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

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Statistical Analysis Plan V1.1

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STATISTICAL ANALYSIS PLAN

Study 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
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LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CRF	case report form
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
ECG	Electrocardiogram
FAS	Full Analysis Set
Hb	Hemoglobin
HBV	hepatitis B virus
HLT	high-level term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ITT	intent to treat
LLT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NrtI	nucleos(t)ide reverse transcriptase inhibitors
PBMC	peripheral blood mononuclear cell
PK	pharmacokinetic
PP	per protocol
PT	preferred term
Q1, Q3	first quartile, third quartile
SAP	statistical analysis plan
SC	subcutaneously
SD	standard deviation
SI (units)	international system of units
SOC	system organ class
SRC	safety review committee
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings

ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study BRII-179-835-001. This SAP is based on the study protocol version 2.1 dated 17 November 2021 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for Study BRII-179-835-001. One interim analysis and one final analysis for efficacy and safety will be performed, the interim analysis will be conducted when the first dosed 50 subjects completed week 40 visit, the final analyses will be conducted when a total of 90 dosed subjects who have completed either (1) 72 weeks treatment and follow-up period for participants not meeting NrtI withdrawal criteria, or (2) last available subject completed thefollow up of the 48 weeks Nrtl Discontinuation Monitoring Period for participants meeting NrtI withdrawal criteria, or (3) withdrawal from the study prematurely. The analysis will provide the results based on 50 dosed subjects and 90 subjects, respectively.

1.1. Study Objectives

The primary objective of this study is as follows:

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

The secondary objectives of this study are as follows:

- 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.

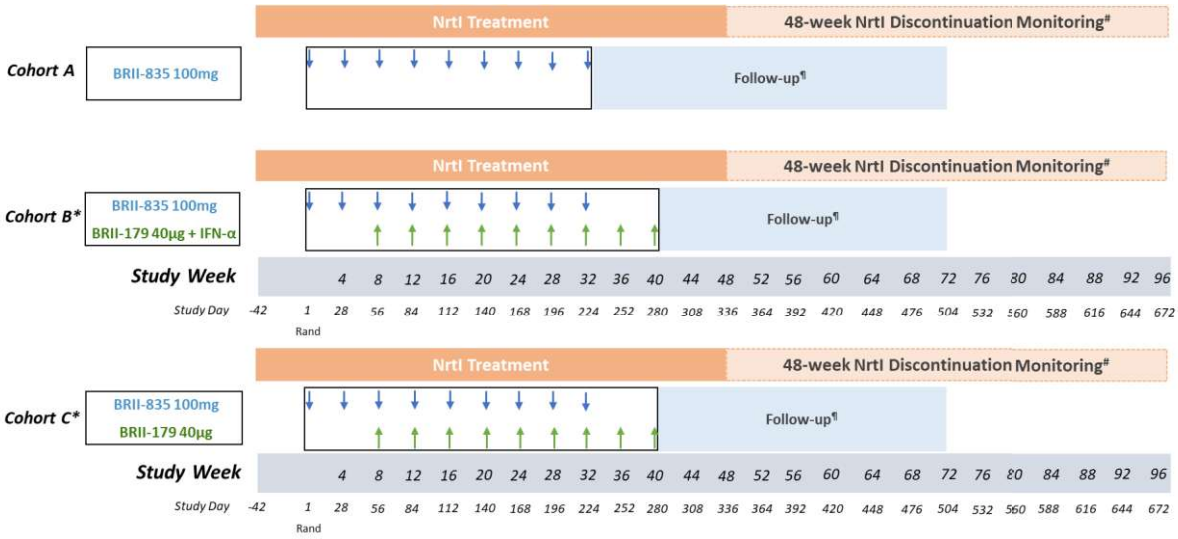
The exploratory objectives are as follows:

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

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

The study design schematic can be found below.



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.

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 and 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 and 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 (protocol 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 who 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 who 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 who 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 protocol Section 8.1.

Floater Participants: Based on SRC review of accumulated safety and efficacy data from planned cohorts, 40 floater participants will be enrolled in APAC regions and up to 20 floater participants may be added in mainland China to expand cohorts B and C to further evaluate safety, efficacy, and dose regimens of combination therapy. The allocation of floater participants is not required to be distributed evenly.

Safety Review Committee: A SRC for this study will monitor participants' 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 that 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.

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 (protocol Section 1.3.3).

NrtI Retreatment: It is recommended that the Investigator should consider retreatment with NrtI therapy during the NrtI Discontinuation Monitoring Period if participants meet the any of 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 in the protocol Section 1.3.3 for the duration of the 48-week NrtI Discontinuation Monitoring Period.

1.3. Sample Size and Power

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.

2. TYPE OF PLANNED ANALYSIS

The timepoint for primary endpoint analysis is defined as subjects who have completed either (1) 72 weeks treatment and follow-up period for participants not meeting NrtI withdrawal criteria, or (2) last available subject complete the follow up of the 48 weeks Nrtl Discontinuation Monitoring Period for participants meeting NrtI withdrawal criteria, or (3) withdrawal from the study prematurely.

2.1. Interim Analyses

Prior to the final analysis, interim analyses may be conducted and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program.

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 assessed 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 and will be tested at the 0.05 significance level. The primary analysis will be based on the 50 subjects meeting the timepoint for primary endpoint analysis.

After SRC review, 40 floater were enrolled in APAC regions to expand Cohort B and C and no floater had been enrolled in mainland China, the enrolment was stopped after 90 subjects were dosed.

One formal interim analysis and one final analysis will be conducted, the interim analysis will be conducted when the first dosed 50 subjects have completed week 40 visit or withdrawn from the study prematurely. This analysis will provide prelimilary efficacy and safety data. Descriptive summary will be presented, therefore no multiplicity is considered.

