Statistical Analysis Plan Amendment 4

Study ID: 209348

Official Title of Study: Phase IIb Multi-Center, Randomised, Open Label Study to Assess the Efficacy and Safety of Sequential Treatment with GSK3228836 followed by Pegylated Interferon Alpha 2a in Participants with Chronic Hepatitis B Virus (B-Together)

NCT number: NCT04676724

Date of Document: 22-MAR-2023

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: Phase IIb Multi-Center, Randomised, Open Label Study to Assess the Efficacy and Safety of Sequential Treatment with GSK3228836 followed by Pegylated Interferon Alpha 2a in Participants with Chronic Hepatitis B Virus (B-Together)

Study Number: 209348

Compound Number: GSK3228836

Abbreviated Title: Phase IIb Study of Sequential GSK3228836 and Peginterferon Treatment in Participants with Chronic Hepatitis B (B-Together)

Acronym: B-Together

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	ID
IND	IND 22685
EudraCT	2020-002979-35

TABLE OF CONTENTS

Version History

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP v.1.0	17-Dec-2021	209348 v.1.0 (16-Oct-2020)	NA	Original version
SAP v.2.0	19-Jul-2022	209348 Amd v.1.0 (24-Sep-2021)	Updated to include details of IA.	IA has been added to the main study SAP for practicality reasons instead of being described in a separate document.
SAP v.3.0	22 Mar 2023	209348 Amd v.1.0 (24-Sep-2021)	Updates to estimand strategy wording throughout	Wording update for clarity and consistency with recent estimand strategy guidelines
			Section 4.2.5.2 Add additional estimand strategy for primary endpoint	Estimand added to investigate impact of wide disruptive events on primary endpoint

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Move decision-making to the iDRC charter	Decision making framework has been moved to simplify and reduce content in SAP
			Section 4.5.2.1 Removal of ISRs from AESIs	Removal of ISR from AESIs as per new safety reporting guidelines
SAP v.4.0	22 Mar 2023	209348 Amd v.1.0 (24-Sep-2021)	Section 4.1.3 Added Relapse Definitions	Additional outputs for EoS include relapse rates on GSK3228836, PegIFN, and OT. Relapse is also defined differently for the conservative and modified definitions of SVR.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Section 4.2.2 Model simplification by combining data across both treatment arms and removal of random effect from Bayesian model	Addresses the quasi-complete separation of the response variable when the model is run separately for each treatment arm (original model). In addition, the parameter estimates for the original hierarchical model do not converge, and the hierarchical model diagnostics are poor.
			Section 4.2.2.1 Definition of worst case selection within analysis windows	Alignment with conservative and modified definitions of SVR
			Section 4.2.2.2 Combined Sections for Handling Missing Data On-treatment, End of Treatment,	Maintain consistency with handling intercurrent events and missing data throughout the study

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			and Post-treatment	
			Section 4.3.1.1 Added Time from Bepi EOT to Relapse by HBsAg Categories Endpoint	Added Time to Event endpoint analysed during administrative IAs (AIAs)
			Section 4.4.1 Moved Exploratory Efficacy Endpoints to main body of SAP with reference in the IA section	Provide clarify that exploratory endpoints will be produced for both the planned IA and for EoS
			Section 4.5.3.1 Added information on handling duplicate LAB values at the same date/ timepoint	Clarity for programming purposes

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Section 6.1.5 Update to study intervention compliance and study dose compliance calculations	Adjust for PegIFN treatment period

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the final planned analyses to be included in the Clinical Study Report (CSR) for Study 209348, and to describe the analyses to be performed for the pre-specified interim analysis, which will be used in early Commit to Phase 3 (C2P3) decision making.

1.1. Objectives, Estimands and Endpoints

Study 209348 is intended to evaluate whether up to 24 weeks of treatment with GSK3228836 followed by up to 24 weeks of pegylated interferon (PegIFN) can increase the rate of hepatitis B virus surface antigen (HBsAg) loss in participants on stable nucleos(t)ide analogue (NA) therapy, and whether virologic response can be sustained once PegIFN treatment is discontinued. Study 209348 will also evaluate the safety and tolerability of the treatment regimen. In addition, pharmacokinetic, virology, and biomarker assessments will be evaluated for exploratory purposes.

Objectives and Estimands:

Objectives	Estimands and Endpoints
Primary	
Efficacy: To investigate the efficacy of two different durations of GSK3228836 followed by up to 24 weeks of PegIFN therapy in participants with CHB on stable NA therapy.	The main Estimand supporting the primary objective is defined as: • Population: Participants with CHB on stable NA therapy • Treatment: 300 mg GSK3228836 for 12 or 24 weeks followed by up to 24 weeks of PegIFN therapy while on stable NA therapy • Variable (Categorical): Participants achieving Sustained Virologic Response (SVR) (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of sequential treatment, without use of any rescue medication • Intercurrent Events: o Discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN not related to any wide disruptive events (such as COVID-19 pandemic) will be ignored (treatment policy strategy). o Ineligibility to receive PegIFN will be ignored (treatment policy strategy) o Use of rescue medication (composite strategy). o Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN will be handled assuming they had not happened (hypothetical strategy). • Population Summary: The percentage of participants in each treatment group who achieve SVR, without use of any rescue medication

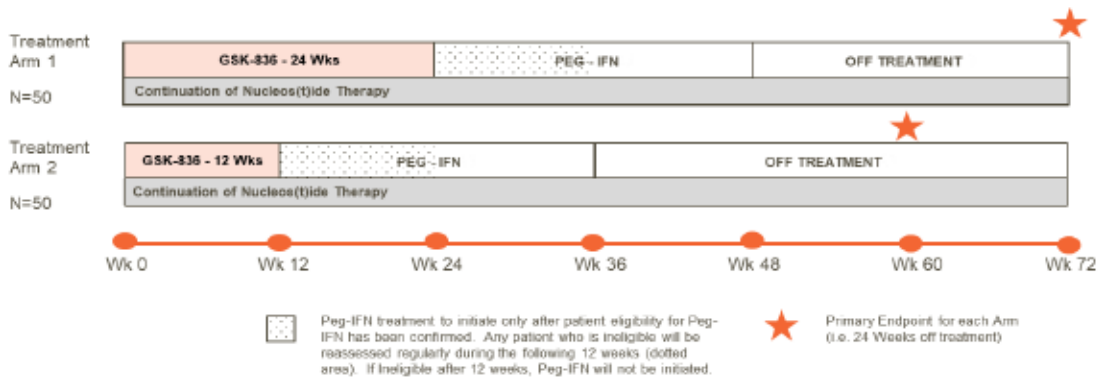
Objectives	Estimands and Endpoints
	The main primary estimand supporting the primary objective in participants with CHB on stable NA therapy in each treatment arm is the percentage of participants that achieve SVR (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of sequential treatment in the absence of rescue medication, regardless of ineligibility to receive PegIFN, discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN, had they not been affected by wide disruptive events. Three supplementary Estimands are defined to support the primary objective: • The first supplementary Estimand is defined in the same way as the main Estimand, except the assessment time frame for patients achieving SVR will be 24 weeks after the actual end of treatment. Therefore, the strategy for intercurrent events of treatment discontinuation will be while-on-treatment. This supplementary estimand supporting the primary objective in participants with CHB on stable NA therapy in each treatment arm is the percentage of participants that achieve SVR (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the actual end of sequential treatment in the absence of rescue medication, regardless of ineligibility to receive PegIFN, discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN, had they not been affected by wide disruptive events. • The second supplementary Estimand is to understand the relationship between the PegIFN duration and achieving SVR for 24 weeks after the actual end of treatment, defined as: o Population: Participants with CHB on stable NA therapy o Treatment: 300 mg GSK3228836 for 12 or 24 weeks followed by 24 weeks of PegIFN therapy while on stable NA therapy o Variable: The relationship between SVR for 24 weeks after actual end of treatment and the duration of PegIFN received by participants o Intercurrent Events: ▪ Discontinuation and delayed start of, PegIFN, will be accounted to reflect the actual duration from the first to the last dose of PegIFN received (while-on-treatment strategy).

Objectives	Estimands and Endpoints
	▪ Interruption in and other non-adherence to PegIFN will be ignored (treatment policy strategy) ▪ Discontinuation of, interruption in and non-adherence to GSK3228836 will be ignored (treatment policy strategy) ▪ Use of rescue medication (composite strategy). ▪ Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation and delayed start of, PegIFN will be handled with while-on-treatment strategy; wide disruptive events leading to interruption in and other non-adherence to PegIFN will be ignored (treatment policy strategy); wide disruptive events leading to discontinuation of, interruption in, and non-adherence to GSK3228836 will be ignored (treatment policy strategy). o Population Summary: The percentage of participants achieving SVR for 24 weeks after the actual end of treatment by PegIFN treatment duration categorical grouping in each treatment arm • The second supplementary Estimand (supporting the primary objective in participants with CHB on stable NA therapy) is the percentage of participants achieving SVR for 24 weeks after the actual end of treatment by PegIFN treatment duration categorical grouping in each treatment arm, taking into account discontinuation and delayed start of PegIFN, regardless of interruption in and other non-adherence to PegIFN, regardless of discontinuation of, interruption in and non-adherence to GSK3228836. • The third supplementary Estimand is defined in the same way as the main Estimand, except the strategy for intercurrent events of PegIFN ineligibility for more than 12 weeks and/or missing more than 12 doses of PegIFN will be principal stratum. This supplementary Estimand supporting the primary objective is the percentage of participants in each treatment arm that achieve SVR (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of sequential treatment in participants with CHB on stable NA therapy and receiving at least 12 doses of PegIFN, in the absence of rescue medication, regardless of discontinuation of, interruptions in or non-adherence to GSK3228836

Objectives	Estimands and Endpoints
	had they not been affected by wide disruptive events.

1.2. Study Design

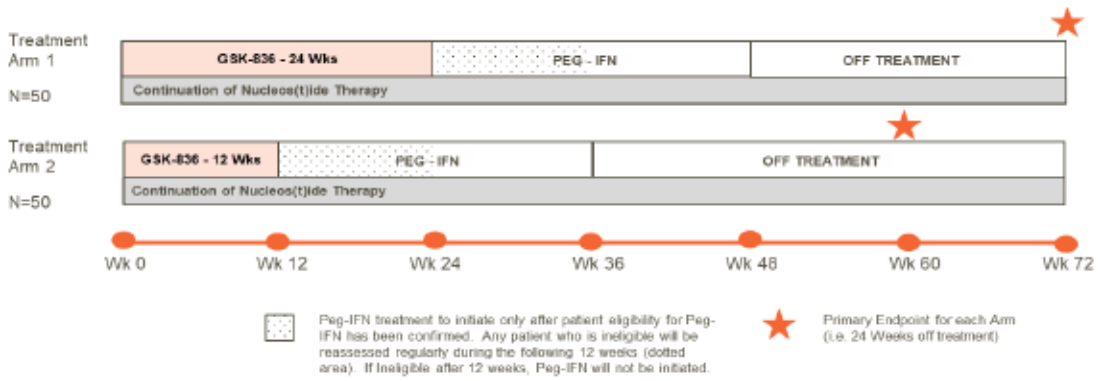
Overview of Study Design and Key Features



Design Features	• Phase IIb, multi-center, randomised, open label study to assess the efficacy and safety of sequential treatment with GSK3228836 followed by Pegylated Interferon Alpha 2a in participants with CHB while on stable nucleos(t)ide treatment.
Study Intervention	• Arm 1: 300 mg GSK3228836 once/week for 24 weeks (plus loading doses of 300 mg GSK3228836 on Day 4 and Day 11) followed by PegIFN (180 mcg/week for up to 24 weeks). • Arm 2: 300 mg GSK3228836 once/week for 12 weeks (plus loading doses of 300 mg GSK3228836 on Day 4 and Day 11) followed by PegIFN (180 mcg/week for up to 24 weeks).
Study Intervention Assignment	• Participants will be randomised in a 1:1 ratio to receive study intervention. Approximately 100 participants are planned to be enrolled in the study. The study team may enrol additional participants to within 10% of the planned 100.
Interim Analyses	• Administrative Interim analyes: interim analyses to support internal decision making at multiple timepoints throughout the study. • Planned efficacy Interim analysis: all participants complete the end-of-treatment visit and a sufficient number of participants complete off-treatment follow-up in order to assess the probability of C2P3. • Independent Data Monitoring Committee (IDMC) safety review: approximately every 3 months.

