.5.2. Prohibited Medications

The following medications are excluded while subjects are participating in the study.

Prior to study enrolment and throughout the duration of study participation:

- Any HBV vaccine (licensed or experimental)
- IFN-α or pegylated-IFN-α (except the adjuvant for this study)

Within 30 days before study drug administration at the Day 1 visit and throughout the duration of study participation:

- Immunosuppressant (including but not limited to corticosteroids at a prednisolone equivalent dose > 20 mg/day)
- Immunization with attenuated vaccines (e.g., Mumps, Measles, Rubella), except COVID vaccines
- Any investigational drug or biologic other than the study product(s) used during this study
- Granulocyte-macrophage colony-stimulating factor (GM-CSF) or erythropoietin (EPO)
- Any OTC medicines or herbal remedies that may cause fluctuations of liver test results

Within 90 days before study drug administration at the Day 1 visit and throughout the duration of study participation:

- Blood products or immunoglobin

6.6. Safety Follow-up and Management of Reactions to Study Drug

The following safety observation procedures will be performed immediately following study drug administration and during the follow-up period for all participants:

- Subjects will remain in the clinic for at least one hour post study drug administration. The observation period will include an assessment for rare adverse reactions.
- Any unusual signs or symptoms reported during the initial one hour of observation will prompt continued close monitoring.
- Based on their condition, subjects may be asked to remain in the clinic for more than one hour after the study drug administration (reason will be recorded in source data).
- All data (including assessment of solicited local and systemic reactions) will be recorded in the source document during and after the post-observation period.

A measurement device template (in mm) for measuring solicited local reactions (erythema [redness] and swelling), and an oral thermometer for measuring daily temperature, will be provided at the first study drug administration visit, study Day 1. Subjects will be advised to record their temperature in the diary card.

Refer to Sections 8.3 and 10.3 for further details on the recording, assessment, and reporting of AEs.

6.6.1. Suicidal Ideation and Behavior Risk Monitoring

Depression and suicidal behavior have been reported in association with systemic treatment with IFNs including IFN-α at therapeutic doses, e.g., 30-35 MIU/week for 16 weeks in HBV treatment. IFN-α is being used in this clinical trial as an adjuvant at the low dose of 3 MIU every 4 weeks for up to 9 total doses. This dose level of IFN-α has previously been tested in more than 200 human subjects, including hemodialysis or renal graft patients, with HBV vaccine and was well tolerated (Grob, 1984; Goldwater, 1994; Miquilena-Colina, 2009; Rizza, 2008).

Subjects being treated with IFN-α should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of intervention. Consideration should be given to discontinuing the study drug in subjects who experience signs of suicidal ideation or behavior, following a risk assessment.

Families and caregivers of subjects being treated with IFN-α should be alerted about the need to monitor subjects for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

6.7. Treatment of Study Intervention Overdose

An overdose is defined as a dose greater than the total doses described per protocol which results in clinical signs and symptoms. These should be recorded by the investigator on the AE/SAE pages. In the event of an overdose of study medication, the investigator should use clinical judgement in treating the overdose and contact the study medical monitor.

The Sponsor is not recommending specific treatment guidelines for overdose and toxicity management. The investigator is advised to refer to the relevant document(s) for detailed information pertaining to the study drug being used in this study. Such documents may include, but not be limited to, the IB or equivalent document provided by the Sponsor, the approved product label for IFN-α, or both.

6.8. Intervention after the End of the Study

The Sponsor will not provide post-study treatment. The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition whether or not the Sponsor is providing specific post study treatment.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant who has received at least one dose of BRII-835 (VIR-2218) or BRII-179 (VBI-2601) will hold the additional doses of either study intervention if any of the following criteria are met:

- Signs or symptoms of severe (NCI-CTCAE Grade 3 or higher) hypersensitivity or anaphylaxis
- Significant abnormalities in liver chemistry, defined as any of the following are met:
  - Serum ALT > 10 × ULN
  - Serum ALT > 5 × ULN, with no change in HBsAg, defined as a < 50% decrease from the baseline predose value
  - Serum ALT or AST > 3 × ULN with a concomitant total bilirubin > 2 × ULN or INR > 1.5
- Any clinical manifestations of hepatic decompensation

The Sponsor may request SRC evaluation of specific data in the event of liver flare to fully characterize transaminase elevations. The participant may be resumed to receive the additional doses of study intervention only following SRC approval.

If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for the rest duration of study participation. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Participants who are withdrawn from the study will NOT be replaced and cannot be rescreened.
- The primary reason for participant withdrawal will be recorded in the eCRF. Primary reasons for withdrawal will be categorized as:
  - Adverse event
  - Protocol deviation
  - Withdrew consent, not due to an AE
  - Lost to follow up
  - Study closed/terminated

7.3. Lost to Follow up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Schedule of Assessments

Study procedures and their timing are summarized in the SoAs (Section 1.3). Adherence to the study design requirements, including those specified in the SoAs, is essential and required for study conduct. Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

8.1.1. Screening

Written informed consent must be obtained prior to initiation of any study procedures. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

Screening will be performed no more than 6 weeks prior to the first dose for each Cohort and will include written consent, determination of participant eligibility, collection of demographics and medical history as well as a physical examination (including vital signs measurement), 12-lead ECG, clinical laboratory tests, and other assessments per the SoAs.

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.

8.1.2. Randomization (Day 1)

Participant eligibility must be confirmed prior to randomization and study drug administration on Day 1. Eligible participants will be randomized 1:2:2 to Cohort A, B, or C within 48 hours prior to study drug administration at the Day 1 visit. Eligible participants will receive their first dose of BRII-835 (VIR-2218) and will be assessed on physical examination (including vital signs measurement), 12-lead ECG, clinical laboratory tests, and other assessments per the SoAs. Participants will have the blood sample collection prior to study drug administration.

8.1.3. Dosing Period

Participants will return to the investigative site on an outpatient basis for safety, tolerability, and antiviral activity monitoring at the specified timepoints per the SoAs.

All participants will receive BRII-835 (VIR-2218) administered SC every 4 weeks, i.e., at Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, and Week 32.

Participants enrolled in Cohort B and Cohort C will also receive 9 doses of BRII-179 (VBI-2601) with or without IFN-α administered IM every 4 weeks from Week 8 to Week 40.