The Final analysis will be conducted when a total of approximately 90 subjects fulfill the primary endpoint analysis timepoint definition. The analysis will provide efficacy and safety data of the first 50 dosed subjects and all 90 dosed subjects, respectively.

2.1.1. Dose Escalation Analysis

Not Applicable.

2.1.2. Planned Internal Analysis

One formal interim analysis and one final analysis for efficacy will be performed.

The interim analysis will be conducted when the first dosed 50 subjects complete Week 40 Visit or withdrawal from the trial prematurely.

2.1.3. SRC (Safety Review Committee) Analysis

An Safety Review Committee (SRC) for this study will monitor participants' 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.

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.

The following data will be summarized to support SRC:

- Demographic information of subjects (ID, age, gender)
- Disease history, general medical history
- Concomitant medication
- IP dosing
- Current status in the study (ongoing, early withdrawal)
- Safety laboratory results (highlight with abnormalities)
- HBsAg quantitative results
- Adverse events
- Vital signs
- ECG

The SRC recommended to allocate the 60 floaters to either Cohort B or Cohort C in a 1:1 randomization ratio on 13 October, 2021.

2.2. Final Analysis

The final analysis will be conducted when all enrolled subjects fulfill the primary endpoint analysis timepoint definition.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

All data collected on the electronic case report form (eCRF) will be presented in the data listings and will be listed by subject identification number (in ascending order), sex, age, screening body weight and visit, where applicable. All summaries will be presented by Cohort.

When reporting descriptive statistics, the following rules will be applied, except for PK concentration data:

- Continuous variables: Descriptive statistics will include the number of non-missing values (n), arithmetic mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum values.

  The minimum and maximum values will be displayed to the same decimal precision as the source data; the Q1, Q3, arithmetic mean and median values will be displayed to one more decimal than the source data; SD value will be displayed to two more decimal than the source data for the specific variable.

  The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the abovementioned rules.

  n will be an integer. If no subjects have data at a given time point, then only n=0 will be presented.

  All data will be presented to a maximum of 3 decimal places.

- Categorical variables: Descriptive statistics will include counts and percentages per category. The denominator in all percentage calculations will be the number of subjects in the relevant analysis set with non-missing data, unless specifically stated otherwise. Percentages will be displayed to one decimal place.

  Percentage change from baseline values will be calculated and displayed to 1 decimal place in the listings. In the summaries, the mean and median percentage change from baseline values will be presented to 2 decimal places, the minimum and maximum values will be presented to 1 decimal place and the SD value will be presented to 3 decimal places.

  For categories where all subjects fulfill certain criteria, the percentage value will be displayed as 100. For categories where zero subjects fulfill certain criteria, there will be no percentage displayed. All other percentage displays will use 1 decimal place. Data listings will contain all reported and derived data.

Unless otherwise stated, the following methods will be applied:

- Repeat/unscheduled assessments: Values collected at unscheduled study visits/time points will be allocated to scheduled visit/time points according to the algorithms of analysis visit window together with values collected at scheduled visits/time points and be presented in summary tables. All collected data will be included in the data listings.

- Assessment windows: All assessments will be included in the data listings and no visit windows will be applied to exclude assessments that were performed outside of the protocol specified procedure windows.
- Result display convention: Results will be center aligned in all summary tables and listings. Subject identifiers, visits, and parameter labels may be left-aligned if required.
- Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:
    - Date only: YYYY-MM-DD
    - Date and time: YYYY-MM-DD HH:MM

If only partial information is available, unknown components of the date or time will be presented as 'NK' (not known), i.e., '2016-NK-NK'. Time will be reported in military time.

3.1. Key Definitions

The following definitions will be used:

- Baseline: The baseline value is defined as the last available, valid (quantifiable continuous or categorical value), and non-missing observation for each subject prior to first study drug administration unless otherwise specified. Repeat and unscheduled assessments will be included in the derivation of the baseline values
- Change from Baseline: The change from baseline value is defined as the difference between the result collected/derived at a post-baseline visit/time point and the baseline value.

  The change from baseline value at each post-baseline visit/time point will be calculated for all continuous parameters using the following formula:

  Change from Baseline Value = Result at Visit/Time Point – Baseline Value

  The change from baseline value will only be calculated if the specific post-baseline visit/time point result and the baseline value for the parameter are both available; otherwise, will be treated as missing.
- Study day: The study day of an event is defined as the relative day of the event starting with the date of the first study drug administration (reference date) as Day 1 (there will be no Day 0).

  The study day of events occurring before the first study drug administration will be calculated as:

  Study Day = (Date of Event - Date of First Study Drug Administration)

  For events occurring on or after Day 1, study day will be calculated as:

  Study Day = (Date of Event - Date of First Study Drug Administration) + 1

Study days will only be calculated for events with complete dates and will be undefined for events that are 'Ongoing' at the end of the study.

- Relative days compared to an alternative reference point will be calculated similarly, but the alternative starting reference start date will be used instead of the date of the first study drug dosing.
- HBsAg loss: HBsAg changing from positive at baseline to <LLOQ at any post-baseline visit.
- Anti-HBs seroconversion: Anti-HBs changing from negative (<10 IU/L) or missing at baseline to positive (>=10 IU/L) at any post-baseline visit.
- Anti-HBs response: at any post-baseline visit with either (i) post-baseline anti-HBs ≥ 2 IU/L if anti-HBs ＜2 IU/L at baseline or (ii) post-baseline anti-HBs ≥ 5 times the baseline anti-HBs if baseline anti-HBs was ≥ 2 IU/L.
- HBsAg seroconversion: HBsAg loss plus anti-HBs positivity (>=10 IU/L) at any post-baseline visit.
- Sustained HBsAg loss: quantitative HBsAg < LLOQ at all visits (scheduled and unscheduled) for ≥ 24 weeks.
- Anti-HBe seroconversion: Anti-HBe changing from negative or missing at baseline to positive at any post-baseline visit.
- HBeAg loss ($HBeAg^+$ subjects only): HBeAg changing from positive at baseline to negative at any post-baseline visit.
- HBeAg Seroconversion (HBeAg+ subjects only): HBeAg loss plus anti-HBe positivity at any post-baseline visit.