1.2. Study Design

Overview of Study Design and Key Features



Design Features	• Phase IIb, multi-center, randomised, open label study to assess the efficacy and safety of sequential treatment with GSK3228836 followed by Pegylated Interferon Alpha 2a in participants with CHB while on stable nucleos(t)ide treatment.
Study Intervention	• Arm 1: 300 mg GSK3228836 once/week for 24 weeks (plus loading doses of 300 mg GSK3228836 on Day 4 and Day 11) followed by PegIFN (180 mcg/week for up to 24 weeks). • Arm 2: 300 mg GSK3228836 once/week for 12 weeks (plus loading doses of 300 mg GSK3228836 on Day 4 and Day 11) followed by PegIFN (180 mcg/week for up to 24 weeks).
Study Intervention Assignment	• Participants will be randomised in a 1:1 ratio to receive study intervention. Approximately 100 participants are planned to be enrolled in the study. The study team may enrol additional participants to within 10% of the planned 100.
Interim Analyses	• Administrative Interim analyes: interim analyses to support internal decision making at multiple timepoints throughout the study. • Planned efficacy Interim analysis: all participants complete the end-of-treatment visit and a sufficient number of participants complete off-treatment follow-up in order to assess the probability of C2P3. • Independent Data Monitoring Committee (IDMC) safety review: approximately every 3 months.

2. STATISTICAL HYPOTHESES

The primary objective of the study is to investigate the effectiveness of GSK3228836 and PegIFN sequential therapy in CHB participants on stable NA therapy. The primary endpoint is achieving a sustained virologic response (SVR, HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of GSK3228836 and PegIFN sequential treatment in the absence of rescue medication. Rescue medication is defined as any medication initiated for the purpose of antiviral suppression other than the background stable NA therapy.

A secondary objective is to compare the efficacy between 24 and 12 weeks of GSK3228836 treatment followed by PegIFN for up to 24 weeks, measured by the proportion of participants that achieve virologic response at the planned end of sequential treatment and sustained for six months or more post-treatment. The aim of the study is to provide evidence for efficacy of GSK3228836 and PegIFN sequential therapy in reaching sustained virologic response, and to inform selection of treatment regimen for Phase III trials based on the comparison between the two arms.

The primary aim for the study is descriptive, hence no formal hypothesis testing is planned. A probability inference approach will be used for decision-making. The primary assessment of interest is the SVR rate of each treatment group. The point estimates for SVR and 95% credible intervals will be calculated using a Bayesian probability approach. In addition, posterior probabilities that the true SVR in each treatment arm is greater than a range of clinically meaningful response rates will be provided.

Comparisons between treatment arms as defined in the key secondary objectives will be assessed using probability inference approaches.

2.1. Multiplicity Adjustment

No adjustments will be made for multiplicity.

3. ANALYSIS SETS

The following populations are defined for the analyses:

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	Study Population
Enrolled	• All participants who passed screening (met eligibility criteria) and entered the study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study are excluded from the Enrolled population as they did not enter the study.	Study Population
ITT	• All randomised participants. • This population will be based on the treatment the participant was randomised to. • Any participant who receives a treatment randomisation number will be considered to have been randomised.	Efficacy
Safety	• All participants who were randomised and received at least one dose of study treatment. • This population will be based on the treatment the participant received. • Note: Participants who were not randomised but received at least one dose of study treatment will be listed.	Safety Virology
Pharmacokinetic (PK)	• All participants in the Safety population who received an active study treatment and had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values) • Note: PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether the sample will be excluded.	PK
Pharmacodynamic (PD)	• All participants in the Safety population for whom a Pharmacodynamic sample was obtained and analysed.	PD

4. STATISTICAL ANALYSES

4.1. General Considerations

All analyses will be performed based on the population of participants with CHB on stable nucleos(t)ide therapy.

The following definitions and abbreviations will be used throughout to define time points for key efficacy endpoints and estimand criteria:

Time point	Definition	Abbreviation
End of treatment	End of sequential treatment of GSK3228836 and Peginterferon. Time point is expected at week 48/36 for Arm 1/Arm 2.	EoT
End of off-treatment follow-up after end of treatment	End of 24 weeks of off-treatment follow-up after end of treatment. Time point is expected at week 72/60 for Arm 1/Arm 2	EoT+24wks
End of study	Final scheduled assessment visit. Time point is expected at week 72 for Arm 1/Arm 2	EoS

The following definitions and abbreviations will be used to define reporting of scheduled efficacy visits:

Time point	Definition	Abbreviation
Scheduled End of GSK3228836 and PegIFN Sequential Treatment	Scheduled visit Week 48 in Arm 1 and Scheduled visit Week 36 in Arm 2.	PegIFN W36/W48
Scheduled End of 24 Weeks after Sequential Treatment	Scheduled visit Week 72 in Arm 1 and Scheduled visit Week 60 in Arm 2.	OT-W24

4.1.1. General Methodology

Participants who prematurely withdrew from study will not be replaced.

In the case of incorrect randomization stratification assignment at the time of randomization, the analyses will be performed based on the actual stratum per data collected in the baseline lab electronic Case Report Form (eCRF). In the case of randomization to the incorrect strata (i.e., if a HBsAg subject is randomised to the HBeAg strata, or vice versa), analysis will be performed based on the actual strata the subject should have been assigned to.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum, and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

Unless otherwise specified, CIs will use 95% confidence levels.

HBV DNA, HBsAg and HBeAg levels below the LLOQ will be imputed for summaries of actual values and change from baseline. The numeric values for HBV DNA <LLOQ (LLOQ=20 IU/mL) will be imputed as 19.9. The numeric values for HBsAg <LLOQ (LLOQ=0.05 IU/mL) will be imputed as 0.04. The numeric values for HBeAg <LLOQ (LLOQ=0.06 U/mL) will be imputed as 0.05."

HBV DNA (IU/mL) and HBV RNA (copies/mL) levels that are "TND" will be imputed as 1. HBcrAg (Log10 U/mL) values that are "TND" will be imputed as 0. Values <LLOQ are imputed based on the number of significant digits, similar to other lab parameters.

4.1.2. Baseline Definition

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. If there are multiple assessments collected at the same scheduled time, the average of these assessments will be used as the baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Baseline of estimated glomerular filtration rate (eGFR) is defined as the mean of all pre-dose values, from screening to Day 1 pre-dose assessment.

4.1.3. Relapse Definition

One way to illustrate response durability and the benefit of adding PegIFN sequential therapy is to consider time to relapse among Bepi and/or PegIFN End of Treatment (EOT) responders. Time to relapse from end of Bepi treatment will be calculated using the Bepirovirsen EOT window with the following limits referred to in Section 4.2.2.1.

Only participants who were virologic responders at the end of Bepirovirsen EOT (See Section 4.2.2.1 windowing rules) without any prior rescue medication will be considered.

The start date used to measure the time to relapse will be the date of the first visit in the appropriate window where the participant is a responder and remains a responder at all subsequent visits within the window. Response and relapse rates can be evaluated under the conservative and modified definition of SVR.

Discontinuation interruption in, or non-adherence to GSK3228836 and PegIFN related or unrelated to wide disruptive events (WDEs) will be analysed as collected when determining relapse (treatment policy strategy).

4.1.3.1. Relapse under Conservative Definition (SVR)

Relapse date is defined as the first visit after the appropriate window end date where observed data for either HBsAg or HBV DNA is greater than the lower limit of quantification (LLOQ) or the use of rescue medication.

4.1.3.2. Relapse under the Modified Definition of SVR

Relapse date is defined as the first visit after the appropriate window end date where observed data for either HBsAg or HBV DNA is >LLOQ at two consecutive visits for the same parameter or the use of rescue medication.

Any observation of HBsAg ≥LLOQ or HBV DNA ≥LLOQ at a visit must be confirmed individually at a consecutive visit (including unscheduled visits or the first visit after the end of the analysis window).

4.2. Primary Endpoint Analyses

HBsAg and HBV DNA assessments from the end of treatment analysis window (Week 48 or Week 36 for Arm 1 and Arm 2 respectively) to the off-treatment Week 24 analysis window will be used to analyse the primary endpoint for each arm. The primary analysis for the primary endpoint will be conducted once the database lock has been achieved and the last participant has completed the Week 72 visit.

The primary efficacy endpoint is achieving a sustained virologic response for 24 weeks after the planned end of GSK3228836 and PegIFN sequential treatment in the absence of rescue medication. Sustained virologic response (SVR) is defined as observing HBsAg <LLOQ and HBV DNA <LLOQ at each analysis window in the 24 weeks after the end of sequential treatment. Analysis windows for the post GSK3228836 treatment assessments are defined in Section 4.2.2.1.

An estimation approach with no hypothesis testing will be used to address the primary objective. The primary assessments of interest are the point estimate of SVR rate and 95% credible intervals. In addition, posterior probabilities that the true SVR rate in each treatment arm is greater than a range of clinically meaningful response rates will be provided. The point estimates for SVR will be calculated using a Bayesian probability approach. Comparisons between treatment arms as defined in the key secondary/exploratory objectives will be assessed using probability inference approaches.

4.2.1. Definition of Estimands

The primary estimand supporting the primary objective is defined as:

- **Population:** Participants with CHB on stable NA therapy.
- **Treatment:** 300 mg GSK3228836 for 12 or 24 weeks followed by up to 24 weeks of PegIFN therapy while on stable NA therapy.
- **Variable (Categorical):** Participants achieving sustained virologic response (SVR) (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of sequential treatment, without the use of rescue medication.
- **Intercurrent Events:**
    - For discontinuation of, interruption in, or non-adherence to GSK3228836 or PegIFN unrelated to any wide disruptive events (such as COVID-19 pandemic), the data will be analysed as collected (treatment policy strategy).
    - For participants that are ineligible to receive PegIFN, the data will be analysed as collected (treatment policy strategy).
    - Use of rescue medication will be incorporated in the definition of the endpoint (composite strategy).
    - For wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, significant interruption in, or non-adherence to GSK3228836 and PegIFN, data collected after the intercurrent event will

be set to missing and the response will be imputed assuming missing at random in the Bayesian model. Additional details provided in Section 4.2.2.2 (hypothetical strategy).

- **Population Summary:** The percentage of participants in each treatment group who achieve sustained virologic response (SVR) (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of sequential treatment without rescue medication usage.

4.2.2. Main Analytical Approach

A Bayesian model will be fitted using Markov Chain Monte Carlo (MCMC) methods, and will be used to estimate the posterior probability of SVR sustained virologic response for each arm incorporating the baseline analysis stratification factors (Table 1) [Jones, 2011].

The model below differs from the Bayesian hierarchical model specified in the 209348 Protocol Amendment v.1.0 (24-Sep-2021), This hierarchical model included a random effect ψ_g for each strata, an interaction term for treatment by stratum, and was applied separately for each arm. However, when the model was run on data from the administrative interim analyses (AIAs) (see Section 4.7), there were stratum with zero counts which caused perfect prediction of the response variable for some values of the predictors (quasi-complete separation). To address this issue, the hierarchical model was simplified to the Bayesian logistic regression model below, with only fixed effects and combined data across arms.

The number of responders is assumed to follow a binomial distribution:

$$Number\ of\ responders\ r_g \sim Binomial(n_g, p_g), \qquad g = 1, 2, 3, 4$$

where we define r_g as the number of SVR responders among n_g participants, p_g as SVR rate $\frac{r_g}{n_g}$, and index g refers to the stratum number as defined in Table 1 below.

The analysis model is defined as:

$$\theta_g = logit(P_g) = \log\left(\frac{P_g}{1-P_g}\right) = \tau + \gamma 1 I_{\{B1+\}} + \gamma 2 I_{\{B2+\}} + \gamma 3\ I_{\{\text{Arm}\}}$$

where τ, γ_1, γ_2, are all parameters. Thus,

$\theta_1 = \tau$

$\theta_2 = \tau + \gamma_1$

$\theta_3 = \tau + \gamma_2$

$\theta_4 = \tau + \gamma_1 + \gamma_2$

Priors:

$$\tau \sim Normal\ (0, 10^6)$$

$$\gamma_k \sim Normal\left(0, 10^6\right), k = 1, 2$$

Table 1 Baseline Analysis Strata

Stratum	B_1: HBsAg	B_2: HBeAg
1: HBsAg ≤3 log IU/mL and Negative HBeAg	B_{1-} (≤3 log IU/mL)	B_{2-} (Negative)
2: HBsAg >3 log IU/mL and Negative HBeAg	B_{1+} (>3 log IU/mL)	B_{2-} (Negative)
3: HBsAg ≤3 log IU/mL and Positive HBeAg	B_{1-} (≤3 log IU/mL)	B_{2+} (Positive)
4: HBsAg >3 log IU/mL and Positive HBeAg	B_{1+} (>3 log IU/mL)	B_{2+} (Positive)

The point estimates and 95% credible intervals of sustained virologic response rate in each of the treatment arms will be calculated.