Prior to study drug administration, there will be a review of ongoing eligibility to receive the study drug and continue with study participation. Diary cards will be collected and there will be a review of any local and systemic reactions. There will also be a blood sample collection prior to each study drug administration. Participants will remain in the clinic at least one hour after each study drug administration to be observed for rare adverse reactions.

8.1.4. Follow-up Period

Participants will return to the investigative site as outpatient for the specified in person assessments per the SoAs, including but not limited to physical examination (including vital signs measurement), clinical laboratory tests (including safety, virological, and serological parameters), and review of adverse events and concomitant medications.

Participants will be assessed by the investigator whether they are eligible for discontinuation of NrtI therapy based on their Week 44 laboratory results. Eligible participants to discontinue NrtI therapy may enter into NrtI Discontinuation Monitoring Period from Week 48.

Participants that have NOT achieved NrtI discontinuation criteria (Section 4.1.4.1) by Week 44 will be discharged from the study after completion of all follow-up visits at Week 72.

8.1.5. NrtI Discontinuation Monitoring Period

Eligible participants who meet NrtI withdrawal criteria will be informed by the investigator to discontinue their NrtI medications on the first day of their Week 48 and enter into NrtI Discontinuation Monitoring Period. These participants will follow the NrtI Discontinuation Monitoring Period SoA (Section 1.3.3).

Participants who discontinue from their NrtI therapy will be followed in the NrtI Discontinuation Monitoring Period for an additional 48 weeks from the day of NrtI discontinuation. Participants who are retreated with NrtI therapy should continue to be followed per SoA for the duration of the 48-week NrtI Discontinuation Monitoring Period.

8.1.6. Unscheduled Visits

Participants may be asked to come for an unscheduled visit for clinical assessment of an adverse event if warranted, as determined by the investigator. The unscheduled visit will be recorded in the eCRF.

8.1.7. Early Termination Visit

In cases where a participant prematurely discontinues from the study, the investigator must make every effort to have the participant return to the clinic within 14 days for an Early Termination (ET) Visit. Assessments for ET visits will include but not limited to physical examination, pregnancy test, clinical laboratory tests, and other assessments per the SoAs.

8.2. Detailed Description of Study Procedures

8.2.1. Medical History

A complete medical history, including details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing, medication history, including prior HBV treatment history and HBV genotype history (if available), will be collected on all subjects during screening and should be updated prior to dosing at the Day 1 visit.

8.2.2. Physical Examinations

A complete physical examination will include, at a minimum, general appearance, head, neck, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, extremities, skin, and neurological assessments. Height and weight will also be measured and recorded. Body mass index will be calculated from height and weight.

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

8.2.3. Fibroscan

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

8.2.4. Alcohol Intake Assessment

Alcohol intake during the study will be recorded.

8.2.5. Vital Signs

Temperature (oral preferred), pulse rate, respiratory rate, and blood pressure will be assessed after the participant has rested comfortably for approximately 10 minutes. Pulse rate and blood pressure measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure should be based on 2 separate measurements. When scheduled at the same timepoints, vital signs and 12-lead ECG must be assessed first before physical examinations, blood sample collections, and urine collection.

8.2.6. Electrocardiograms

12-lead ECGs will be recorded and reviewed on-site by the investigator as outlined in SoA Section 1.3.

8.2.7. Laboratory Assessments

8.2.7.1. Screening Viral Serology

The screening viral serology parameters will include chronic HBV infection and active infection with HIV, HCV, and hepatitis Delta virus. Chronic HBV infection is defined as serum HBsAg > 6 months.

8.2.7.2. Clinical Safety Laboratory Assessments

Clinical safety laboratory tests to be performed are described in Section 10.2.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

In the event of an unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed at investigator discretion until it has returned to normal or baseline, and/or a diagnosis is made to adequately explain the abnormality.

8.2.7.3. Pregnancy Testing

A pregnancy test or confirmation of post-menopausal status must be confirmed for all female participants. Post-menopausal status is defined as 12 months with no menses without alternative medical cause. Pregnancy tests will be performed for WOCBP only. Serum and urine 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. During the study, the results of these pregnancy tests must be known prior to study drug administration. A WOCBP determined to be pregnant while on study will be followed until the pregnancy outcome is known, as described in Section 8.3.5.

8.2.7.4. Assessment of Antiviral Activity and Development of Resistance

Assessment of antiviral activity will include HBsAg, HBeAg, anti-HBs, anti-HBe, HBV DNA, CCI [redacted] and assessment of BRII-835 (VIR-2218) or NrtI resistance if indicated.

To assess for resistance, HBV genome will be sequenced and analyzed for mutations that may confer resistance to BRII-835 (VIR-2218) or NrtIs in participants with confirmed

HBV breakthrough as defined by HBV DNA ≥ 500 IU/mL measured at 2 consecutive study visits. CCI may be sequenced to determine if nucleotide changes within the BRII-835 (VIR-2218) target site may impact responsiveness.

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

8.2.7.5. Assessment of Immunological Activity

Assessment of immunological activity will include CCI, HBV-specific cellular immunity, CCI.

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

8.2.8. Laboratory Events of Clinical Interest

A clinical laboratory event of clinical interest (ECI) is a laboratory value of scientific and medical interest specific to understanding of the investigational product and may require additional follow-up testing, close monitoring, and rapid communication by the investigator to the Sponsor.

Laboratory events of ECI for this study are the following:

- ALT > 3x ULN, if Day 1 predose ALT ≤ ULN
- ALT > 2x baseline, if Day 1 predose ALT > ULN

All laboratory ECIs must be reported to the Sponsor within 24 hours of the investigator's knowledge of the event. See Section 10.3.5. In addition, the assessments outlined in Section 10.5 should be performed as soon as possible and no later than two weeks after the initial ALT value meeting criteria for a laboratory ECI.

The laboratory ECI will also be evaluated by the investigator to determine if the event meets criteria for an AE. If AE criteria are met, all clinical sequelae in relation to these laboratory ECIs will be reported as AEs or SAEs, if applicable.