The LLOQ for HBsAg is defined as 0.05 IU/mL.

3.2. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion will be provided.

A listing of exclusion from analysis sets will be provided by subject.

3.2.1. Screened Analysis Set

The Screened Analysis Set will consist of all subjects who sign the informed consent form. The listing of eligibility criteria will be based on this population.

3.2.2. All Randomized Analysis Set

The All Randomized Analysis Set will include all randomized subjects, irrespective of whether they received any study treatment. Subjects will be summarized by the Cohort to which they were randomized, regardless of treatment actually received.

Important protocol deviation, demographic and baseline characteristics will be summarized by All Randomized Analysis Set.

3.2.3. Full Analysis Set

All participants, who are randomized and have received at least one dose of study intervention; and have evaluable measurements of antiviral activity and immunological markers will be included in Full Analysis Set.

It will be used as analysis population for sensitivity analysis of antiviral activity and immunological markers.

If total number of subjects achived sustained HBsAg loss is less than 2 the statistical analysis for the primary endpoint will not be performed and the corresponding sensitivity analysis will not be applicable, only descriptive statistics based on Full Analysis Set and Per Protocol Set will be provided instead.

3.2.4. Per Protocol Set

All participants, who are randomized; and not identified with important 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 (PP) Set.

Subjects fulfil the below compliance criteria will be include in the PP Set;

- Subjects who did not enter NrtI Discontinuation Monitoring Period completed Week 72 Visit or subjects who entered NrtI Discontinuation Monitoring Period completed at least 24 week NrtI Discontinuation Monitoring follow-up visit
- Subjects in cohort A received at least 8 doses of BRII-835, subjects in cohort B received at least 8 doses of BRII-835 and 8 doses BRII-179+IFN-α and subjects in cohort C received at least 8 doses of BRII-835 and 8 doses of BRII-179
-

In additional to the above compliance requirement a Per Protocol review meeting will be held to go through the important protocol deviations to identify the PP population prior to database lock.

PP Set will be used as analysis population of antiviral activity and immunological markers**.**

3.2.5. Peripheral Blood Mononuclear Cells (PBMC) Set

Participants are evaluable for cell mediated immunity will be included in the PBMC Analysis Set. Here "evaluable" refers to whose PBMC are collected and qualified for the ELISpot analysis. The analysis for the PBMC data will be based on this set.

3.2.6. Safety Analysis Set

All participants, who are randomized and take at least 1 dose of study intervention will be included in Safety Analysis Set. It will be used for reporting safety parameters. The Safety Analysis Set will be based on actual treatment received in case subjects receive any different treatment between which they are randomized. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration. For example, for subjects randomized to Cohort B or Cohort C but only receive the BRII-835 monotherapy treatment will be allocated to BRII-835 monotherapy treatment group (Cohort A).

All safety analyses will be based on Safety Analysis Set.

3.2.7. PK Analysis Set

All participants randomly assigned to Cohort A, B, or C, who have received at least 1 dose of BRII-835 (VIR-2218) and have at least 1 non-missing BRII-835 (VIR-2218) concentration data, will be included in PK Analysis Set.

3.3. Subject Grouping

For analyses based on the All Randomized Analysis Set, Full Analysis Set and PP Set, subjects will be grouped according to the Cohort which they are randomized. For analyses based on Safety Analysis Set, subjects will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

3.4. Strata and Covariates

Subjects will be randomly assigned to either Cohorts A, B or C via the interactive web response system (IWRS) in a 1:2:2 ratio using a stratified randomization schedule. Stratification will be based on the following variables:

- HBeAg status at screening (HBeAg-negative or HBeAg-positive)

If there are discrepancies in stratification factor values between the IWRS and the clinical database, the values recorded in the clinical database will be used for analyses.

3.5. Subgroup analysis

- HBeAg status at baseline will be conducted with respect to the percentage of participants with sustained HBsAg loss.

- All analysis for the whole population will be performed for subjects enrolled in Taiwan to fulfill the Taiwan regulatory requirement.

3.6. Multiple Comparisons

For the primary endpoint*:* Percentage of participants with sustained HBsAg loss (defined as undetectable HBsAg for at least 24 weeks) during the 48-week follow-up period after Nrtl withdrawal, in order to control the Family-wise Type I error, a hierarchal test will be used to compare each Cohort and spontaneous annual HBsAg loss of 2%.

Testing for superiority will be performed as follows:

1) Cohort B will be tested at Step 1. If p-value is < 0.05 at Step 1, Cohort B superiority will be claimed, otherwise the testing procedure will be stopped.

2) If Step 1 is passed, Cohort C will be tested at Step 2. If p-value is < 0.05 at Step 2, Cohort C superiority will be claimed, otherwise the testing procedure will be stopped.

3) If Step 2 is passed, Cohort A will be tested at Step 3. If p-value is <0.05, Cohort A superiority will be claimed.

3.7. Missing Data and Outliers

3.7.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.1.1, the handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for prior HBV and concomitant medications in Section 7.4.

3.7.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.8. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed.