For each arm, the posterior distribution of SVR rate P(p_g|data), g=1,2,3,4 will be derived for each analysis stratum using the model specified above:

$$P(p_1|data) = P(\frac{e^{\theta_1}}{1+e^{\theta_1}}|data)$$

$$P(p_2|data) = P(\frac{e^{\theta_2}}{1+e^{\theta_2}}|data)$$

$$P(p_3|data) = P(\frac{e^{\theta_3}}{1+e^{\theta_3}}|data)$$

$$P(p_4|data) = P(\frac{e^{\theta_4}}{1+e^{\theta_4}}|data)$$

The posterior distribution of the arm-level SVR rate will be derived using a mixture of the posterior distributions of SVR rate for each analysis stratum in that arm. The weights are proportional to the sample size of each analysis stratum in each arm:

$$P(p|data) = \sum_{g=1}^{4} w_g P\left(p_g|data\right), \text{ where } w_g = \frac{n_g}{\sum_{g=1}^{4} n_g}$$

Posterior probabilities of SVR rates exceeding a range of clinically meaningful response rates, e.g., 30%, 35%, 40%, will be generated using the approach specified above for each arm. If monotherapy in study 209668 (B-Clear) is deemed successful, then posterior probabilities will be derived for a difference > 10% and <15% of the SVR rates between any B-Together arm and the B-Clear chosen arm to evaluate whether sequential therapy is successful.

4.2.2.1. Visit Windowing and Multiple Measurements at One Analysis Timepoint

Visit windowing for the primary end-point will be applied as specified in Table 2 and Table 3, and the windowed results will be used to determine the primary endpoint of SVR. Unscheduled assessments will be included in the analysis window. No imputation of missing data will be performed prior to visit windowing.

If there are multiple values within an analysis window the following rules will be applied:

For the end of GSK3228836 treatment and PegIFN treatment analysis timepoints, the latest available assessment in the window will be selected, with the worst non-missing value chosen first. The worst case ordering is as follows:

1. No Virologic Response
2. Missing due to WDE[1]
3. Virologic Response
4. Missing (unrelated to WDEs)

For post end of sequential treatment analysis timepoints:

1. Worst non-missing value in the analysis window will be selected.
   a) If values are the same, then the value closest to target day will be selected. If there are multiple values equidistant from the target day, the earliest will be selected.
   b) If all values within an analysis window are missing, then the result is missing for the analysis window.
2. Worst value is defined in the order of highest actual value, then <LLOQ, and then TND.

[1] Missing due to WDE will be considered based on whether original value for the assessment is missing or is a non-response. If the original value at an assessment is 'No Virologic Response' prior to imputation for WDEs, then the assessment will be classified as 'Missing to due WDEs'. If the original value at an assessment is 'Missing' prior to imputation for WDEs, then the preceding non-missing value within the window will be selected.

Table 2 Primary Endpoint Analysis Visit Windows for Arm 1

Analysis Set	Parameter	Target Study Day	Analysis Window		Analysis Timepoint	Protocol Visit
			Beginning Timepoint	Ending Timepoint		
Efficacy	HBsAg and HBV DNA	162	148	Minimum of (182, PegIFN First Dosing Study day)	End of GSK3228836 treatment	Week 24
Efficacy	HBsAg and HBV DNA	330	295	350	End of PegIFN treatment / EoT	Week 48
Efficacy	HBsAg and HBV DNA	386	351	406	Post PegIFN treatment Week 8	Off-treatment Week 8
Efficacy	HBsAg and HBV DNA	456	407	462	Post PegIFN treatment Week 18	Off-treatment Week 18
Efficacy	HBsAg and HBV DNA	498	463	518	Post PegIFN treatment Week 24	Off-treatment Week 24

Table 3 Primary Endpoint Analysis Visit Windows for Arm 2

Analysis Set	Parameter	Target Study Day	Analysis Window		Analysis Timepoint	Protocol Visit
			Beginning Timepoint	Ending Timepoint		
Efficacy	HBsAg and HBV DNA	78	64	Minimum of (98, PegIFN First Dosing Study day)	End of GSK3228836 treatment	Week 12
Efficacy	HBsAg and HBV DNA	246	211	266	End of PegIFN Treatment / EoT	Week 36
Efficacy	HBsAg and HBV DNA	302	267	322	Post PegIFN treatment Week 8	Off-treatment Week 8
Efficacy	HBsAg and HBV DNA	372	323	378	Post PegIFN treatment Week 18	Off-treatment Week 18
Efficacy	HBsAg and HBV DNA	414	379	434	Post PegIFN treatment Week 24	Off-treatment Week 24

The primary analysis will be based on planned end of treatment regardless of whether a patient discontinued treatment.

For the first and second supplementary estimands described in Section 4.2.4.1 and Section 4.2.4.2, SVR will be measured from actual rather than planned end of treatment and the analysis windows should be amended accordingly. For these estimands, the date of last dose should be treated as the reference date and the rules in Table 4 should be used to determine the endpoint of SVR.

Table 4 Supplementary Endpoint Analysis Visit Windows for Arm 1 and Arm 2

Analysis Set / Domain	Parameter	Reference Day	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Efficacy	HBsAg and HBV DNA	Reference date	Reference date - 35	Reference date + 20	End of Actual treatment
Efficacy	HBsAg and HBV DNA	Reference date + 56	Reference date + 21	Reference date + 76	Post treatment Week 8
Efficacy	HBsAg and HBV DNA	Reference date + 126	Reference date + 77	Reference date + 132	Post treatment Week 18
Efficacy	HBsAg and HBV DNA	Reference date + 168	Reference date + 133	Reference date + 188	Post treatment Week 24

If all analysis windows have non-missing response information, a participant's response (Responder or Non-responder) is determined as follows:

1. If rescue medication was used during on-treatment or off-treatment period, then the participant is a non-responder.
2. If HBsAg <LLOQ and HBV DNA <LLOQ in each of the analysis windows, then the participant is a responder, otherwise the participant is non-responder.
3. A result of TND is considered as <LLOQ.

4.2.2.2. Intercurrent Events and Missing Data

Intercurrent events during the on-treatment phase of the study can result in missed on-treatment visits and participant data not being collected. This missing data can potentially confound the interpretation of the primary endpoint. The intercurrent event of use of rescue medication has been incorporated into the definition of the variable (composite strategy). The intercurrent event of discontinuation of, interruption of, and adherence to investigational product (IP) unrelated to wide disruptive events (WDEs) will be analysed as collected (treatment policy).

Missing Primary Data On-Treatment, End of Treatment (EOT) and Off-Treatment

For participants where WDEs on-treatment result in discontinuation of, significant interruption of, and adherence to investigational product (IP), and the participant returns to the study and has data in the on-treatment period, the data will be handled in the following two ways:

1. For observed VR responders, the data will be analysed as collected (treatment policy). No imputation of missing data will be performed.
2. For observed VR non-responders, data collected after the intercurrent event will be set to missing. Their SVR response will be imputed assuming missing at random using all available data from participants for whom SVR can be assessed (hypothetical strategy).

Significant interruption/non-adherence is defined as a gap of >=21 days between treatment doses at any time during the on-treatment period (excluding the PegIFN Eligibility Period). The final inference from the Bayesian model will account for the missing data assuming MAR. End of treatment (EoT) VR response will be determined using the end of treatment analysis windows defined in Table 2, Table 3, and Table 4. In the absence of rescue medication usage, if all HBsAg and HBV DNA data within the analysis window for the EoT visit is missing and the missingness is not due to wide disruptive events, the subject will be considered as an SVR non-responder. No imputation of missing data will be performed.

If all HBsAg and HBV DNA data within the analysis window for the EOT visit is missing due to a WDE, and the participant withdraws from the study due to the WDE, the participant will be classified as not reaching EOT at follow-up. Data after the intercurrent event will be set to missing, and their SVR response will be imputed assuming missing at random using all available data from participants for whom SVR can be assessed.

If all HBsAg and HBV DNA data within the analysis window for the EOT visit is missing due to a WDE, but the participant later returns to study and has non-missing data in an analysis window, the data will be handled in the following two ways:

1. For observed VR responders, the data will be analysed as collected (treatment policy). No imputation of missing data will be performed.
2. For observed VR non-responders, data collected after the intercurrent event will be set to missing. Their SVR response will be imputed assuming missing at random using all available data from participants for whom SVR can be assessed (hypothetical strategy).

If all HBsAg and HBV DNA data within an analysis window after the planned end of sequential treatment (EoT) is missing unrelated to wide disruptive events, missing data will be considered as an SVR non-responder. No imputation of missing data will be performed.

If all HBsAg and HBV DNA data within an analysis window after the planned end of sequential treatment (EoT) is missing due to wide disruptive events, the participant's SVR status will be considering as missing due to WDE. Data after the intercurrent event will be set to missing, and the SVR response will be imputed using all available data from participants for whom SVR can be assessed.

If the participant has any HBsAg ≥LLOQ or HBV DNA ≥LLOQ or rescue medication usage at or after the planned end of sequential treatment (EoT), the subject will be classified as an SVR non-responder. No imputation of missing data will be performed.

If a participant has any assessments that are affected by a wide disruptive event, but the participant's HBsAg and HBV DNA within an analysis window are collected and the participant is a VR responder, the subject will be classified as an SVR responder.

4.2.2.3. Model Checking and Diagnostics – MCMC Mixing Diagnosis

Two sampling chains will be run, with differing starting values and each with a burn-in period of 5,000 samples, to ensure adequate sampling from the posterior. The starting values will be as described above in Section 4.2.2.

Mixing will be regarded as "each chain is independently realizing values similar to those for which the other chains have also sampled." Adequate mixing will be concluded if the chains meet following conditions:

1. The Brooks-Gelman Ratio (BGR) (Brooks, 1998) for each parameter is in the interval (0.8, 1.2).
2. Each chain appears mix well, upon visual inspection of each chain's trace plot, including assessing the mutual overlap of the chains for each parameter.
3. Each kernel density plot appears smooth upon visual inspection.

4.2.3. Sensitivity Analyses

For the primary estimand, a sensitivity analysis will be performed using the Bayesian model described in Section 4.2.2. The final inference from the Bayesian model will account for the missing data assuming MAR, regardless of the reason for missingness.

4.2.4. Supplementary Estimands

The following supplementary estimands are defined to support the primary objective.

4.2.4.1. Measuring SVR from Actual End of Treatment instead of Planned End of Treatment

The first supplementary estimand is defined in the same way as the primary estimand, except the assessment time frame for participants achieving SVR will be 24 weeks after the actual end of treatment. The estimand strategy for handling treatment discontinuation unrelated to wide disruptive events will be while-on-treatment, which calculates the actual duration from the first to the last dose of treatment received. See Section 4.2.1 for additional details.

4.2.4.2. Measuring SVR from Actual End of Treatment by Categorical Subgroups of PegIFN Treatment Duration

The second supplementary estimand supporting the primary objective measures SVR from actual end of treatment by categorical subgroups of PegIFN treatment duration.

The second supplementary estimand is defined as:

- **Population:** Participants with CHB on stable NA therapy that are eligible for PegIFN.
- **Treatment:** 300 mg GSK3228836 for 12 or 24 weeks followed by up to 24 weeks of PegIFN therapy while on stable NA therapy.
- **Variable:** The percentage of participants that achieve SVR for 24 weeks after the actual end of sequential treatment without the use of rescue medication

- **Intercurrent Events:**
    - Significant interruption in or non-adherence to PegIFN related or unrelated to WDEs will be analysed as collected (treatment policy strategy).
    - Discontinuation and delayed start of PegIFN related or unrelated to WDEs will be handled by calculating the actual duration using the first to the last dose of PegIFN received (while-on-treatment strategy).
    - Use of rescue medication will be incorporated in the definition of the endpoint (composite strategy).
- **Population Summary:** The percentage of participants achieving SVR for 24 weeks after the actual end of treatment by PegIFN treatment duration categorical grouping of at least 12, 16, 20, and 24 weeks of PegIFN treatment in each treatment arm.