8.2.9. Pharmacokinetic Assessments

- Blood samples will be collected for measurement of blood concentrations of BRII-835 (VIR-2218) and its metabolites as specified in the SoAs.
- Timepoints for the collection of samples for BRII-835 (VIR-2218) PK analysis of the study are provided in Table 5 Pharmacokinetics Assessment Timepoints
- Instructions for the collection and handling of blood samples will be provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of BRII-835 (VIR-2218). Samples collected for analyses of BRII-835 (VIR-2218) blood concentration may also be

used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Table 5 Pharmacokinetics Assessment Timepoints

Study Day/Week	Protocol Time		
	Predose	Dose	Postdose
Day 1	X[a]		X[b]
Day 224/ Week 32	X[a]		X[b]

[a] At ≤ 2 hours prior to dosing
[b] At ≥ 2 hours and ≤ 12 hours after dosing

8.2.10. Assessment of Anti-Drug Antibody to BRII-835 (VIR-2218)

Blood samples will be collected for analyses of ADA to BRII-835 (VIR-2218). See the Laboratory Manual for instructions on sample processing and storage.

8.3. Adverse Events and Serious Adverse Events

AEs will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 10.3).

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

All SAEs will be collected from the signing of the informed consent form (ICF) until the last follow-up visit at the time points specified in the SoA (Section 1.3).

All AE will be collected from the signing the ICF until the last follow-up visit at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent, that are deemed not related to the screening activities, will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Special Situations

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

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

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

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

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

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

8.3.5.1. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention through 12 weeks after last study drug administration.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Other Special Situations

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

8.4. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.5. Genetics

Human genetics are not evaluated in this study.

8.6. [Health Economics] OR [Medical Resource Utilization and Health Economics]

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The null hypothesis is that the percentage of sustained HBsAg loss (defined as undetectable HBsAg for at least 24 weeks) during 48 weeks after NrtI withdrawal in each of the 3 cohorts is not different from a spontaneous annual HBsAg loss of 2%; the alternative hypothesis is that the percentage of sustained HBsAg loss in each cohort is at least 20%.

To adjust for multiple testing, hypothesis testing for sustained HBsAg loss will be conducted in the following prespecified order.

Cohort B will be tested at Step 1. If p-value is < 0.05 at Step 1, then Cohort C will be tested at Step 2. If p-value is < 0.05 at Step 2, then Cohort A will be tested at Step 3. If p-value is ≥ 0.05 at Step 1, then testing at Steps 2 and 3 will not be conducted. If p-value is < 0.05 at Step 1 but ≥ 0.05 at Step 2, then testing at Step 3 will not be conducted.

9.2. Sample Size Determination

A total of 50 subjects will be randomized in a 10:20:20 ratio to Cohorts A, B, and C. This sample size will provide 78% power for Cohort A and 91% power for Cohorts B and C, respectively, to detect a difference of 18% in sustained HBsAg loss, as compared to a spontaneous HBsAg loss of 2%, using a two-sided exact test with a significance level (alpha) of 0.05.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
All Participants Screened	All participants, for whom a record exists on the clinical database, will be included in All Participants Screened. It will be used for reporting study disposition, inclusion and exclusion criteria deviations, etc.
All Participants Randomized	All participants, who are randomized to any cohort will be included in All Participants Randomized. It will be used for reporting demographics, baseline characteristics, medical history, etc.
Per Protocol Set	All participants, who are randomized; and not identified with major protocol deviation that substantially affects the treatment effect of study medication; and have evaluable measurements of antiviral activity and immunological markers will be included in Per Protocol Set.

	It will be used as analysis population for antiviral activity and immunological markers.
Full Analysis Set	All participants, who are randomized; and have evaluable measurements of antiviral activity and immunological markers will be included in Full Analysis. It will be used as analysis population for sensitivity analysis of antiviral activity and immunological markers.
Safety Analysis Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention will be included in Safety Analysis Set. It will be used for reporting safety parameters.
PK Analysis Set	All participants randomly assigned to Cohort A, B, or C; have received at least 1 dose of BRII-835 (VIR-2218); and have at least 1 non-missing concentration data to provide interpretable results for the specific PK parameters will be included in PK Analysis Set.

9.4. Statistical Analyses

This section outlines the general analytic strategy for the study. The statistical analysis plan (SAP) will be finalized prior to Database Lock (DBL) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General considerations

Unless otherwise stated, the following rule will apply:

- Summaries and displays will be presented by cohorts.
- For categorical variables, the frequency and percentage will be applied as descriptive statistics.
- For continuous variables, the mean, standard variation, median, and ranges will be applied as descriptive statistics.
- Missing value will be handled using the Data-As-Observed (DAO) approach, that is, any missing value will be excluded from the analysis, except for the baseline value, which will be replaced with the latest pre-treatment result, if available.
- Only scheduled visits will be presented of summaries; unscheduled visits will be listed but will not be summarized.

9.4.2. Primary endpoint(s)

The primary objective is to evaluate the safety, efficacy, and dose regimen of combination therapy of BRII-835 (VIR-2218) and BRII-179 (VBI-2601) which will be assess by calculating the percentage of participants with sustained HBsAg loss (defined

as undetectable HBsAg for at least 24 weeks) during 48 weeks follow-up period after NrtI withdrawal, as well as incidences of AEs and laboratory abnormalities.

The Per Protocol population will be used for calculating the percentage of participants with sustained HBsAg loss by cohort. Each cohort will be compared with a 2% spontaneous annual HBsAg loss using a two-sided exact test at an alpha level of 0.05.

The Safety Analysis population will be used for safety parameters.

- All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-Emergent Adverse Events (TEAEs) are defined as any AEs occurred or worsened following the first administration of study drug. Number and percentage of TEAEs will be summarized by cohort.
- Graded laboratory abnormalities will be defined using NCI-CTCAE Version 5.0 grading scale. The incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any postbaseline timepoint up to 30 days after permanent discontinuation of study drug will be summarized by cohort.

Additionally, subgroup analysis stratified by HBeAg status at baseline will be conducted with respect to the percentage of participants with sustained HBsAg loss.

9.4.3. Secondary endpoint(s)

The secondary objective is to evaluate the antiviral activity of combination therapy of BRII-835 (VIR-2218) and BRII-179 (VBI-2601) as well as to assess PK profiles of BRII-835 (VIR-2218).

- Percentage of participants meeting NrtI withdrawal criteria at Week 44 and selected data relating to the antiviral activity, such as HBsAg, anti-HBs, HBeAg, anti-HBe, and HBV DNA levels, will be summarized by cohort and study visit along with corresponding change from baseline. Summaries of HBsAg loss, anti-HBs seroconversion, HBeAg loss, and anti-HBe seroconversion will be provided by cohort and study visit.
- BRII-835 (VIR-2218) plasma exposure will be evaluated. PK analysis may be conducted to explore exposure-response relationships between drug exposure and selected antiviral variables. These analyses may include graphical plots, tabular summaries, and various linear and/or non-linear analyses. Details of the analysis will be provided in the SAP.
- HBV specific immunological markers, including CCI [redacted], will be summarized by cohort. Details of the analysis will be provided in the SAP.