If age at Day 1 is not available for a subject, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled subject was not dosed with any study drug, the randomization date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (e.g age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.
- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

Plasma concentrations that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. BLQ concentrations will be treated as 0 at predose time points, and as missing at postdose time points for determination of summary and order statistics. Geometric mean and geometric CV% will not be calculated if the concentrations is BLQ or missing at predose.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the subjects have concentration values of BLQ for a given time point, the minimum value will be displayed as "BLQ."
- If more than 50% of the subjects have concentration values of BLQ for a given time point, the minimum and median values will be displayed as "BLQ."
- If more than 75% of the subjects have concentration values of BLQ for a given time point, the minimum and median values will be displayed as "BLQ."
- If all subjects have concentration values of BLQ for a given time point, all order statistics (minimum, median, and maximum) and summary statistics will be displayed as "BLQ."

3.9. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows. The analysis visit windows for the parameters at different periods are listed in Table 3.1 – Table 3.15

- Prior to NrtI Discontinuation Monitoring Period

Table 3.1 Analysis Visit Windows for HBsAg Prior to NrtI Discontinuation Monitoring Period (Cohort A)

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	None	1
Week 4	28	2	42
Week 8	56	43	84
Week 16	112	85	140
Week 24	168	141	196
Week 32	224	197	252
Week 40	280	253	294

Week 44	308	295	406
Week 72	504	≥407	None

Table 3.2 Analysis Visit Windows for HBsAg Prior to NrtI Discontinuation Monitoring Period (Cohort B/C)

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	None	1
Week 4	28	2	42
Week 8	56	43	84
Week 16	112	85	140
Week 24	168	141	196
Week 32	224	197	252
Week 40	280	253	294
Week 44	308	295	336
Week 52	364	337	434
Week 72	504	≥435	None

Table 3.3 Analysis Visit Windows for Anti-HBs Prior to NrtI Discontinuation Monitoring Period(Cohort A)

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	None	1
Week 16	112	2	140
Week 24	168	141	196

Week 32	224	197	252
Week 40	280	253	294
Week 44	308	295	406
Week 72	504	≥407	None

Table 3.4 Analysis Visit Windows for Anti-HBs Prior to NrtI Discontinuation Monitoring Period(Cohort B/C)

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	None	1
Week 16	112	2	140
Week 24	168	141	196
Week 32	224	197	252
Week 40	280	253	294
Week 44	308	295	336
Week 52	364	337	434
Week 72	504	≥435	None

Table 3.5 Analysis Visit Windows for HBV DNA Prior to NrtI Discontinuation Monitoring Period (Cohort A)

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	None	1
Week 16	112	2	140

Week 24	168	141	196
Week 32	224	197	252
Week 40	280	253	294
Week 44	308	295	406
Week 72	504	≥407	None

Table 3.6 Analysis Visit Windows for HBV DNA Prior to NrtI Discontinuation Monitoring Period (Cohort B/C)

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	None	1
Week 16	112	2	140
Week 24	168	141	196
Week 32	224	197	266
Week 40	280	253	294
Week 44	308	295	336
Week 52	364	337	434
Week 72	504	≥435	None

Table 3.7 Analysis Visit Windows for HBeAg , Anti-HBe Prior to NrtI Discontinuation Monitoring Period (Cohort A/B/C)

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	None	1
Week 32	224	2	266

Week 44	308	267	406
Week 72	504	≥407	None

Table 3.8 Analysis Visit Windows for CCI [redacted] Prior to NrtI Discontinuation Monitoring Period (Cohort A/B/C)

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	None	1
Week 32	224	2	364
Week 72	504	≥365	None

Tabel 3.9 Analysis Visit Windows for Safety Laboratory Assessments Prior to NrtI Discontinuation Monitoring Period (Cohort A)

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	None	1
Week 4	28	2	42
Week 8	56	43	70
Week 12	84	71	98
Week 16	112	99	126
Week 20	140	127	154
Week 24	168	155	182
Week 28	196	183	210
Week 32	224	211	238
Week 36	252	239	266

Week 40	280	267	294
Week 44	308	295	406
Week 72	504	≥407	None

Tabel 3.10 Analysis Visit Windows for Safety Laboratory Assessments Prior to NrtI Discontinuation Monitoring Period (Cohort B/C)

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	None	1
Week 4	28	2	42
Week 8	56	43	70
Week 12	84	71	98
Week 16	112	99	126
Week 20	140	127	154
Week 24	168	155	182
Week 28	196	183	210
Week 32	224	211	238
Week 36	252	239	266
Week 40	280	267	294
Week 44	308	295	322
Week 48	336	323	350
Week 52	364	351	434
Week 72	504	≥435	None

Table 3.11 Analysis Visit Windows for Vital Signs Prior to NrtI Discontinuation Monitoring Period(Cohort A)

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	None	1
Week 16	112	2	168
Week 32	224	≥169	None

Table 3.12 Analysis Visit Windows for Vital Signs Prior to NrtI Discontinuation Monitoring Period(Cohort B/C)

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	None	1
Week 20	140	2	210
Week 40	280	≥211	None

Tabel 3.13 Analysis Visit Windows for ADA Prior to NrtI Discontinuation Monitoring Period(Cohort A/B/C)

Analysis Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	None	1
Week 16	112	2	168
Week 32	224	169	266
Week 44	308	≥267	None

- After NrtI Discontinuation Monitoring Period (Apply for Cohort A/B/C)

Table 3.14 Analysis Visit Windows for HBsAg, Anti-HBs, CCI after NrtI Discontinuation Monitoring Period

Analysis Visit	NDMP Day	Lower Limit	Upper Limit
NDMP Baseline	1	None	1
NDMP Week 8	56	2	84
NDMP Week 16	112	85	140
NDMP Week 24	168	141	196
NDMP Week 32	224	197	252
NDMP Week 40	280	253	308
NDMP Week 48	336	≥309	None

*NDMP: NrtI Discontinuation Monitoring Period

Table 3.15 Analysis Visit Windows for Safety Laboratory Assessments, HBV DNA and HBV sequence after NrtI Discontinuation Monitoring Period

Analysis Visit	NDMP Day	Lower Limit	Upper Limit
NDMP Baseline	1	None	1
NDMP Week 4	28	2	42
NDMP Week 8	56	43	70
NDMP Week 12	84	71	98
NDMP Week 16	112	99	126
NDMP Week 20	140	127	154
NDMP Week 24	168	155	196
NDMP Week 32	224	197	252

NDMP Week 40	280	253	308
NDMP Week 48	336	≥309	None

*NDMP: NrtI Discontinuation Monitoring Period

3.9.1. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity (e.g., normal will be selected over abnormal for safety electrocardiogram findings) for categorical data, and the most conservative value will be selected for efficacy data (e.g., negative will be selected over positive for HBeAg and HBsAg, whereas positive will be selected over negative for Anti-HBe and Anti-HBs).