4.2.4.3. Measuring SVR from Planned End of Treatment for Participants who Received At Least Twelve Doses of PegIFN

The third supplementary estimand examines the effect of the intercurrent event of a participant failing to meet PegIFN eligibility criteria by PegIFN Eligibility Week 13 (i.e. can no longer receive at least 12 weeks of PegIFN treatment). The estimand strategy for this intercurrent event will be principal stratum, which restricts the population to participants for whom the intercurrent event did not occur. The third supplementary estimand is defined as:

- **Population:** Participants with CHB on stable NA therapy that have received at least 12 doses of PegIFN
- **Treatment:** 300 mg GSK3228836 for 12 or 24 weeks followed by up to 24 weeks of PegIFN therapy while on stable NA therapy.
- **Variable:** The percentage of participants that achieve SVR for 24 weeks after the planned end of sequential treatment without the use of rescue medication
- **Intercurrent Events:**
    - For discontinuation of, interruption in, or non-adherence to GSK3228836 or PegIFN unrelated to any wide disruptive events (such as COVID-19 pandemic), the data will be analysed as collected (treatment policy strategy).
    - For participants that are ineligible to receive PegIFN, the data will be analysed as collected (treatment policy strategy).
    - Use of rescue medication will be incorporated in the definition of the endpoint (composite strategy).
    - For wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, significant interruption in, or non-adherence to GSK3228836 and PegIFN, data collected after the intercurrent event will be set to missing and the response will be imputed assuming missing at random in the Bayesian model (hypothetical strategy).

- **Population Summary:** The percentage of participants in each treatment group who achieve SVR for 24 weeks after the planned end of sequential treatment without use of any rescue medication.

4.2.5. Additional Estimands

The following additional estimands are included to support the primary objective.

4.2.5.1. Using a Modified Definition of SVR

Note for this section: upon review of AIA results, this definition does not meet the scientific intent of the modified definition of SVR. The definition of modified SVR described in this section will be programmed as is. The intended application of this definition will be documented in note to file (NTFs) for this study and for B-clear (209668).

An additional estimand is defined in the same way as the primary estimand, except the population summary is defined using a modified definition of sustained virologic response (SVR) for 24 weeks after the planned end of sequential treatment (EoT) in the absence of rescue medication. The modified definition of SVR is observing HBsAg <LLOQ and HBV DNA <LLOQ at each analysis window in the 24 weeks after the planned end of sequential treatment (EoT). Any observation of HBsAg ≥LLOQ or HBV DNA ≥LLOQ at a visit must be confirmed individually at a consecutive visit (including unscheduled visits or the first visit after the end of the analysis window). If the consecutive visit for the same parameter is also ≥LLOQ, the SVR status for the participant at the initial visit will be an SVR non-responder. If the consecutive visit for the same parameter is also <LLOQ, the SVR status for the participant at the initial visit will be an SVR responder under the modified definition.

4.2.5.2. Impact of WDE on SVR

An additional estimand is defined in the same way as the primary estimand, except for how the subjects with missing visits due to a WDE leading to discontinuation of, interruption in, or non-adherence to GSK3228836 or PegIFN are handled. For these participants that restart GSK3228836 or PegIFN, data will be analysed as collected (treatment policy strategy).

4.3. Secondary Endpoint Analyses

4.3.1. Secondary Endpoints

For the secondary end-points relating to "Achieving HBsAg <LLOQ and HBV DNA <LLOQ", in Section 4.3.1, the same analysis visit windows for Arm 1 and Arm 2 will be used as defined in Table 2 Table 1and Table 3 respectively.

For other secondary endpoints (actual values and change from baseline over time, antibody levels over time, etc.) the data will be summarized as collected. Three groups of estimands are defined below for the key secondary efficacy objectives.

4.3.1.1. Efficacy of GSK3228836 and PegIFN Sequential Therapy on Biomarkers and Virus Specific Antibody Responses

The estimand strategy supporting this secondary objective is defined below. Missing data for variables defined below, except for time to ALT normalisation, will be analysed as collected. Only available data will be summarised.

- **Population:** Participants with CHB on stable NA therapy; For the time to ALT normalisation variable, population will be aforementioned participants with baseline ALT >ULN.
- **Treatment:** 300 mg GSK3228836 for 12 or 24 weeks followed by up to 24 weeks of PegIFN therapy while on stable NA therapy.
- **Intercurrent Events:**
    - Discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN analysed as collected (treatment policy).
    - PegIFN ineligibility will be analysed as collected (treatment policy)
    - Rescue medication will be analysed as collected (treatment policy), except for ALT normalisation which can only be achieved in the absence of rescue medication.
    - Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption in, or non-adherence to GSK3228836 and PegIFN will be analysed as collected (treatment policy strategy).

Categorical Variables

The following categorical variables are defined for the objective:

- Achieving HBsAg <LLOQ and HBV DNA <LLOQ at two time points: (1) the planned end of treatment analysis window and (2) at the end of 24 weeks follow-up analysis window. Data will be presented overall and by the baseline stratification factors defined in Table 1. Analysis windows at planned end of treat and end of 24 weeks follow-up will be identical to those for the primary endpoint (see Table 2 and Table 3).
- Categorical changes from baseline in HBsAg (e.g., <0.5, ≥0.5, ≥1, ≥1.5, ≥3 log10 IU/mL) and in HBV DNA (e.g., <1, ≥1, ≥2, ≥3 log10 IU/mL). Change from baseline will be presented at each visit and for the following time periods: up to and including Week 6, up to and including Week 12, up to and including Week 24, up to and including off-treatment Week 24. Data will be presented overall and by the baseline stratification factors defined in Table 1. Data will be summarized using planned visits.
- ALT normalisation (ALT≤ULN) over time in absence of rescue medication in participants with baseline ALT>ULN.
- HBe antibody (anti-HBeAg) levels.

Population Summary: Percentage of participants in each category for each treatment arm.

Continuous Variables

Continuous variables for the secondary objective are defined as follows:

- Actual values and change from baseline over time of HBsAg, HBV DNA, and HBeAg levels (only in HBeAg Positive Participants at baseline).
- Actual values and change from baseline over time for HBs antibody (anti- HBsAg) levels.
- Actual values and change from baseline over time for ALT.

Population Summary: Mean values and mean changes from baseline of each variable for participants in each treatment arm.

Time to Event Variables:

A time to event variable for this objective is defined as:

- Time to ALT normalisation in absence of rescue medication in participants with baseline ALT>ULN.

Population Summary: Turnbull's estimator for nonparametric estimation of Time to ALT normalisation in each treatment arm.

ALT normalization is defined in participants with ALT>ULN at baseline as a return to <ULN (ULN = 40 for males and 33 in females). Time to ALT normalization is defined as time from baseline to the first follow-up where subject's ALT has returned to normal.

For participants who withdraw from the study or Participants with ALT>ULN at the end of study (EoS), time to ALT normalization will be censored after the time of the last visit with non-missing ALT value available. Participants who receive rescue medication cannot go on to achieve the event of 'ALT normalization in the absence of rescue medication'; such participants will be censored at the end of the follow up period.

In order to determine if the addition of a PegIFN treatment after completing 12 or 24-weeks of Bepirovirsen delays relapse, an additional time to event variable is defined as follows:

- Time from Bepi EOT to Relapse by HBsAg Categories

Population summary: summary statistics of the time from Bepirovirsen end of treatment to relapse including: N(%) with relapse, mean, standard deviation, median, minimum, and maximum using the number of participants achieving VR at Bepi EOT. Additionally, a Kaplan-Meier plot and associated percentiles will be produced to provide a graphical comparison of time to relapse between treatment arms.

Only participants who were virologic responders at the end of Bepirovirsen treatment will be considered, since they are the only ones who can relapse. Time to relapse is defined as the first time point where the participant can no longer be considered a responder by the primary estimand for the conservative definition. This includes observed elevation(s) in either HBsAg or HBV DNA or rescue medication usage. Generally, time from end of Bepirovirsen treatment to relapse will be calculated from the date of the planned Week 24 or 12 visit (for arms 1 and 2 respectively), where HBsAg<LLOQ and HBV DNA<LLOQ,

until the first visit after the planned Week 24 or 12 visit where HBsAg>=LLOQ or HBV DNA>=LLOQ.

4.3.1.2. Durability of Virological Response after Sequential Therapy with 12 Weeks of GSK3228836 Followed by up to 24 Weeks of PegIFN

The estimand strategy supporting this secondary objective is the same strategy defined in Section 4.3.1.1 and focuses on the timepoints following the 24 weeks off-treatment period(i.e., Week 30 and Week 36).

4.3.1.3. Comparison of Efficacy Between Treatment Arms of 12 and 24 Weeks of GSK3228836 Followed by up to 24 Weeks of PegIFN

The estimand strategy for this objective are defined as follows:

- **Population:** Participants with CHB on stable NA therapy, regardless of discontinuation of, interruptions in or adherence to GSK3228836 or PegIFN, had they not been affected by wide disruptive events.
- **Treatment:** 300 mg GSK3228836 for 12 or 24 weeks followed by up to 24 weeks of PegIFN therapy while on stable NA therapy. One treatment comparison between Arms 1 and 2 up to 24 weeks off treatment.

- **Intercurrent Events:**
    - Discontinuation of, interruption in, and non-adherence to GSK3228836 and PegIFN will be analysed as collected (treatment policy).
    - PegIFN ineligibility will be analysed as collected (treatment policy)
    - Participants who have used rescue medication will be incorporated in the definition of the endpoint (composite strategy)
    - For wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, significant interruption in, or non-adherence to GSK3228836 or PegIFN, data collected after the intercurrent event will be set to missing and the response will be imputed using all available data for participants for whom SVR can be assessed. (hypothetical strategy).

Population Summary: Difference in percentage of participants who achieve SVR for 24 weeks after the planned end of sequential treatment between treatment arms

Categorical Variables

The following categorical variables are defined for this objective:

- Achieving SVR (HBsAg <LLOQ and HBV DNA <LLOQ) at the planned end of sequential treatment and over the 24 weeks follow-up for each treatment arm.

Main Analytical Approach

The secondary efficacy comparison of interest is the difference in sustained virologic response rate for 24 weeks after the planned end of sequential treatment between treatment arms:

- Arm 1 vs. Arm 2 in percentage of participants achieving SVR for 24 weeks after the planned end of sequential treatment, without use of any rescue medication.

Comparison between treatment arms will be made by calculating the difference between the posterior distributions of the response rate in each arm which will be summarised to obtain posterior means and CIs. Samples from the posterior distribution of the response rates in each arm will also be used to obtain posterior probabilities of interest. The point estimates of differences in SVR rate with 95% credible intervals will be calculated for the treatment comparisons described in the estimands. Posterior probabilities Pr(Arm 1 – Arm 2 > 0) and Pr(Arm 2 – Arm 1 > -0.05) will be presented to aid selection of treatment regimen.

Model Checking and Diagnostics – MCMC Mixing Diagnosis

The same approach in model checking and diagnostics will be applied as for the primary analysis (Section 4.2.2.3).

4.3.1.4. Sensitivity Analyses

For the estimand supporting the objective of comparing efficacy between treatment arms, a sensitivity analysis will be performed using the Bayesian model described in Section 4.2.2 assuming missing at random whereby a participant's response will be imputed using all available data (on- and off-treatment values) for participants who completed the study.