9.4.4. Exploratory endpoint(s)

Summaries of other antiviral activity and HBV specific immunological responses, such as cellular immunity responses CCI [redacted], will be provided by cohort and/or NrtI withdrawal status at Week 44 as well as study visit. Details of the analysis will be provided in the SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Data Quality Assurance

- All relevant participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source data refer to all information recorded in the original record of certified copy of the clinical study, including clinical findings, observation results and other relevant activity records needed for reconstruction and evaluation of the clinical study.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

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

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

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

10.1.8. Publication Policy

The sponsor intends to publish the results of clinical trials regardless of outcome. Results may be published in peer-reviewed journals and/or presented at scientific congresses. The sponsor will comply with the requirements for publication and disclosure of clinical trial information. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. Authorship will be determined by mutual agreement based upon International Committee of Medical Journal Editors criteria and guidelines [ICMJE, 2018]. Individuals who do not meet authorship criteria do not warrant named authorship. Nonauthor contributors may be acknowledged in the manuscript when published or recognized in a manner consistent with the target journal policy.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6Table 6: Protocol-Required Safety Laboratory Assessments

will be performed by the central laboratory. Urine pregnancy test will be performed by the local or central laboratory.

Investigators must document their review of each laboratory safety report.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6: Protocol-Required Safety Laboratory Assessments

Hematology	
Complete blood count with differential, including red blood cell count, hemoglobin, hematocrit, white blood cell count, count and percentage of neutrophils, lymphocytes, eosinophils, basophils, and monocytes, and platelet count	
Chemistry	
Albumin	Estimated glomerular filtration rate (eGFR)
Blood urea nitrogen (BUN)	Gamma glutamyl transferase (GGT)
Calcium	Glucose
Carbon dioxide/bicarbonate	Lactate dehydrogenase (LDH)
Chloride	Potassium
Creatine kinase	Sodium
Creatinine	Uric acid
Liver Function Tests	
Alkaline phosphatase (ALP)	Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)	Bilirubin (total and direct)
Coagulation Parameters	
International normalized ratio (INR)	Prothrombin time (PT)

Urinalysis	
Bilirubin	Proteins
Glucose	Red blood cells (RBCs)
Ketones	Screen for drugs of abuse
Leukocytes	Specific gravity
Microscopy (if clinically indicated)	Urobilinogen
Nitrite	Visual inspection for appearance and color
pH	
Pregnancy Testing	
Beta-human chorionic gonadotropin (WOCBP only)	Urine pregnancy test
Thyroid Panel [a]	
Thyroid stimulating hormone (TSH)	

[a] Thyroid panel will be assessed only in Cohort B and Cohort C.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant 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. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

Assessment of Causality

- The investigator or a qualified assistant investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- Relationship between AEs and the study intervention: "related" should be entered when there is either (a) a *reasonable possibility* that the AE/SAE is associated with study intervention **or** (b) no reasonable alternative explanation can be found. Otherwise, the relationship between AEs and the study intervention should be classified as "unrelated".

- A "*reasonable possibility*" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to the Sponsor via a Paper SAE Reporting Form

- The investigator must complete a paper SAE report form and send to the Sponsor or its representative within 24 hours of the investigator's knowledge of the event.

- Contacts for SAE reporting can be found on the SAE Reporting Form.

10.3.5. Reporting of Laboratory Events of Clinical Interest

All laboratory ECIs must be reported to the Sponsor or its representative within 24 hours of the investigator's knowledge of the event. Contact for laboratory ECIs reporting can be found on the ECI Reporting Form.

The laboratory ECI will also be evaluated by the investigator to determine if the event meets criteria for an AE. If AE criteria are met, all clinical sequelae in relation to these laboratory ECIs will be reported as AEs or SAEs, if applicable.

10.4. Appendix 4: Contraceptive Requirements and Collection and Reporting of Pregnancy Information

Contraceptive Requirements:

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

WOCBP must be willing to use highly effective methods of contraception 14 days before dose, throughout study participation, and for 12 weeks after last dose of study drug administration. Highly effective methods of birth control result in a low failure rate (ie, less than 1% per year). Birth control methods which are considered highly effective include:

- Established use of combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal methods of contraception associated with inhibition of ovulation **OR** established use of progestogen-only oral, injectable, or implantable hormonal methods of contraception associated with inhibition of ovulation. It is not currently known whether study intervention will impact the effectiveness of hormonal contraceptive methods; therefore, it is recommended to use an additional form of contraception (ie, barrier method) throughout the study and for 12 weeks after last study drug administration.
- Placement of an intrauterine device
- Placement of an intrauterine hormone-releasing system
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female subjects on the study, the vasectomized male partner should be the sole partner for that subject)
- True sexual abstinence, when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent subjects have to agree to use 1 of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 12 weeks after last dose of study drug administration, or for as long as the subject is followed on study, whichever is longer.
- Barrier method in combination with hormonal contraceptive, as described above

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

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

- Vasectomy with documentation of azoospermia

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

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

Collection of Pregnancy Information:

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this

information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5. Appendix 5: Assessments in Participants Meeting Laboratory ECI Criteria

Additional assessment will be performed in participants who experience ALT elevations meeting laboratory ECI criteria (Section 8.2.8). Following the occurrence of event of ECI, the following assessments in Table 7 will be performed one time, as soon as possible, and no later than two weeks after the initial ALT value meeting criteria for a laboratory ECI. The full panel of assessments should only be performed once; individual assessments may be repeated per investigator discretion, as needed.