- For post-baseline values:

    - Categorical variables:

— The most conservative value (e.g., abnormal will be selected over normal for safety ECG) within the analysis window will be selected, except for HBV serology (HBsAg, anti-HBs, HBeAg, and anti-HBe), for which the most favorable value (ie, <LLOQ will be selected over positive for HBsAg and HBeAg, whereas positive will be selected over negative for anti-HBs and anti-HBe) will be selected.

    - Continuous variables:

— If there are more than 1 value within an analysis window, the value collected closet to the nominal day will be selected.

— If there are 2 records that are equidistant from the nominal day, the later record will be selected.

— If there is more than 1 record on the selected day, the latest record will be selected; if these measurements were recorded at the same time or no time recorded, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by Cohort for each country, investigator and site name and presented in All Randomized Analysis Set. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of subjects in the stratum will be the total number of enrolled subjects. If there are discrepancies in the value used for stratification assignment between the IWRS and the clinical database, the value collected in the clinical database will be used. A listing of subjects with discrepancies in the value used for stratification assignment between the IWRS and the clinical database at the time of data finalization will be provided.

The randomization schedule used for the study will be provided as an appendix in the CSR.

- A summary of subject disposition will be provided by Cohort. This summary will present the number of subjects screened, subjects who meet all eligibility criteria but not randomized, , , and the number of subjects in each of the categories listed below:
- All screened subject
- Subjects meet eligibility but not randomized
- All randomized subject
- All treated subject
- Completed study drug administration
- Did not complete study drug administration with reasons for premature discontinuation of study drug
- Completed study
- Did not complete the study with reasons for premature discontinuation of study

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the All Randomized Analysis Set corresponding to that column. In addition, a flowchart will be provided to depict the disposition.

The following by-subject listings will be provided by subject identification (ID) number (in ascending order), age, sex and screening body weight to support the above summary tables:

- Reasons for premature study drug or study discontinuation
- Reasons for screen failure (will be provided by screened subject ID number in ascending order)

4.1.1. Duration of Exposure to Study Drug

Duration of treatment is calculated as (Date of Last Dose - Date of First Dose + 1) for the completers and calculated as (Discontinued Date-Date of First Dose +1) for subjects with prematurely discontinuation, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (e.g., 4.5 weeks). If the last study drug dosing date is missing, the latest date among the clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the dosing-treatment period will be used.

Duration of Treatment and Total number of injections for BRII-835, BRII-179+IFNα and BRII-179 will be summarized, respectively using descriptive statistics (n, mean, STD, Median, Q1, Q3, Min, Max) for the Safety Analysis Set.

No formal statistical testing is planned.

A by-subject listing of study drug administration and drug accountability will be provided separately by subject ID number, sex, age, race, body weight at Screening, and visit in chronological order.

4.1.2. Adherence to Study Drug

The level of prescribed adherence to the study drug regimen will be determined by the total doses of study drug taken relative to the total doses of study drug specified by the protocol.

The level of prescribed adherence of BRII-835, BRII-179+IFN-α and BRII-179 will be expressed as a percentage using the following formula:

$$\text{Prescribed Adherence (\%)} = \left(\frac{\text{Total Doses of Study Drug}}{\text{Total Doses of Study Drug Specified by Protocol}}\right) \text{x } 100$$

Descriptive statistics for the level of prescribed adherence with the number and percentage of subjects belonging to adherence categories (e.g., *{< 80%, ≥ 80 to ⩽ 90%, > 90%}*) will be provided by treatment group for the Safety Analysis Set.

No formal statistical testing is planned.

4.2. Protocol Deviations

Subjects who do not meet the eligibility criteria for study entry but enrolled in the study, will be summarized regardless of whether they are exempted by the sponsor or not. The summary will present the number and percentage of subjects who do not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by Cohort based on the All Randomized Analysis Set. A by-subject listing will be provided for those subjects who do not meet at least 1 eligibility criterion. The listing will present the eligibility criterion that subjects do not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring.The number and percentage of subjects with important protocol deviations, and the total number of important protocol deviations by deviation reason (e.g., nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by Cohort for the All Randomized Analysis Set. A by-subject listing will be provided for those subjects with protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic variables (i.e., age, sex, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2]) will be summarized by Cohort and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of demographic data will be provided for the All Randomized Analysis Set.

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number (in ascending order), sex, age, race, and body weight at Screening.

5.2. Other Baseline Characteristics

Other baseline characteristics include HBsAg, Log10 transformed HBsAg, HBeAg at Screening and ALT. These baseline characteristics will be summarized by Cohort and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of these baseline characteristics will be provided for the All Randomized Analysis Set. No formal statistical testing is planned.

A by-subject listing of other baseline characteristics will be provided by subject ID number (in ascending order), sex, age, race, and body weight at Screening.

5.3. Medical History

Medical history will be collected at screening.

Medical history will be summarized by treatment group and overall by the number and percentage of subjects using the Safety Analysis Set. No formal statistical testing is planned.