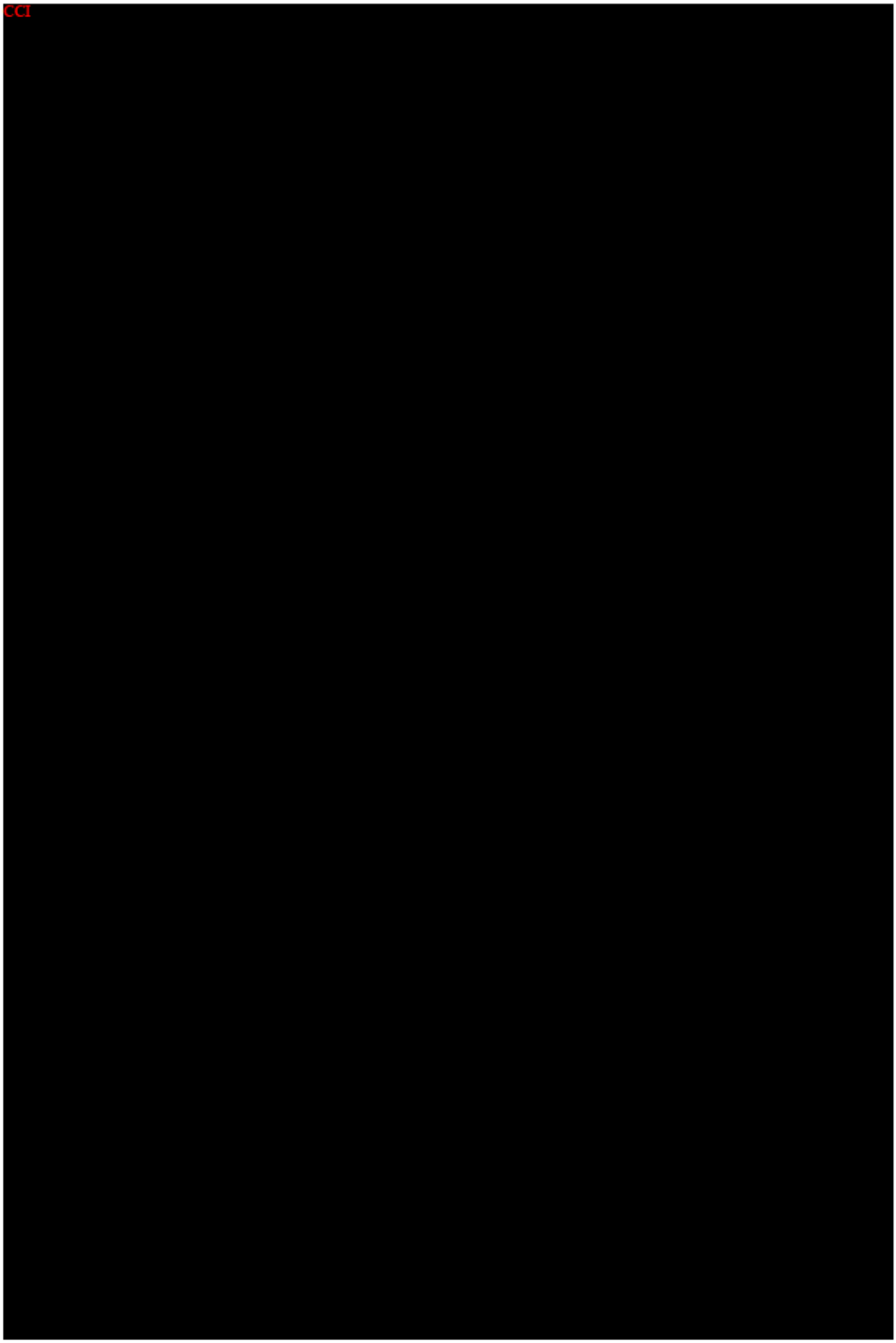
4.3.1.5. Other Secondary Endpoints

Other than the HBsAg and HBV DNA data supporting the secondary objective of comparing efficacy between treatment arms, missing data for variables defined in any other secondary or exploratory estimand will be analysed as collected, assuming missing completely at random.

4.4. Exploratory Endpoint Analyses

CCI

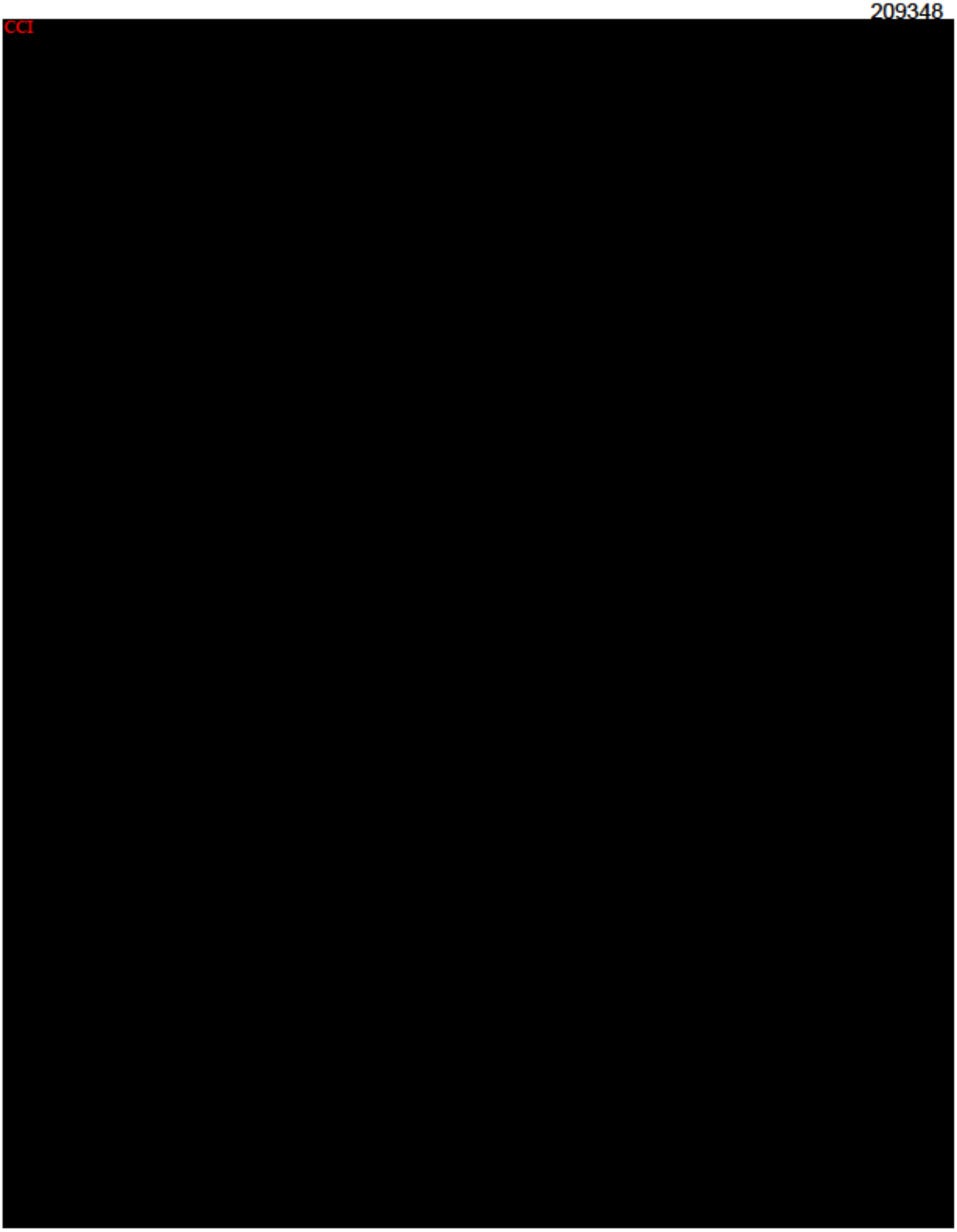
CCI



CCI

[redacted]

CCI



4.4.2. Pharmacokinetic (PK) Analyses

Pharmacokinetic analyses will be based on the PopPK analysis instead of the pharmacokinetic population, as no intensive PK was collected.

Controlled early access to unblinded PK and PKPD related data will be granted to the designated representative(s) to perform the population PK and PKPD dataset preparation, model development and any PK review necessary for planned or unplanned safety reviews.

4.4.2.1. PK Endpoints / Variables

PK of GSK3228836 and PegIFN will be characterised. In all participants, GSK3228836 and PegIFN concentration at the end of dosing interval (Cτ) and terminal half-life (t½) will be estimated, as data permits.

PK parameters will be calculated by standard non-compartmental analysis using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. PK parameters listed will be determined from the plasma concentration-time data, as data permits.

Table 6 PK Parameters and Parameter Description

Parameter	Data	Analyte	Parameter Description
Cτ	All Participants	GSK3228836 PegIFN	Concentration at the end of the dosing interval.
t½	All Participants	GSK3228836 PegIFN	Terminal half-life determined using concentrations collected during the off-treatment period.

Cτ = concentration at the end of dosing interval; t½ = terminal half-life.

4.4.2.2. Statistical Analyses / Methods

Unless otherwise specified, endpoints/variables defined in Table 6 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed. Descriptive statistics for continuous variables will summarise n, arithmetic mean, SD, 95% CI, median, minimum, maximum, geometric mean with associated 95% CI, and the between-participant CV (%CV_b) for the geometric mean.

PK parameters (Cτ and t½) of GSK3228836 and PegIFN will be summarised and listed by treatment arm, IP, and study visit (only applies to Cτ). PK Cτ-time plots will be created and compared by the same factors.

4.4.2.3. PK-PD Endpoints / Variables

PK-PD relationships including PK-efficacy relationships and PK-safety relationships will be evaluated using the pre-specified interim and end of study data, as data permits.

To evaluate PK-efficacy relationship and PK-safety relationship, exploratory graphical analyses will be initially performed for efficacy and safety endpoints. If a relationship between exposure and efficacy and/or safety endpoints is present, population PK-PD modelling may be conducted using nonlinear mixed effect methods. Data from this study may be combined with other studies for population PK/PD modelling.

Full details of PK-PD and Population PK analysis will be described in a separate analysis plan developed by CPMS. Results of the PK-PD analyses will be summarized in a separate report.

Efficacy Assessments

Efficacy assessments for PK-PD relationship may include but are not limited to, as data permits:

- **Categorical:** virologic response, seroclearance (HBsAg <LLOQ, HBV DNA<LLOQ), and seroconversion (anti-HBsAg and anti-HBeAg).
- **Change from Baseline:** HBsAg, HBV DNA, anti-HBsAg and anti-HBeAg levels.
- **Time to Event:** virologic response (HBsAg and HBV DNA levels < LLOQ), nadir of HBsAg and HBV DNA, HBsAg<LLOQ, HBV DNA <LLOQ, seroconversion (anti-HBsAg and anti-HBeAg), peak of ALT flares.

Safety Assessments

Safety assessments for PK-PD relationship include but are not limited to vital signs, laboratory measurements and AEs.

PK Assessments

PK assessments include but are not limited to Cτ and terminal half-life (t½). Data from this study may be combined with other studies for population PK modelling.

4.4.3. Safety and Tolerability

The safety profile of sequential therapy with GSK3228836 (up to 24 weeks) followed by PegIFN (up to 24 weeks) in participants with CHB on stable NA therapy will be investigated.

Clinical assessments for safety and tolerability evaluation include laboratory measurements and AEs at timepoints specified in the SoA.

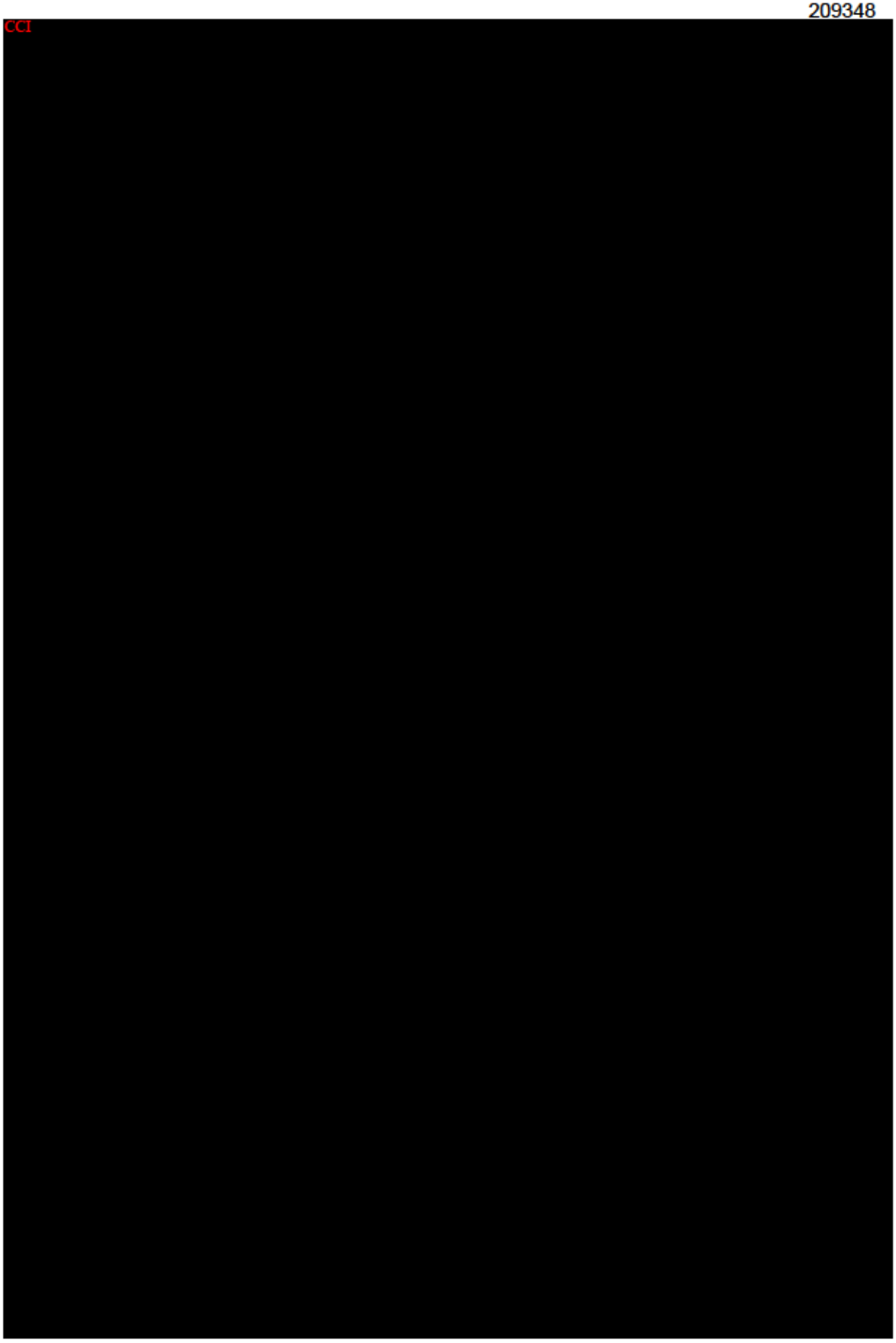
4.4.4. Pharmacodynamic Effect of GSK3228836 and PegIFN Sequential Therapy on Exploratory Biomarkers

The pharmacodynamic effect of GSK3228836 and PegIFN sequential therapy will be assessed on the exploratory viral biomarkers HBV core related antigen (HBcrAg) and HBV RNA at timepoints specified in the SoA. Details will be described in a separate PK-PD analysis plan developed by CPMS.