Table 7 Assessments in Participants Meeting Laboratory ECI Criteria

Hematology	
Complete blood count with differential, including red blood cell count, hemoglobin, hematocrit, white blood cell count, count and percentage of neutrophils, lymphocytes, eosinophils, basophils, and monocytes, and platelet count	
Chemistry	
Albumin	Estimated glomerular filtration rate (eGFR)
Blood urea nitrogen (BUN)	Gamma glutamyl transferase (GGT)
Calcium	Glucose
Carbon dioxide/bicarbonate	Lactate dehydrogenase (LDH)
Chloride	Potassium
Creatine kinase	Sodium
Creatinine	Uric acid
Liver Function Tests	
Alkaline phosphatase (ALP)	Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)	Bilirubin (total and direct)
Coagulation Parameters	
International normalized ratio (INR)	Prothrombin time (PT)
Extended Hepatic Panel	
Quantitative HBsAg	Ferritin
Quantitative HBV DNA	Aldolase

Quantitative HBeAg	Blood phosphatidylethanol
HAV antibody IgM	Urinary ethyglucuronide
HCV antibody and HCV RNA	Anti-nuclear antibodies
HDV antibody or RNA	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
HDV antibody or RNA	Anti-mitochondrial antibodies
Epstein-Barr Virus antibodies, IgM and IgG	Anti-SLA antibodies
Cytomegalovirus antibodies, IgM and IgG	
Ceruloplasmin	
Imaging	
Abdominal ultrasound, including Doppler flow, if applicable; CT or MRI acceptable in place of ultrasound if clinically indicated	
Focused Medical History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption and drugs of abuse
Exposure to other potentially hepatotoxic agents including any work-related exposures (eg. solvents, pesticides, etc.)	Exercise history

CT = computed tomography; HAV = hepatitis A virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HEV = hepatitis E virus; IgG = immunoglobulin G antibody; IgM = immunoglobulin M antibody; LKM1 = liver/kidney microsome-1 antibody; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; RNA = ribonucleic acid; SLA = soluble liver antigen.

10.6. Appendix 6: Protocol Amendment History

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

Amendment 1.1 (Version 2.1) 17 November 2021

Overall Rationale

The changes from this amendment are to clarify that blood samples for PBMC isolation will be collected in planned participants only. Other minor changes include clarifications of study procedures.

Method of Amendment

The specific areas where changes were made to the protocol are listed below. Wording that has been deleted will be indicated with a strikethrough (ex. ~~Word~~) and new wording will be indicated in Bold type (ex. **Word**).

Amendment Details

Section 1.3.1 and Section 1.3.2 Schedule of Activities (SoA) Cohort A/B/C

Applied the existing footnote g to symptom-directed physical exam.

Added footnote to specify sample collection for PMBC analysis.

Footnote s: Blood sample for PBMC isolation will be collected in the planned participants (defined in Section 5.1 Number of Participants) only.

Corrected wording for AE collection.

Footnote v: All AEs related to screening activities must be collected from the time of consent ~~until end of study~~ **onwards**; any other events occuring during the screening period should be reported as medical history.

Section 1.3.3 Schedule of Activities (SoA) NrtI Discontinuation Monitoring Period

Added footnote to specify sample collection for PMBC analysis.

Footnote e: Blood sample for PBMC isolation will be collected in the planned participants (defined in Section 5.1 Number of Participants) only.

Section 4.1.1. Planned Cohorts and Dosing

Added clarifications to the duration of BRII-835 dosing period in each cohort.

Cohort A: Each participant will receive 9 doses of BRII-835 (VIR-2218) 100 mg administered SC every 4 weeks, **from Day 1 to Week 32**.

Cohort B: Each participant will receive 9 doses of BRII-835 (VIR-2218) 100 mg administered SC every 4 weeks, **from Day 1 to Week 32**; and will receive 9 doses of BRII-179 (VBI-2601) 40 µg with IFN-α 3 MIU administered IM every 4 weeks, from Week 8 to Week 40.

Cohort C: Each participant will receive 9 doses of BRII-835 (VIR-2218) 100 mg administered SC every 4 weeks, **from Day 1 to Week 32**; and will receive 9 doses of BRII-179 (VBI-2601) 40 µg administered IM every 4 weeks, from Week 8 to Week 40.

Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AE ~~related to screening activities~~ will be collected from the signing of ICF until the last follow-up visit at the time points specified in the SoA.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent, **that are deemed not related to the screening activities,** will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

Section 9.4.2 Primary endpoints

Clarified the definition of TEAEs.

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

Amendment 1 (Version 2.0) 04 March 2021

Overall Rationale

Based on the emerging data from non-clinical and clinical studies investigating the combination therapy of BRII-835 (VIR-2218) and BRII-179 (VBI-2601) treating chronic HBV infection, an optimized dose regimen has been proposed to achieve the functional cure. The changes implemented in the protocol amendment are to reflect the optimized dose regimen to be investigated in this clinical study.

Method of Amendment

The specific areas where changes were made to the protocol are listed below. Wording that has been deleted will be indicated with a strikethrough (ex. ~~Word~~) and new wording will be indicated in Bold type (ex. **Word**).

Amendment Details

Section 1.2 Schema

The schema is updated to reflect the updated dose regimen.

Section 1.3.1 Cohort A Schedule of Activities

Added ECI surveillance during Dosing Period and Follow-up Period.

Footnote o: Study drug BRII-835 will be administered via SC injection at Day 1, Week 4, Week 8, **Week 12**, Week 16, **Week 20**, Week 24, **Week 28**, and Week 32.

Footnote v: Participant will be monitored for clinical laboratory events of clinical interest (ECI) and additional assessments may be performed if indicated. ECI for this study include ALT > 3x ULN, if Day 1 predose ALT ≤ ULN; ALT > 2x baseline, if Day 1 predose ALT > ULN. See Section 8.2.8.

Section 1.3.2 Cohort B/**C** Schedule of Activities

Added ECI surveillance during Dosing Period and Follow-up Period.

Footnote o: Study drug BRII-835 will be administered via SC injection at Day 1, Week 4, Week 8, **Week 12**, Week 16, **Week 20**, Week 24, **Week 28**, and Week 32. Study drug BRII-179 with IFN-α **(Cohort B) or without IFN-α (Cohort C)** will be administered via IM injection starting from Week 8 and every 4 weeks for 9 doses.

Footnote v: Participant will be monitored for clinical laboratory events of clinical interest (ECI) and additional assessments may be performed if indicated. ECI for this study include ALT > 3x ULN, if Day 1 predose ALT ≤ ULN; ALT > 2x baseline, if Day 1 predose ALT > ULN. See Section 8.2.8.

~~Section 1.3.3 Cohort C Schedule of Activities~~

The entire section is removed. Cohort C SoA has been incorporated into Cohort B SoA.

Section **1.3.3** ~~1.3.4~~ NrtI Discontinuation Monitoring Period

Added additional visits at W16, W20, W32, and W40.