Listing of General medical history data will be provided.

6. EFFICACY ANALYSES

Efficacy endpoints analyses will be based on FAS and PP.

The interim analysis will be conducted when the first dosed 50 subjects from Cohort A, B or C complete week 40 visit or withdrawal from the trial prematurely, descriptive analysis will be conducted for all available data but statistical analysis for primary efficacy endpoint will not be conducted.

The final analysis will be conducted when a total of approximately 90 subjects fulfill the primary endpoint analysis timepoint definition, the analysis will provide efficacy and safety data of the first 50 dosed subjects and all 90 dosed subjects, respectively.

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint:

The primary Efficacy Endpoint is defined as 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.

Null hypothesis: there is no difference in percentage of participants with sustained HBsAg loss between each Cohort and a spontaneous HBsAg loss of 2% in a hierarchy test order (Cohort B → Cohort C → Cohort A).

H_0: P_t-P = 0

Alternative hypothesis: there is a difference in percentage of participants with sustained HBsAg loss between each Cohort and a spontaneous HBsAg loss of 2% in a hierarchy test order (Cohort B → Cohort C → Cohort A).

H_1: P_t-P ≠ 0

P_t indicates the percentage of participants with sustained HBsAg loss in Cohort A, Cohort B or Cohort C.

P indicates a spontaneous HBsAg loss of 2%

6.1.2. Estimand

The estimand for the primary objective is the difference in percentage of participants with sustained HBsAg loss between each Cohort and a spontaneous HBsAg loss of 2%.

Two Treatment strategies will be employed in this trial including below:

Treatment policy strategy: The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

Composite variable strategy: An intercurrent event is considered in itself to be informative about the patient's outcome and is therefore incorporated into the definition of the variable. A patient who discontinues treatment or trial prematurely will be considered as treatment failure (fail to achieve sustained HBsAg loss).

The estimand summary information are listed in the below table

Target Population	Analysis set (analysis population)
The target population are defined according to the inclusion/exclusion criteria in the protocol.	Full Analysis Set
Treatment	
Cohort A: BRII-835 monotherapy, Cohort B: BRII-835+BRII-179+ IFN-α or Cohort C: BRII-835+BRII-179	
Endpoint	
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.	
Handling of intercurrent events	
A treatment policy strategy and composite strategy will be used. Further details are provided after the table.	
Population-level summary measure	Analysis approach

Differences in percentage of participants with sustained HBsAg loss between each of 3 cohort and a spontaneous annual HBsAg loss of 2%.	Fisher exact test will be used to compare the percentage of participants with sustained HBsAs loss in each of 3 cohorts and a spontaneous annual HBsAg loss of 2% . Further details are provided after the table.

Intercurrent events and handling strategies:

In general subjects who remain in the trial throughout the trial period and use rescue treatment not due to HBV DNA rebound will be handled by treatment policy strategy, and subjects who discontinue from the trial prematurely during dosing period or fail to meet the criteria of entering NtrI withdrawal follow-up visits will be handled as treatment failure using composite variable strategy. The below table lists the details.

Intercurrent events	**Primary treatment strategy**	**Remark for the primary strategy**
Pause treatment (intermittent treatment)	Treatment policy	Comply with clinical practice
Discontinue from treatment prematurely but remain in the trial	Treatment policy	Comply with clinical practice
Use rescue treatment	Treatment policy	Comply with clinical practice
Initiate NrtI retreat during NrtI withdrawal follow up visit	Composite variable, patient will be treated as treatment failure	Lack of Efficacy is considered as treatment failure
Change background NrtI treatment	Treatment policy	Comply with clinical practice
Discontinue from the trial prematurely due to adverse event at IMP dosing period	Composite variable, patient will be treated as treatment failure	Patient can't tolerate the treatment and discontinue the treatment, which is regarded as treatment failure

Discontinue from the trial prematurely not due to adverse event at IMP dosing period	Composite variable, patient will be treated as treatment failure	Patient who does not enter the NtrI withdrawal follow up visits, will be treated as treatment failure
Fail to meet the criteria of entering NrtI withdrawal follow-up visits	Composite variable, patient will be treated as treatment failure	
Discontinue from the trial before the first 24 weeks during 48-week NtrI withdrawal follow up visits	Composite variable, patient will be treated as treatment failure	
Discontinue from the trial after maintaining sustained HBsAg loss at least 24 weeks during NtrI withdrawal follow up visits	Treatment policy, patient will be treated as treatment success	
Discontinue prematurely from the NtrI withdrawal 48-week follow up visits after completing 24-week follow up visits and does not meet at least 24 weeks sustained HBsAg loss	Composite variable, patient will be treated as treatment failure	
Provide 2 assessments of undetectable HBsAg in an interval of time not less than 24-week and the HBsAg values are either undetectable or missing in the intermittent visits between the two assessements during 48-week NtrI withdrawal follow up visits	Treatment policy, the subject will be treated as treatment sucess	

*Treatment failure: patient fails to achieve sustained HBsAg loss. IMP: Investigational Medical Product. rebound: Undetectable and/or HBV DNA detectable

6.1.3. Analysis methods for the primary endpoint

Fisher exact test will be used to compare the percentage of participants with sustained HBsAg loss and spontaneous annual HBsAg loss 2% in each cohort at a two-sided alpha level of 0.05 according to the pre-specified test order (B-C-A). Proportion point estimate and the 2-sided 95% exact confidence interval will be calculated based on the Clopper-Pearson method.

The SAS program is listed at below:

```
proc freq data=inputdata;
tables response/ binomial(p=0.02  level='Yes');
exact binomial;
run;
```

Assuming the response='Yes' when subject achieved sustained HBsAg loss at above SAS procedure.

The estimand together with the strategies of treatment policy and composite policy to handle intercurrent events will serve as primary analysis.