CCI

[redacted]

CCI



CCI

[redacted]

4.4.6. Biomarker Analyses

The effect of GSK3228836 and PegIFN sequential therapy on immunological biomarkers will be assessed. The relationship(s) between virology biomarkers including HBsAg and immunological biomarkers will be described. Details of the immunology endpoints will be included in a separate biomarker analysis plan.

4.5. Safety Analyses

All safety analyses will be based on the Safety population.

Exposure to study medication, measured by the number of injections and proportion of planned number of injections of study drug, will be summarised by treatment arm.

4.5.1. Extent of Exposure

Extent of exposure will be summarized by presenting number of participants in various exposure duration categories, overall duration of exposure, and study intervention compliance.

Number of days of exposure to study drug will be calculated separately for GSK3228836 and PegIFN based on the formula:

- Duration of Exposure in Days = Last injection date – First injection date + 1

The duration of exposure in weeks will be calculated as duration of exposure in days divided by 7.

The cumulative actual dose will be calculated separately for GSK3228836 and PegIFN based on the formula:

- Cumulative Actual Dose = Sum of Dose administered during GSK3228836 or PegIFN dosing period

The dose intensity (mg/wk) will be calculated separately for GSK3228836 and PegIFN based on the formula:

- Dose Intensity = Cumulative Actual Dose / Total Actual Number of Weeks of Dose administration

The cumulative injected volume will be calculated separately for GSK3228836 and PegIFN based on the formula:

- Cumulative Injected Volume = Sum of Injected Volume during GSK3228836 or PegIFN dosing period

The weekly injected volume (mL/wk) will be calculated separately for GSK3228836 and PegIFN based on the formula:

- Weekly Injected Volume = Cumulative Injected Volume / Total Actual Number of Weeks of Dose administration

4.5.2. Adverse Events

All AE summaries will be based on treatment emergent events unless otherwise specified. An adverse event (AE) is considered treatment emergent if the AE onset date is on or after treatment start date. If AE start date is completely missing and the end date is on or after the treatment start date, the AE will be assumed to be treatment emergent. AEs with onset date on or after start date of treatment with GSK3228836 will be classified as occurring during the GSK3228836 treatment period, and AEs with onset date on or after start date of treatment with PegIFN will be classified as occurring during the PegIFN treatment period. AEs starting after end of GSK3228836 treatment period and prior to PegIFN treatment start will be considered as AEs occurring during PegIFN eligibility period.

Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Authorities (MedDRA) coding dictionary, to give a preferred term and a system organ class. These preferred terms and system organ classes will be used when summarizing the data.

The severity of AEs and SAEs will be determined by the investigator according to the 'Division of Acquired Immune Deficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (2017)', unless specified otherwise in the protocol. For AEs by maximum determined grade summary tables, for AEs occurred more than once, the most severe intensity will be included in summaries. Relationship to study treatment, as indicated by the investigator, is classified as not related or related to GSK322836, PegIFN, or both. Adverse events with a missing relationship to study treatment will be regarded as related to the ongoing study treatment or the last study treatment if no treatment is received at the time of AEs.

The following AE summaries will be presented overall and by treatment arm:

1. AEs overview: summarize the number and percentage of participants with any adverse event, AEs related to study treatment, AEs leading to permanent discontinuation of study treatment, withdrawal from the study, any serious adverse events (SAE), SAEs related to study treatment, fatal SAEs and fatal SAEs related to study treatment.
2. All AEs by system organ class (SOC) and preferred term (PT)
3. All AEs by SOC and PT and maximum grade
4. All drug-related AEs by SOC and PT
5. All drug-related AEs by SOC and PT and maximum grade
6. Serious AEs (SAEs) by SOC and PT
7. Serious AEs (SAEs) by SOC and PT and maximum grade
8. Serious Adverse Events by system organ class and preferred term (number of participants and occurrences)
9. AEs leading to withdrawal from the study by SOC and PT
10. AEs leading to withdrawal from the study by SOC and PT and maximum grade
11. AEs leading to permanent discontinuation of study treatment by SOC and PT
12. AEs leading to permanent discontinuation of study treatment by SOC and PT and maximum grade
13. Serious fatal and non-fatal drug/related AEs by SOC and PT
14. AEs by overall frequency
15. Non-serious AEs by SOC and PT (number of participants and occurrences)
16. Non-Serious drug-related adverse events by overall frequency

The above listed summaries will also be presented separately for events occurring during treatment with GSK3228836 and PegIFN, overall and by treatment arm within each treatment period. Drug-related AEs will be summarised for the two treatment periods as follows:

1. Summary of GSK3228836 drug-related adverse events by system organ class and preferred term
2. Summary of GSK3228836 drug-related adverse events by system organ class and preferred term and maximum grade
3. Summary of PegIFN drug-related adverse events by system organ class and preferred term
4. Summary of PegIFN drug-related adverse events by system organ class and preferred term and maximum grade

Number of participants with AEs will be summarized if it is not specified otherwise.

In summary tables where AEs are presented by SOC, PT, and maximum grade, SOCs will be sorted in descending order of the total incidence then alphabetically, PTs will be sorted in descending order of the total incidence then alphabetically within the SOC.

For completely missing or partial missing AE start date or end date, imputation rules will be applied following rules stated in the Output and Programming Specifications (OPS).

Deaths will be listed including primary cause of death.

4.5.2.1. Adverse Events of Special Interest

The following AEs of special interest will be reported:

- ALT increase
- Vascular inflammation and complement activation
- Thrombocytopenia
- Renal injury

An up-to-date list of specific MedDRA Queries (SMQs), high level terms (HLTs) or individual preferred terms (PTs) used to identify adverse events of special interest (AESIs) is periodically updated and stored in a central location. At the time of database lock, the latest version of the terms will be extracted and used to identify AESIs.

All AEs of special interest will be summarized by SOC and PT, and, also summarized by SOC, PT and maximum grade. Serious AESIs will be summarized by SOC and PT. All AEs of special interest will be listed.

Separate outputs will be created for each AESI category (ALT increase, vascular inflammation and complement activation, thrombocytopenia, renal injury) to explore the data in more detail if data permits.

Event Characteristics: The characteristics of all event occurrences during the post-baseline period will be summarized, which looks at event characteristics (serious, drug-related, leading to withdrawal, severe or Grade 3-4, fatal), number of events per participant, outcome, maximum grade or intensity and action taken.

4.5.2.2. COVID-19 Assessment and COVID-19 AEs

A standardized MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

The overall incidence of AEs and SAEs of COVID-19, COVID-19 AEs leading to study intervention discontinuation, COVID-19 AEs leading to study withdrawal, and Grade 3 and 4 COVID-19 AEs / severe COVID-19 AEs will be summarized. The incidence of these events at individual PT level can be obtained from the standard AE/SAE summaries.

COVID-19 assessments for participants with potential, suspected or confirmed COVID-19 AEs will be summarized.

If >5% participants overall report ≥1 COVID-19 AE, then onset and duration of the first occurrence of COVID-19 AEs, and COVID-19 AE symptoms (from the COVID-19 eCRF page) will be summarized. The same rule will apply to COVID-19 SAEs.

4.5.2.3. Impact of COVID-19 Pandemic on Safety Results

The impact of the COVID-19 pandemic on the safety results will be assessed. Pandemic measures began in different countries at different times. A dataset containing the date when pandemic measures began, as determined by the GSK country Issue Management Teams

(IMT), will be used to determine the start date of each wave of pandemic measures within each country.

Summaries of the incidence rates of AEs, SAEs, and Grade 3 and 4 AEs / severe AEs, before (AE onset date < pandemic measure start date) and after (AE onset date >= pandemic measure start date) the start of the COVID-19 pandemic will be produced, overall and by country/region, gender, and age group.

4.5.3. Additional Safety Assessments

4.5.3.1. Laboratory Data

Only central lab data will be used for summary analyses and figures; local lab data will be included in listings, as appropriate.

If normal LAB ranges are collected and there are duplicate LAB records at the same date/timepoint, the "worst-case" value will be selected. Specifically:

- For LAB result > Lower Normal range, select Maximum of Lab result (AVAL).
- For LAB result <= Lower Normal range, select minimum of Lab result (AVAL).

For virology LAB parameters, if time information is missing from collection and from the test performed, the maximum lab value should be selected. If first run has values outside acceptance criteria, and the sample was re-run, the latest LAB result should be selected by the vendor.

Summary statistics for changes from baseline for each numeric parameter at each visit will be presented, separately for all clinical chemistry parameters, all haematology parameters, and all urinalysis parameters.

For immunology parameters, summary statistics for actual value and change from baseline data for each parameter at each visit will be presented, separately for all numeric parameters. Listings will also be created.

For categorical immunology parameters c-ANCA and p-ANCA, summary table of baseline Negative to post-baseline Positive, baseline value no change, and baseline Positive to post-baseline Negative will be created. Listing will be created as well.

For coagulation parameters prothrombin international normalised ratio (INR), prothrombin time (PT_{test}) and activated partial thromboplastin time (aPTT), summary statistics for actual at each visit will be presented. Listing will be created as well.

Shift tables for laboratory parameters showing baseline toxicity versus maximum post-baseline (on-treatment and off-treatment periods combined) toxicity for each grade (Grade1, Grade 2, etc.) for chemistry and haematology parameters will be provided.

Increase to Grade 3 or higher lab abnormalities for platelets, ALT, aspartate aminotransferase (AST), INR, total bilirubin, serum creatinine, eGFR, albumin to creatinine ratio (ACR) will be summarized.

Laboratory values outside of normal range will be summarized and listed.

Grading categories for laboratory tests are determined using the DAIDS grading system Version 2.1 [National Institute of Allergy and Infectious Diseases. Division of AIDS, 2017].

Summary of post-baseline hepatobiliary laboratory abnormalities will be provided.

The worst-case urinalysis results post-baseline (on-treatment and off-treatment periods combined) relative to baseline will be summarized.

Summaries of result shifts from baseline, worst-case results post-baseline relative to baseline, and results with increase to >= maximum toxicity grade post-baseline for chemistry, haematology, urinalysis, and immunology as applicable, will also be presented for treatment with GSK3228836 and PegIFN separately, by treatment arm and in total within each treatment period.

GSK3228836 liver chemistry monitoring and stopping event reporting will be summarized and listed. The liver monitoring and stopping criteria are described in the protocol Section 7.1.1.

GSK3228836 haematological monitoring and stopping events will be summarized and listed based on laboratory parameters (platelet count and anti-platelet antibodies). The haematological stopping criteria are described in the protocol Section 7.1.2.

GSK3228836 drug induced kidney injury (renal) monitoring and hold or stopping events will be identified programmatically and will be summarized and listed based on laboratory parameters (ACR, urinalysis red blood cells (RBC), serum creatinine, and eGFR). The kidney injury monitoring and stopping criteria are described in the protocol Section 7.1.3.

Drug induced vascular injury and complement monitoring/stopping event will be summarized and listed based on laboratory parameters (C3, C4, Bb, C5a, hs-CRP, MCP-1, p-ANCA, c-ANCA, eGFR, bilirubin, and platelet count). The drug induced vascular injury and complement monitoring and hold/stopping criteria are described in the protocol Section 7.1.4.