Footnote d: Participants from Cohort B **or Cohort C** will receive full safety laboratory assessments for Day 1 and Week 4 visits and liver function tests afterwards. ~~Participants from Cohort C will receive full safety laboratory assessments for Day 1, Week 4, and Week 8 visits and liver function tests afterwards.~~

~~Footnote e: Participants from Cohort A and B will only be assessed at Week 36; participants from Cohort C will only be assessed at Week 48.~~

Section 2.2.2 Rationale for Admixture of BRII-179 (VBI-2601) and IFN-α for Treatment of Chronic HBV Infection

In a recent study in an AAV-HBV mouse model of persistent HBV infection, BRII-179 demonstrated its ability to break the immune tolerance and to induce antigen specific

immune responses. **These BRII-179 induced HBV antigen specific immune responses were further enhanced by admixture with IFN-α.**

In this study, IFN-α will be **evaluated as a co-adjuvant** ~~used as an adjuvant~~ to BRII-179 (VBI-2601) by co-administering as a single intramuscular injection.

Section 2.3 Benefit/Risk Assessment

Therefore, the safety profile of BRII-835 (VIR-2218) supports exploration of the proposed treatment regimens of ~~6 doses of~~ BRII-835 (VIR-2218) **100 mg every 4 weeks for 9 doses** ~~for a treatment duration of 32 or 20 weeks~~.

The proposed **nine** ~~six~~ dose regiments for BRII-835 (VIR-2218) was designed to provide a greater magnitude and duration of HBsAg suppression than those that have been studied, i.e., two doses administered every four weeks, in order to maximize the probability of a favorable response.

Section 3.1 Objectives

The exploratory objective**s** ~~is~~ **are**:

- **To assess other antiviral activity of the combination therapy**

Section 3.2.1 Primary Endpoints

- **Percentage of participants with sustained HBsAg loss (defined as undetectable HBsAg for at least 24 weeks) during the 48-week follow-up period after NrtI withdrawal**
- ~~Percentage of participants meeting the NrtI withdrawal criteria at Week 44 (Cohort A/B) or Week 32 (Cohort C)~~
- Number of participants with Adverse Events (AE) and Serious Adverse Events (SAE) (up to Week 96 ~~[Cohort A/B] or Week 84 [Cohort C]~~)
- Number of participants with abnormalities in clinical laboratory tests~~, 12 lead electrocardiogram (ECG), and vital signs~~ (up to Week 96 ~~[Cohort A/B] or Week 84 [Cohort C]~~)

Section 3.2.2 Secondary Endpoints

- **Percentage of participants meeting the NrtI withdrawal criteria at Week 44**
- Percentage of participants with HBsAg loss with or without anti-HBs seroconversion **at Weeks 72**~~, and HBV DNA < LLOQ 24 weeks after NrtI withdrawal~~
- ~~Percentage of participants with HBsAg loss with or without anti-HBs seroconversion, and HBV DNA < LLOQ at Week 72 (Cohort A/B) or Week 60 (Cohort C) in those continuing NrtI treatment~~
- ~~Percentage of participants with sustained HBsAg loss (defined as undetectable HBsAg for > 24 weeks) 48 weeks after NrtI withdrawal~~
- Percentage of participants with HBsAg loss at any timepoint

- Percentage of participants with HBsAg seroconversion at any timepoint
- ~~Percentage of participants with HBV-DNA < LLOQ 48 weeks after NrtI withdrawal~~
- ~~Frequency of virologic and clinical relapse 48 weeks after NrtI withdrawal. Virologic release is defined as > 1 log increase from baseline in HBV DNA levels measured at 2 consecutive study visits; clinical relapse is defined as virologic relapse AND ALT > 2x ULN.~~
- ~~Percentage of participants requiring NrtI retreatment within 48 weeks after NrtI withdrawal~~
- **Change from baseline in serum HBsAg at Week 72**
- ~~Maximum change of serum HBsAg from Day 1 to Week 44 (Cohort A/B) or Week 32 (Cohort C)~~
- ~~Maximum change of serum HBsAg from Day 1 to End of Study~~
- Percentage of participants with Hepatitis B e-antigen (HBeAg) loss and/or Hepatitis B e-antigen antibody (anti-HBe) seroconversion at Week 44 ~~(Cohort A/B) or Week 32 (Cohort C)~~ in those that are HBeAg positive at screening
- Time to achieve HBsAg ~~and HBeAg~~ seroclearance ~~and seroconversion~~
- **Time to achieve HBsAg seroconversion**
- **Time to achieve HBeAg seroconversion**
- ~~Assessment of the effect on other markers of HBV infection including but not limited to~~ CCI [redacted]
- Evaluation of plasma exposure of BRII-835 (VIR-2218) **and its metabolites**
- Evaluation of ADA to BRII-835 (VIR-2218)
- Change from baseline in serum appearance **and/or titer** of **anti-HBs**, CCI [redacted] at any timepoint

Section 3.2.3 Exploratory Endpoints

- Change from baseline in HBV specific cellular immunity at any timepoint
- CCI [redacted]
- **Percentage of participants with HBsAg loss with or without anti-HBs seroconversion at 24 and 48 weeks after NrtI withdrawal**
- **Percentage of participants with HBsAg loss with or without anti-HBs seroconversion at Week 72 in those continuing NrtI therapy**
- **Frequency of virologic and clinical relapse 48 weeks after NrtI withdrawal. Virologic relapse is defined as > 1 log increase from baseline in HBV DNA levels measured at 2 consecutive study visits; clinical relapse is defined as virologic relapse AND ALT > 2x ULN.**
- **Percentage of participants requiring NrtI retreatment within 48 weeks after NrtI withdrawal**
- Percentage of participants with undetectable HBV-DNA (HBV DNA < LLOQ and Target Not Detected) **24 and** 48 weeks after NrtI withdrawal
- **Assessment of the effect on other markers of HBV infection including but not limited to** CCI [redacted]

Section 4.1 Overall Design

The study will include three cohorts evaluating different dose regiments of BRII-835 (VIR-2218) and/or BRII-179 (VBI-2601) with **or without** IFN-α in combination with NrtI for treatment of chronic HBV infection.

A total of **10** ~~15~~ evaluable adult participants are planned for Cohort A. **20** ~~30~~ evaluable adult participants are planned for both Cohort B and C, respectively.