Subgroup analysis stratified by HBeAg status at screening will be conducted with respect to the percentage of participants with sustained HBsAg loss.

If total number of subjects achived sustained HBsAg loss is less than 2 the statistical analysis for the primary endpoint will not be performed and only descriptive statistics will be conducted.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of the Secondary Efficacy Endpoint

- 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
- Change from baseline in serum appearance and/or titer of anti-HBs at any timepoint

6.2.2. Exploratory Endpoints:

- Change from baseline in HBV specific cellular immunity at any timepoint
- 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

- HBV seroconversion definitions:

HBsAg Seroconversion: HBsAg loss plus anti-HBs positivity at any postbaseline visit.

The LLOQ for HBV DNA is defined as 10 IU/mL.

- NrtI withdrawal criteria definition

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).

6.2.3. Analysis Methods for Secondary Efficacy Endpoint

Kaplan-Meier plots will be created for the three Cohorts for the below three endpoints. Censoring rules are listed in the below table

- Time to achieve HBsAg seroclearance
- Time to achieve HBsAg seroconversion
- Time to achieve HBeAg seroconversion

	Data of event/censoring	Censoring
Patients who lost to follow up or patients who withdraw from the trial	Time from randomization to last lab test date	Y
Patients who don't achieve the HBsAg seroclearance	Time from randomization to last HBsAg, Anti-HBs, or Anti-HBe sample collection date, respectively	Y
Patients who don't achieve the HBsAg seroconversion		
Patients who don't achieve the HBeAg seroconversion		

Patients who achieve the HBsAg seroclearance	Time from randomization to date of achieving the target	N
Patients who achieve the HBsAg seroconversion		
Patients who achieve the HBeAg seroconversion		

Kaplan-Meier estimates (product-limit estimates) will be presented by Cohort together with the median time of achieving HBsAg seroclearance, HBsAg seroconversion and HBeAg seroconversion, respectively.

The proportion of percentage of participants meeting the NrtI withdrawal criteria at Week 44 will be summarized.

Summary table will be provided for HBsAg and HBeAg related serology results. The proportion of subjects who have ever had HBsAg loss, HBsAg loss with/without anti-HBs seroconversion, sustained HBsAg loss, undetectable HBV DNA, HBeAg loss and/or anti-HBe seroconversion, Virologic relapse, Clinical relapse will be summarized by Cohort, overall and visit.

For HBV specific cellular immunity, at each postbaseline visit, we claim a subject is a T cell responder if spot forming unit (SFU, sum of anti-HBsAg/anti-PreS1/anti-PreS2) >3 times the baseline SFU. Baseline is defined as the value of Day 1.

Where the following imputation rule will be implemented when calculating SFU:

1. Exclude datapoints if the SFU results were less than 2 times the maximum of the two negative controls.
2. For anti-HBsAg, anti-PreS1, and anti-PreS2, any results ≤ 0 will be imputed as 0.
3. SFU will be calculated based on the imputed anti-HBsAg, anti-PreS1, and anti-PreS2.
4. At baseline, if SFU ≤ 10 spots/1E6, it will be imputed as 10 spots/1E6. If baseline data is not available, the subject will be excluded from analysis.

If a subject is a T cell responder at any post-baseline visit, she/he will be classified as T cell responder during the study. The number and percentage of subject responded or not during the study will be summarized by treatment.

For HBV RNA result of "TND" or a numerical result smaller than the LLOQ (ie, 857 copies/mL) will be imputed as 856 copies/mL.

For HBcrAg result of "BQL" or a numerical result smaller than the LLOQ (ie, 3.0 log10 U/mL) will be imputed as 2.9 log10 U/mL.

All immunogenicity data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables.

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, Anti-HBs (IU/L). Parameters will be sorted within parameter class (if present) in alphabetical order within the tables and listings.

Measurements will present summary statistics for the results at the baseline and each scheduled post-baseline visit for each of the parameters. In addition, summaries will be presented for the change from baseline at each scheduled post-baseline visit.

Categorical summaries (% of participants) will present counts and percentages for the reported results at baseline and each post-baseline time point.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the vender Drug Safety before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date
- Any existing AEs worsen after treatment

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if the AE onset is the same as or after the month and year (or year) of the first dosing date of study drug.

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent.

In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

7.1.6.1. Summaries of AE Incidence by Severity

A brief, high-level summary of the number of percentage of subjects who experienced at least 1 TEAE in the categories described below will be provided by treatment. All deaths observed in the study will also be included in this summary.

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC and PT by treatment and overall.

For the AE categories described below, summaries will be provided by SOC, PT and treatment:

- TEAEs by maximum severity
- TEAEs with Grade 3 or higher
- TE treatment-related AEs
- BRII-835 treatment-related AEs
- BRII-179+IFN-α treatment-related AEs
- BRII-179 treatment-related AEs
- TE treatment-related AEs of Grade 3 or higher
- BRII-835 TE treatment-related AEs of Grade 3 or higher
- BRII-179+IFN-α TE treatment-related AEs of Grade 3 or higher

- BRII-179 TE treatment-related AEs of Grade 3 or higher
- TE treatment-related AEs by maximum severity
- TE SAEs
- TE treatment-related SAEs
- BRII-835 treatment-related SAEs
- BRII-179+IFN-α treatment-related SAEs
- BRII-179 treatment-related SAEs
- Injection site reaction
- TEAEs leading to premature discontinuation of BRII-835
- TEAEs leading to premature discontinuation of BRII-179+IFN-α
- TEAEs leading to premature discontinuation of BRII-179
- TEAEs leading to premature discontinuation of study
- TE SAEs leading to death (i.e., outcome of death)

Adverse events will be summarized and listed first in descending order of total frequency of SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a given subject during the study.