Hold/stopping event profile for GSK3228836 will be provided for any subject who has met hold or stopping criteria specified in protocol Section 7.1. Relevant information will be reported, including baseline characteristics, AEs/SAEs, concomitant medication, medical history/current medical conditions, study treatment administration details, laboratory values, and individual line plots of complement (C3/C4/C5a/Bb), inflammatory markers (hs-CRP/MCP-1), serum creatinine/creatinine clearance or eGFR/ACR, and platelet count.

Haematological (absolute neutrophil count (ANC), platelet count, haemoglobin), ALT elevation (greater than 5 x ULN, greater than 10 X ULN) and psychiatric disorder (C-SVRRS, BDI-II) dose modification and discontinuation guidelines for PegIFN will be summarized and are described in protocol Section 7.2.1, Section 7.2.2, and Section 7.2.3 respectively.

GSK3228836 restart after liver stopping criteria has been met will be summarized based on ALT, bilirubin, and INR, and is described in protocol Section 7.3.

4.5.3.2. Vital Signs

Summaries of grade increase in temperature, systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be provided separately. These summaries will display the number and percentage of participants with any grade increase, increase to Grade 2, increase to Grade 3 and increase to Grade 4 (for temperature only), for worst case post-

baseline only. The grade definition for non-axillary temperature is: Grade 1 (38.0°C – <38.6°C), Grade 2 (38.6°C – <39.3°C), Grade 3 (39.3°C – <40.0°C), Grade 4 (>=40.0°C). The grade definition for SBP is: Grade 1 (140-159), Grade 2 (160-179), Grade 3 (>=180). The grade definition for DBP is: Grade 1 (90-99), Grade 2 (100-109), Grade 3 (>=110). The summaries will be produced for worst case post baseline only.

4.5.3.3. Electrocardiogram (ECG)

ECG data (absolute values and change from Baseline) will be summarised by visit and treatment arm only for the end of study analysis and won't be included in the interim analysis outputs.

4.6. Other Analyses

4.6.1. Subgroup Analyses

Descriptive summaries by subgroups defined in Table 7 will be provided. Number of responders, posterior mean and 95% equal-tail credible interval of the SVR response rate will be reported by subgroups as defined in the model specification section for each treatment arm. The corresponding posterior probability of SVR rate exceeding a range of clinically meaningful response rates will also be reported by subgroups as defined in the model specification section for each treatment arm. No statistical comparison between subgroups will be performed.

If the number of participants is too small (<5 per subgroup category) within a subgroup, then the subgroup categories may be redefined prior to unblinding the study. If the category cannot be refined further, then descriptive rather than statistical summaries may be presented for the specific subgroup.

Table 7 Subgroups and Subgroup Categories

Subgroup	Categories
HBeAg Status	Positive (≥0.09 U/mL); Negative (<0.09 U/mL)
Baseline HBsAg	Low (≤ 3 log10 IU/mL); High (>3log10 IU/mL) <=3, >3-3.5, >3.5-4 and >4
Age group	**EMA:** <18; ≥18-64; ≥65 – 84, ≥85: **FDAAA:** ≤18; ≥19-64; ≥65 **Clinical and Epi (Group 1):** <50; ≥50
Sex	Male; Female
Race	American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White
Baseline viral genotype	A; B; C; D; Other; Unknown
Baseline BMI	<30; ≥30
Baseline ALT	<=ULN; >ULN; =<ULN, > ULN to <= 2x ULN, > 2x ULN to <= 3x ULN, > 3x ULN to <= 5x ULN, > 5x ULN to <= 10x ULN, >10x
Baseline METAVIR Fibrosis Score	If enough data are available (≥5 participants per group per arm): F0 – F2; F3
Time on current NUC	< 3 years; >=3 years
Type of current NUC	TAF/TDF; Entecavir; Other

Subgroup	Categories
Duration of Hep B Infection	<5 years; ≥ 5 years - <10 years; ≥ 10 years - <20 years; ≥ 20 years
Baseline mutations in the binding site	Present; Absent
Phase of HBV Infection (Strict Criteria)	Phase 1; Phase 2; Other HBeAg-positive; Phase 3; Phase 4; Other HBeAg-negative, where phases are defined as below. Phase 1 = HBeAg-positive, ALT <= ULN during screening and at baseline, HBV DNA > 10^6 IU/ml during screening and at baseline Phase 2 = HBeAg-positive, ALT > ULN either during screening or at baseline, HBV DNA > 10^4 IU/ml during screening and at baseline Other HBeAg-positive = HBeAg-positive, neither Phase 1 nor Phase 2 Phase 3 = HBeAg-negative, ALT <= ULN during screening and at baseline, HBV DNA < 20,000 IU/ml during screening and at baseline Phase 4 = HBeAg-negative, ALT > ULN either during screening or at baseline, HBV DNA > 2,000 IU/ml during screening and at baseline Other HBeAg-negative = HBeAg-negative, neither Phase 3 nor Phase 4
Phase of HBV Infection (Loose Criteria)	Phase 1 loose; Phase 2 loose; Phase 3 loose; Phase 4 loose, where phases are defined as below. Phase 1 loose= HBeAg-positive, ALT <= ULN during screening and at baseline Phase 2 loose = HBeAg-positive, ALT > ULN either during screening or at baseline Phase 3 loose = HBeAg-negative, ALT <= ULN during screening and at baseline Phase 4 loose = HBeAg-negative, ALT > ULN either during screening or at baseline

4.6.2. Subpopulations to Support Regulatory Consultation

To support consultation with regulators, key study population, efficacy, safety, and pharmacokinetic analysis will be repeated for the following subpopulations in the end of study analysis:

Japan subpopulation: All participants of Japanese heritage enrolled at sites in Japan.

China mainland subpopulation: All participants enrolled at sites in China Mainland.

East Asia subpopulation: All participants of a relevant Asian heritage (Asian – Japanese Heritage, Asian – East Asian Heritage or Asian – South East Asian Heritage) enrolled at sites in Japan, South Korea and China mainland.

4.7. Interim Analyses

Approximately every 3 months, an external IDMC will review results throughout the study to periodically evaluate safety data. Two interim analyses will be conducted for the study in addition to regular IDMC safety reviews.

There will be an initial unplanned, i.e. not pre-specified in the protocol, interim analysis of unblinded efficacy data to support internal decision making at a Development Review Board (DRB) meeting for the GSK3228836 platform trial (Study 218309) planned for 21-Apr-2022. Only a small sub-team of project-level team members will view these unblinded results and no changes to trial conduct or primary endpoint analyses will be made based on the results of this interim analysis. Further details describing this unplanned analysis will be provided in a separate analysis outline document.

Additionally, a series of administrative interim analyses (AIAs) not planned for in the protocol commenced September-2022 (see note to file: TMF-14859422 and Analysis Outline TMF-14917190) for the purpose of determining whether internal GSK resource should be allocated at-risk for future development of bepirovirsen followed by PegIFN sequential treatment. These future administrative interims will be provided on an ongoing basis (approximately monthly) to the GSK internal Data Review Committee (iDRC) for reference to support their formal decision-making. Below is a table with the monthly projections for the number of subjects with SVR data in each arm available at each AIA (and planned IA). Full details of the internal decision-marking framework are included in the iDRC charter.

Table 8 Projections for the Number of subjects with Primary Endpoint Available at planned IA (PIA) and each AIA

Note: September and October 2022 AIAs occurred prior to this iDRC being developed and approved. Details are included in the table below for awareness.

Review Month	Data Cut	AIA/ Planned IA	Total number of subjects	Projected number of subjects at Primary End point (OT WK 24) Arm 1	Projected number of subjects at Primary End point (OT WK 24) Arm 2
Sep 22	22Aug22	AIA	28	1	27
Oct 22	03Oct22	AIA	58	13	45
Nov 22	11Oct22	PIA	66	18	48
Dec 22	28Nov22	AIA	88	35	53
Jan 23	09Jan23	AIA	100	47	53

There will also be a planned interim analysis as pre-specified in the protocol. The iDRC will have primary review responsibility of the pre-specified interim analysis results and determine if the data support an early Commit to Phase 3 (C2P3) recommendation to DRB. The pre-specified interim analysis will be triggered when all participants complete the end of treatment (EoT) visit (Week 48 for Arm 1 and Week 36 for Arm 2), and a sufficient number of participants have completed the 24-week off-treatment follow-up period (EoT+24wks) in order to assess the probability of C2P3. At this timepoint, it is expected that approximately 18 participants in Arm 1 and 48 participants in Arm 2 will be completers at the time of IA, i.e., participants who will have reached the end of the 24 week off-treatment follow-up period (EoT+24wks).

The primary objective of the pre-specified interim analysis is early assessment of program-level futility and success. Full details of the internal decision-marking framework for the planned IA are included in the iDRC charter.

4.7.1. Primary Endpoints / Variables

All participants are anticipated to have reached the planned end of sequential treatment (EoT) at the time of interim analysis. The primary endpoints of interest for the interim analysis to assess futility and success (as per the iDRC charter) in each arm are:

1) The number of participants who have reached 24 weeks after the planned end of sequential treatment (EoT+24wks) and have virological response (VR) at the planned end of treatment (EoT) visit window in the absence of rescue medication.
2) The number and proportion of participants achieving SVR (HBsAg < LLOQ and HBV DNA < LLOQ) for 24 weeks after the planned end of treatment (EoT+24wks) in the absence of rescue medication:
    - Arm 1: Week 72 analysis window SVR rate
    - Arm 2: Week 60 analysis window SVR rate
3) The number of participants who have not yet reached 24 weeks after the planned end of sequential treatment (EoT+24wks) and have VR at planned end of treatment (EoT) visit window in the absence of rescue medication.
4) The number of participants who have not yet reached 24 weeks after the planned end of sequential treatment (EoT+24wks) and have sustained virologic response from planned end of treatment (EoT) to IA data cut-off date in the absence of rescue medication.

4.7.2. Other Endpoints / Variables

The following endpoints, in addition to primary endpoints, will be summarised using descriptive statistics by treatment arm. All of the endpoints below except for 8,13, and 14-21 are also included and defined in the end of study analyses.

1) Summary of proportion of participants who achieve HBsAg <LLOQ and HBV DNA <LLOQ over time.

2) Summary of proportion of participants who achieve HBsAg <LLOQ and HBV DNA <LLOQ at end of treatment by baseline stratification.
3) Summary of proportion of participants who achieved <0.5, ≥0.5, ≥1, ≥1.5, ≥3 log10 IU/mL decline in HBsAg over time by baseline stratification.
4) Summary of proportion of participants who achieved <1, ≥1, ≥2, ≥3 log10 IU/mL decline in HBV DNA over time by baseline stratification.
5) Summary of actual values and change from baseline over time of HBsAg (log10 IU/mL) and HBV DNA (log10 IU/mL).
6) Summary of actual values and change from baseline over time of HBsAg (log10 IU/mL) and HBV DNA (log10 IU/mL) by genotype.
7) Summary of HBe antibody (anti-HBeAg) levels over time in HBeAg positive participants.
8) Summary of HBe antibody (anti-HBeAg) levels over time in HBeAg positive participants who achieve SVR.
9) Summary of actual values and change from baseline over time of HBs antibody (anti-HBsAg).
10) Summary of HBs antibody (anti-HBsAg) levels over time.
11) Summary of HBs antibody (anti-HBsAg) levels over time in participants who achieve SVR.
12) Proportion of participants who achieved ALT normalization with Baseline ALT >ULN over time.
13) Summary of proportion of participants who achieved HBV DNA TND over time.
14) Summary of concordance of an early virologic response with achieving SVR at PegIFN on-treatment visits Week 6, Week 13, Week 16, Week 20, and Week 24.
15) Association between HBV DNA 'Target Not Detected' and relapse in participants who achieve virologic response at end of treatment.
16) Summary of ROC analysis for baseline HBsAg as a predictor of SVR in participants who reached end of off-treatment follow-up (EoT+24wks) by IA.
17) Summary of baseline characteristics for responders and non-responders.
18) Summary of SVR rates for variables potentially associated with response.
19) Statistical analysis of variables associated with SVR success - logistic regression – all arms.
20) Statistical analysis of variables associated with SVR success - logistic regression – Arm 1 300mg GSK3228836 x24W + PegIFN x24W.
21) Statistical analysis of variables associated with SVR success - logistic regression – Arm 2 300mg GSK3228836 x12W + PegIFN x24W.

4.7.3. Statistical Analyses / Methods

An estimation approach with no hypothesis testing will be used to address the primary objective (see Section 4.7.3.1). The analysis will be conducted separately for each arm.