Section 4.1.1. Planned Cohorts and Dosing

- **Cohort A:** Each participant will receive **9** ~~6~~ doses of BRII-835 (VIR-2218) 100 mg administered SC ~~(3 doses administered~~ every 4 weeks ~~followed by 3 doses administered every 8 weeks)~~.
- **Cohort B:** Each participant will receive **9** ~~6~~ doses of BRII-835 (VIR-2218) 100 mg administered SC ~~(3 doses administered~~ every 4 weeks ~~followed by 3 doses administered every 8 weeks)~~ and will receive 9 doses of BRII-179 (VBI-2601) 40 µg with IFN-α 3 MIU administered IM every 4 weeks, from Week 8 to Week 40.
- **Cohort C:** Each participant will receive **9** ~~6~~ doses of BRII-835 (VIR-2218) 100 mg administered SC every 4 weeks and will receive **9** ~~7~~ doses of BRII-179 (VBI-2601) 40 µg ~~with IFN-α 3 MIU~~ administered IM every 4 weeks, from Week 8 to Week **40** ~~32~~.

Participants will be assessed by the investigator for their eligibility of NrtI discontinuation at Week 44 ~~(Cohort A and B) or Week 32 (Cohort C)~~. Participants that meet NrtI withdrawal criteria may enter a 48-week NrtI discontinuation monitoring period for additional follow-up of the efficacy and safety of study intervention. Participants that do not meet NrtI withdrawal criteria ~~at the respective timepoints~~ will be followed until Week 72 ~~(Cohort A and B) or Week 60 (Cohort C)~~.

Estimated total duration for each participant will include the following: screening (up to 6 weeks), dosing period (32 weeks [Cohort A], 40 weeks [Cohort B and ~~]~~, ~~32 weeks [~~Cohort C]), and follow-up period (40 weeks [Cohort A], 32 weeks [Cohort B and ~~]~~, ~~28 weeks [~~Cohort C]). Eligible participants that meet NrtI withdrawal criteria at Week 44 ~~(Cohort A and B) or Week 32 (Cohort C)~~ may enter a 48-week NrtI discontinuation monitoring period from Week 48 ~~(Cohort A and B) or Week 36 (Cohort C)~~. Study assessments and procedures for each cohort are further described in Section 8.1.

Section 4.1.4.1 NrtI Discontinuation Criteria

- HBeAg negative (HBeAg **loss** ~~seroconversion~~ for participant with positive HBeAg at screening)
- HBsAg **loss** ~~< 100 IU/mL~~

Participants who are eligible to discontinue from NrtI therapy may enter NrtI Discontinuation Period on the first day of Week 48 ~~(Cohort A and B) or Week 36 (Cohort C)~~.

Participants discontinuing NrtI therapy will complete ~~additional~~ assessments of NrtI Discontinuation Monitoring Period ~~in addition to the scheduled follow-up assessments of respective cohorts per the SoA~~.

Section 4.1.4.2 NrtI Retreatment

- ALT 5-**15**~~10~~x ULN with elevated total bilirubin > 2 mg/dL (predominantly direct) and/or prolongation of prothrombin time (PT) **≥ 3 seconds**

Section 4.3 Justification for Dose

The entire section was updated based on the emerging data from non-clinical and clinical studies of the two agents.

Section 5.1 Number of Participants

A total of **50** ~~75~~ evaluable adult participants with virologically suppressed chronic HBV infection without cirrhosis on NrtI therapy are planned for this study.

- Cohort A: **10** ~~15~~ adult participants with chronic HBV infection without cirrhosis on NrtI therapy will be enrolled in Cohort A.
- Cohort B and C: **20** ~~30~~ adult participants each with chronic HBV infection without cirrhosis on NrtI therapy will be enrolled in Cohort B and Cohort C.
- Floater participants: up to 60 floater participants can be enrolled into **any existing cohort(s)** ~~Cohort B and/or Cohort C~~.

Section 5.2 Inclusion Criteria

9. Must be on NrtI therapy consisting of either entecavir, tenofovir disoproxil ~~fumarate~~ or tenofovir alafenamide for at least 12 months.

Section 5.2 Inclusion Criteria

10. HBsAg > 150 IU/mL **and < 3000 IU/mL** at screening.

Section 5.3 Exclusion Criteria

9. Previous treatment with IFN-α or pegylated-IFN-α.

Section 6.1.2 Dosage and Administration

Cohort	C
Intervention Name	BRII-835 (VIR-2218); BRII-179 (VBI-2601) ~~IFN-α~~

Type	Drug
Dose Formulation	Solution for Injection
Dose Level(s)	BRII-835 100 mg; BRII-179 40 μg; ~~IFN-α 3 MIU~~
Route of Administration	Prepare 0.5 mL of BRII-835 in one syringe; administer via SC injection. Prepare the ~~admixture of~~ required amount of BRII-179 ~~and IFN-α~~ in one syringe; administer via IM injection. Refer to the Pharmacy Manual for the details.

Section 6.5 Concomitant Therapy

Allowed NrtI therapy must be consisting of the following:

- Entecavir
- Tenofovir disoproxil ~~fumarate~~
- Tenofovir alafenamide

Section 6.5.1 Permitted Medications

- **Licensed SARS-CoV-2 vaccines, including those approved for emergency use by local authorities, for the prophylaxis of COVID-19 are allowed. Each COVID-19 vaccine administration should be ideally with a minimum of 14 days before or after BRII-179 (VBI-2601) administration. However, COVID-19 vaccines may be administered within a shorter period in situations to avoid barriers or delays to COVID-19 vaccination.**

Section 8.1.3 Dosing Period

All participants will receive BRII-835 (VIR-2218) administered SC every 4 weeks, i.e., at Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, and Week 32.

Participants enrolled in Cohort B and Cohort C will also receive 9 doses of BRII-179 (VBI-2601) with or without IFN-α administered IM every 4 weeks from Week 8 to Week 40.