In addition to the above summary tables, all TEAEs, TE SAEs, TE treatment-related AEs, and TE treatment-related SAEs will be summarized by PT only in descending order of total frequency.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- All Deaths
- All SAEs leading to death (i.e., outcome of death)
- All AEs leading to premature discontinuation of study drug

- All AEs leading to premature discontinuation of study

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data throughout the trial.

For subjects who have permanently discontinued study drug, or all available data at the time of the database snapshot for subjects who were ongoing at the time of an interim analysis. The analysis will be based on values in standard units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics. Hemolized test results will not be included in the analysis, but they will be listed in by-subject laboratory listings.

A by-subject listing for laboratory test results will be provided by subject ID number, age, sex, race, body weight at Screening and visit in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity of Grade 1 or higher based on NCI-CTCAE Version 5.0 grading scale will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each post-baseline visit
- Change from baseline at each post-baseline visit

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a post-baseline visit will be defined as the visit value minus the baseline value.

7.2.2. Graded Laboratory Values

The NCI-CTCAE Version 5.0 will be used to assign toxicity grades (1 to 5) to laboratory results for analysis. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (i.e., increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any post-baseline visit. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment-emergent laboratory abnormalities.

7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of subjects in the study with the given response at baseline and each scheduled post-baseline visit.

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment; subjects will be categorized according to the most severe post-baseline abnormality grade for a given lab test:

- Graded laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with non-missing post-baseline values.

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Alanine aminotransferase (ALT): (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Total bilirubin: > 2 x ULN
- Alkaline phosphatase (ALP) > 1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN

The summary will include data from all post-baseline visits. For individual laboratory tests, subjects will be counted once based on the most severe post-baseline values. For both the composite endpoint of AST or ALT and total bilirubin, subjects will be counted once when the criteria are met at the same post-baseline visit date. The denominator is the number of subjects in the Safety Analysis Set who have non-missing post-baseline values of all relevant tests at the

same post-baseline visit date. A listing of subjects who met at least 1 of the above criteria will be provided.

7.3. Vital Signs

Descriptive statistics will be provided by Cohort for vital signs as follows:

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Vital signs measured at unscheduled visits will be included for the baseline value selection.

No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number, sex, age, race, screening body weight and visit in chronological order.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

Prior HBV medications are defined as any medications taken before a subject took the first study drug.

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 3 and preferred name using the number and percentage of subjects for each treatment and overall. A subject reporting the same medication more than once will be counted only once within each ATC drug class when calculating the number and percentage of subjects who received that medication. Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC medical class and then by preferred term in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year

(if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 3 and preferred name using the number and percentage of subjects for each treatment. A subject reporting the same medication more than once within each ATC drug class will be counted only once when calculating the number and percentage of subjects who received that medication. Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC medical class and then by preferred term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number, age, sex, race, screening body weight and administration date in chronological order.

7.5. Electrocardiogram Results

Electrocardiogram(ECG) will be summarized by treatment and visit.

The summary of overall interpretation findings table will present counts and percentages for the reported results at baseline and each post-baseline visit. Result categories will be ordered as 'Normal', 'Abnormal - Not Clinically Significant (NCS)' and 'Abnormal - Clinically Significant (CS)'.

The worst post baseline value will be the worst non-missing value after baseline and during the reference period. Scheduled visits, unscheduled visits, and repeat measurements will be included to derive the worst post baseline values (Abnormal CS is the worst, Abnormal NCS is next, then normal).

Additionally, shift tables from baseline in categories as 'Normal', 'Abnormal - Not Clinically Significant (NCS)', 'Abnormal - Clinically Significant (CS)' and 'Missing', will be summarized by counts and percentages.

A by-subject listing for ECG assessment results will be provided by subject ID number, sex, age, race, screening body weight and visit in chronological order.

7.6. ADA

Desriptive statistics based on Safety Analysis Set will be performed for ADA.

7.7. Other Safety Measures

No additional safety measures are specified in the protocol.

7.8. Changes From Protocol-Specified Efficacy Analyses

- CCI [redacted] will not be tested, CCI [redacted] had only been tested in a few subjects . Therefore sponsor decided that the corresponding endpoints will not be analyzed.
- Added if total number of subjects achived sustained HBsAg loss is less than 2, no formal analysis statistical analyses will be performed and only descriptive statistics will be provided instead.

7.9. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC EVALUATION/ANALYSIS

Individual subject concentration data for BRII-835 and it's metabolics CCI will be listed and summarized using descriptive statistics by treatment based on PK Analysis Set. Summary statistics (numbers of subjects, arithmetic mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean and Geometric CV) will be presented by time point and treatment.

No PK parameters will be reported in this study since only limited (sparse) PK samples were collected. The concentration data from this study will be pooled with data from other studies for population PK analysis, which will be reported separately.

9. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

10. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision
1.1	2.1,3.2	1. Reduced total analyses from 4 times to 2 times. 2. Took out the analyses for CCI [redacted] from the SAP 3. Added PK part statistical analysis 4. Added PBMC Set	1. Changed 3 times interim analyses and one time final analysis to one time interim analaysis and one time final analysis. 2. Sponsor decides to not to test CCI [redacted]. 3. Incorporate PK part statistical analiysis to the SAP as only descriptive statistics for PK concentration will be conducted. 4. Added PBMC Set to specify the analysis for PBMC will be based on this set.
	6.2.3	Updated the HBV T cell analysis derivation rule	The baseline has been changed from maximum value between randomization and Week 8 to the value at Day 1. The definition of a T cell responder has been changed to "A subject is defined as a T cell responder if the spot forming unit (SFU, sum of anti-HBsAg+anti-PreS1+anti-PreS2) >3 times of the baseline SFU at any postbaseline visit" instead of >3 times.