~~Participants enrolled in Cohort A will receive BRII-835 (VIR-2218) administered SC at Day 1, Week 4, Week 8, Week 16, Week 24, and Week 32.~~

~~Participants enrolled in Cohort B will receive BRII-835 (VIR-2218) administered SC at Day 1, Week 4, Week 8, Week 16, Week 24, and Week 32, and will receive 9 doses of BRII-179 (VBI-2601) with IFN-α administered IM from Week 8 to Week 40, administered every 4 weeks.~~

~~Participants enrolled in Cohort C will receive BRII-835 (VIR-2218) 100 mg administered SC at Day 1, Week 4, Week 8, Week 12, Week 16, and Week 20 and will receive 7 doses of BRII-179 (VBI-2601) with IFN-α administered IM from Week 8 to Week 32, administered every 4 weeks.~~

Section 8.1.4 Follow-up Period

Participants will be assessed by the investigator whether they are eligible for discontinuation of NrtI therapy based on their Week 44 ~~(Cohort A and B) or Week 32 (Cohort C)~~ laboratory results. Eligible participants to discontinue NrtI therapy may enter into NrtI Discontinuation Monitoring Period from Week 48 ~~(Cohort A and B) or Week 36 (Cohort C)~~.

Participants that have NOT achieved NrtI discontinuation criteria (Section 4.1.4.1) by Week 44 ~~(Cohort A and Cohort B)~~ will be discharged from the study after completion of all follow-up visits at Week 72. ~~Participants that have NOT achieved NrtI discontinuation criteria by Week 32 (Cohort C) will be discharged from the study after completion of all follow-up visits at Week 60.~~

Section 8.1.5 NrtI Discontinuation Monitoring Period

Eligible participants who meet NrtI withdrawal criteria will be informed by the investigator to discontinue their NrtI medications on **the first day of their Week 48 and enter into** NrtI Discontinuation Monitoring Period ~~Day 1 (Week 48 [Cohort A and B] or Week 36 [Cohort C])~~. These participants will follow the NrtI Discontinuation Monitoring Period SoA (Section **1.3.3**~~1.3.4~~).

- ~~Cohort A and B: Participants discontinuing NrtI will enter into NrtI Discontinuation Monitoring Period (Section 1.3.4) as Day 1 on the first day of their Week 48.~~
- ~~Cohort C: Participants discontinuing NrtI will enter into NrtI Discontinuation Monitoring Period (Section 1.3.4) as Day 1 on the first day of their Week 36.~~

Section 8.2.9 Pharmacokinetic Assessments

Table 5 Pharmacokinetics Assessment Timepoints

Study Day/Week	**Protocol Time**		
	Predose	Dose	Postdose
Day 1	X[a]		X[b]

Day 224/ Week 32 ~~(Cohort A and B ONLY)~~ ~~Day 140/ Week 20 (Cohort C ONLY)~~	X[a]		X[b]

Section 9.1 Statistical Hypothesis

~~This an estimation study without formal hypothesis, and hence there is no multiplicity adjustment and statistical power consideration.~~

The null hypothesis is that the percentage of sustained HBsAg loss (defined as undetectable HBsAg for at least 24 weeks) during 48 weeks after NrtI withdrawal in each of the 3 cohorts is not different from a spontaneous annual HBsAg loss of 2%; the alternative hypothesis is that the percentage of sustained HBsAg loss in each cohort is at least 20%.

To adjust for multiple testing, hypothesis testing for sustained HBsAg loss will be conducted in the following prespecified order.

Cohort B will be tested at Step 1. If p-value is < 0.05 at Step 1, then Cohort C will be tested at Step 2. If p-value is < 0.05 at Step 2, then Cohort A will be tested at Step 3. If p-value is > 0.05 at Step 1, then testing at Steps 2 and 3 will not be conducted. If p-value is < 0.05 at Step 1 but > 0.05 at Step 2, then testing at Step 3 will not be conducted.

Section 9.2 Sample Size Determination

A total of 50 subjects will be randomized in a 10:20:20 ratio to Cohorts A, B, and C. This sample size will provide 78% power for Cohort A and 91% power for Cohorts B and C, respectively, to detect a difference of 18% in sustained HBsAg loss, as compared to a spontaneous HBsAg loss of 2%, using a two-sided exact test with a significance level (alpha) of 0.0500.

The rest of the previous sample size determination was removed.

Section 9.4.2 Primary Endpoints

The primary objective is to evaluate the safety, efficacy, and dose regimen of combination therapy of BRII-835 (VIR-2218) and BRII-179 (VBI-2601) which will be assess by calculating the percentage of participants **with sustained HBsAg loss (defined as undetectable HBsAg for at least 24 weeks) during 48 weeks follow-up period after NrtI withdrawal** ~~meeting NrtI withdrawal criteria at specified timepoints in respect of the dose regimens~~, as well as **incidences of** ~~clinical review of safety relevant parameters including~~ AEs and laboratory **abnormalities** ~~assessments~~.

The Per Protocol population will be used for calculating the percentage of participants **with sustained HBsAg loss by cohort** ~~meeting NrtI withdrawal criteria~~**. Each cohort**

will be compared with a 2% spontaneous annual HBsAg loss using a two-sided exact test at an alpha level of 0.05.

Additionally, subgroup analysis stratified by HBeAg status at baseline will be conducted with respect to ~~primary endpoints~~ **the percentage of participants with sustained HBsAg loss**.

Section 9.4.3 Secondary Endpoints

- **Percentage of participants meeting NrtI withdrawal criteria at Week 44 and** selected data relating to the antiviral activity, such as HBsAg, anti-HBs, HBeAg, anti-HBe, and HBV DNA levels, will be summarized by cohort and study visit along with corresponding change from baseline. Summaries of HBsAg loss, anti-HBs seroconversion, HBeAg loss, **and** anti-HBe seroconversion~~, clinical/virological relapse, and NrtI retreatment~~ will be provided by cohort and study visit.
- ~~Effect on other markers of HBV infection including~~ CCI ~~will be assessed by cohort. Details of the analysis will be provided in the SAP.~~

~~Additionally, subgroup analysis stratified by HBeAg status at baseline will be conducted with respect to secondary endpoints.~~

Section 9.4.4 Exploratory Endpoints

Summaries of other **antiviral activity and** HBV specific immunological responses, such as cellular immunity responses CCI will be provided by cohort **and/or NrtI withdrawal status at Week 44 as well as** ~~and~~ study visit.

Section 10.5 Appendix 5: Assessments in Participants Meeting Laboratory ECI Criteria

Additional assessment will be performed in participants who experience ALT elevations meeting laboratory ECI criteria (Section 8.2.8) ~~during the NrtI Discontinuation Monitoring Period~~.

In the Extended Hepatic Panel:

Blood ~~Serum~~ phosphatidylethanol

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