Endpoints / variables specified in Section 4.7.1 and Section 4.7.2 (endpoints 1-13) will be summarised using descriptive statistics, graphically presented (where appropriate), and listed.

Endpoints 14-21 will be analysed as described in Section 4.7.8 as appropriate.

4.7.3.1. Model Specification and Decision Criteria

Predictive probability of meeting SVR thresholds (30 or 35%) will be presented for both arms.

For the posterior probability of SVR rate, with complete data, the number of responders is assumed to follow a Binomial distribution

$$Y \sim \text{Binomial}(N, p)$$

where p is the response rate, with a non-informative prior Beta (0.5,0.5), and the posterior distribution for p is

$$\text{Prob}(p|y, N) \sim \text{Beta}(y + 0.5, N - y + 0.5)$$

At the defined time of interim, participants will be at one of two stages in terms of follow-up in the study:

1. **Stage 1:** participants eligible for end of off-treatment follow-up (EoT+24wks) assessment at IA (including participants who have completed at least one visit within their EoT+24wks assessment window and early termination participants who should have completed at least one visit within their EoT+24wks assessment window by the time of the IA data cut).
    - The VR success/failure rate at the end of treatment and SVR success/failure rate at the end of 24-week off-treatment follow-up period (EoT+24wks) will be known for these participants.
    - Participants who fail to achieve VR at end of treatment or fail to sustain a VR from end of treatment (EoT) to the end of follow-up (EoT+24wks), will be classified as SVR failures.
    - Participants achieving SVR at the end of follow-up (EoT+24wks) will be considered SVR successes.
2. **Stage 2:** Participants not yet eligible for end of off-treatment follow-up (EoT+24wks) assessment, i.e., participants between end of treatment (EoT) and EoT+24wks by the time of IA data cut.
    - For these participants, the VR success/failure rate at the end of treatment (EoT) and SVR success/failure rate to the point of IA data cut will be known.
    - Participants who fail to achieve VR at end of treatment (EoT) or fail to sustain a VR from end of treatment (EoT) to the point of IA data cut-off, will be classified as SVR failures.
    - Participants achieving SVR at the time of IA data cut will be considered as potential SVR successes.

Participants who withdraw prior to completing their SVR assessment will be considered as failures. The number of VR/SVR successes for participants at the two stages are summarised in Table 9.

Table 9 Interim Analysis Stages of Follow-Up

	Stage 1: (n.elig)	Stage 2: (n.nelig = N – n.elig)	
	VR Success at EoT	VR Success at EoT and SVR at IA	VR Success at EoT but not SVR at IA
VR Successes	nvr1	nvr2	nvr3
SVR Successes	nSVR1	nSVR2	0
SVR Failures (incl. VR relapse or lost-to-follow-up)	nvr1 – nSVR1	nvr2 – nSVR2	nvr3

EoT = end of treatment; IA = interim analysis; n.elig = eligible for EoT+24wks assessment at IA; n.nelig = not eligible for EoT+24wks assessment at IA; nvr = number of virologic responses; nSVR = number of sustained virologic responses.

For each arm, the predictive probability of meeting the end of off-treatment follow-up (EoT+24wks) success rule is determined from

- nSVR1 (known) out of nvr1, and
- the posterior predictive distribution for nSVR2 out of nvr2+nvr3.

For participants eligible for end of off-treatment follow-up (EoT+24wks) assessment at IA , the SVR success is assumed to follow a binomial distribution

$$Y \sim \text{Binomial}(nvr1, p)$$

where p is the SVR rate, with a non-informative prior Beta (0.5,0.5). If SVR success is obtained, the posterior distribution of p is

$$\text{Prob}(p|nSVR1, nvr1) \sim \text{Beta}(nSVR1 + 0.5, nvr1 - nSVR1 + 0.5)$$

For Stage 2 participants, the predicted number of SVR successes can be obtained from the truncated Beta-Binomial distribution

$$nSVR2 \mid nSVR1, nvr1, nvr2, nvr3 \sim \text{Beta-Binomial}(nvr2 + nvr3,$$

$$0.5 + nSVR1,$$

$$0.5 + nvr1 - nSVR1)$$

where nvr2+nvr3 is the total number of participants who were VR successes at EoT but are ineligible for end of off-treatment follow-up assessment at IA. The maximum predicted number of SVR successes (nSVR2) may not exceed the number of participants that have the potential to achieve SVR. Thus, nSVR2 must be in the range [0, nvr2].

The prediction model for the "complete data" number of SVR successes will account for the number of participants who have reached end of treatment (EoT) but not the end of off-treatment follow-up (EoT+24wks) and have failed to either achieve VR or sustain VR. For these participants, it is impossible for them to achieve SVR and must be accounted for in the model.

The predicted number of responders for complete data is nSVR1 + nSVR2, where nSVR2 is obtained from the truncated Beta-Binomial (nvr2 + nvr3, 0.5 + nSVR1, 0.5 + nvr1 − nSVR1) distribution, with the number of predicted additional SVR events (nSVR2) being ≤ the number of participants with SVR pending.

4.7.3.2. Model Checking and Diagnostics

No model checking is planned for the interim analysis.

4.7.4. Intercurrent Events

Endpoints in Section 4.7.1 and Section 4.7.2 will be summarized regardless of discontinuation of, interruption in, or non-adherence to GSK3228836 or PegIFN treatment unrelated to wide disruptive events (treatment policy strategy). For participants where WDEs on-treatment result in discontinuation of, significant interruption of, and adherence to investigational product (IP), and the participant withdraws from the study, data collected after the intercurrent event will be set to missing and their SVR response will be imputed using all available data for participants for whom SVR can be assessed (hypothetical strategy).

If the participants take rescue medication post-baseline and before/at the assessment of the endpoints, the participants will be considered as non-responders in the interim analysis (composite strategy).

Wide disruptive event includes COVID-19 pandemic related visits. The impact will be captured on COVID-19 eCRF page.

For participants who achieved VR at end of treatment (EoT) and maintained it until the time of IA, but have not reached end of follow-up (EoT+24wks), data for future visits will not be classified as missing. These participants will be classified as potential SVR responders.

Assuming that no rescue medication was taken, missing data at the various stages of the study for endpoints described in Section 4.7.1 will be handled as described below.

4.7.4.1. Missing Primary Data at End of Treatment

End of treatment (EoT) VR response will be determined using the end of treatment analysis window defined in Section 4.2.2.1. If all HBsAg and HBV DNA data within the analysis window for the end of treatment visit is missing and the missingness is not due to wide disruptive events, no imputation of missing data will be performed, and the subject will be considered as a non-responder.

If all HBsAg and HBV DNA data within the analysis window for the EOT visit is missing due to a WDE, and the participant withdraws from the study, the participant will be

classified as not reaching EOT at follow-up. Data after the intercurrent event will be set to missing.

If all HBsAg and HBV DNA data within the analysis window for the EOT visit is missing due to a WDE, but the participant later returns to study and has non-missing data in a later analysis window, the data will be handled in the following two ways:

1. For observed VR responders, the data will be analysed as collected (treatment policy).
2. For observed VR non-responders, data collected after the intercurrent event will be set to missing. The response will be imputed assuming missing at random using all available data from participants for whom SVR can be assessed (hypothetical strategy).

4.7.4.2. Missing Primary Data Post End of Treatment

If all HBsAg and HBV DNA data within an analysis window post the planned end of sequential treatment (EoT) and before/at the assessment is missing not due to wide disruptive events, missing data will be considered as a non-response.

If all HBsAg and HBV DNA data within an analysis window post the planned end of sequential treatment (EoT) and before/at the assessment is missing due to wide disruptive events (such as COVID-19 pandemic) and the participant doesn't have any HBsAg ≥LLOQ or HBV DNA ≥LLOQ or rescue medication at or post planned end of sequential treatment (EoT), the subject will be classified as a potential SVR responder and will be counted among number of participants with VR success at end of treatment (EoT) and maintained until IA (nvr2 in Table 9).

If a participant has any assessments that are affected by a wide disruptive event, but the participant's HBsAg and HBV DNA within an analysis window are collected and the participant is a VR responder, the subject will be classified as a potential SVR responder and will be counted among number of participants with VR success at end of treatment (EoT) and maintained until IA (nvr2 in Table 9).

4.7.4.3. Missing Data for Other Endpoints

In Section 4.7.2, for the proportion of participants in each treatment arm who achieve HBsAg <LLOQ and HBV DNA <LLOQ in the absence of rescue medication at the end of treatment (EoT), the outcome will be determined using the end of treatment analysis window defined in Section 4.2.2.1. In line with the primary endpoint, missing data not due to wide disruptive events will be imputed as a non-response. Missing data due to wide disruptive events will be analysed as collected without any imputation.

Other endpoints will be summarized regardless of completing IP, interruptions in IP or adherence to IP and regardless of rescue medication (except for ALT normalization which can only be achieved in the absence of rescue medication and proportion of participants who achieve HBsAg <LLOQ and HBV DNA <LLOQ). Missing data for these endpoints will be analysed as collected without any imputation. Only available data will be summarized.

HBV DNA, HBsAg, HBeAg levels that are below the LLOQ will be imputed for summaries of actual values and change from baseline following the same rules as in Section 4.1.1.

4.7.5. Subgroup Analyses

Descriptive summaries by baseline strata subgroups defined in Section 4.2.2 will be provided as specified in the OPS. Proportion of participants with HBsAg <LLOQ and HBV DNA <LLOQ at end of treatment will be presented by subgroups defined in Section 4.6.1. No statistical comparison between subgroups will be performed.

4.7.6. Sensitivity Analyses

The analysis using the modified definition of SVR, as detailed in Section 4.7.3.1, will be repeated at the interim analysis.

For the interim analysis, participants who have a value of HBsAg ≥ LLOQ or HBV DNA ≥ LLOQ at their last visit, which cannot be confirmed due to no further follow up, will be treated as responders/ potential responders as the follow-up is incomplete.

4.7.7. Supplementary Analyses

In addition to the main analysis, a supplementary analysis will be performed to evaluate whether there is an impact on the primary outcome if HBV DNA TND is observed. For this estimand, the outcome of SVR is defined as observing HBsAg<LLOQ and HBV DNA TND at each analysis window for 24 weeks after the planned end of treatment (EoT). All other elements of this estimand are defined in the same way as in the main analysis.

4.7.8. Exploratory Analyses

4.7.8.1. Efficacy Analyses

Refer to Section 4.4.1 for details.

4.8. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 10

Table 10 Changes to Protocol Defined Analyses

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
Section 3 Objectives and Estimands and where applicable throughout	Updated text defining the population for the efficacy objectives align with the definition of intent-to-treat (ITT) population which will be used in efficacy analyses and is defined as all randomized participants.	To align with Study 209668 (B-Clear).
Section 3 Objectives and Estimands and Section 9.4.3.1 Secondary Estimands	Secondary Efficacy Endpoints: moved HBe antibody (anti-HBeAg) levels from a continuous variable to a categorical variable.	Correction.
NA – addition	SAP Section 4.2.5.1: Additional estimand to assess efficacy using a modified definition of SVR	Rationale is based on B-clear study, i.e. there are possible subjects with single lab values that are aberrant in terms of the individual's overall trajectory of response. There is some evidence that the aberrant values have occurred because of an unresolvable error at the site/lab. As the issues cannot be resolved in the data, this analysis will be used to support the primary objective.
Section 9.5 Interim Analysis	Unplanned interim analysis added	Support of internal decisions for platform trial (Study 218309)

5. SAMPLE SIZE DETERMINATION

For the entire study, approximately 100 participants will be enrolled and randomised to achieve approximately 50 participants in each treatment group:

- 24 weeks treatment of GSK3228836 followed by up to 24 weeks treatment of PegIFN
- 12 weeks treatment of GSK3228836 followed by up to 24 weeks treatment of PegIFN

It is assumed that the number of responders follows a Binomial distribution, with a weakly informative prior (Beta (0.5, 0.5)) for the true RR. The precision for a range of RRs with 95% credible intervals are shown in Table 11.

Table 11 95% Credible Interval of Response Rate

Number of Responders	Response Rate	95% Credible Interval*
9	18%	9% - 30%
10	20%	11% - 33%
11	22%	12% - 35%
12	24%	14% - 37%
13	26%	15% - 39%
14	28%	17% - 41%
15	30%	19% - 44%
16	32%	20% - 46%
17	34%	22% - 48%
18	36%	24% - 50%
19	38%	26% - 52%
20	40%	27% - 54%

*95% equal-tailed interval

The historical RR of a combination therapy of NA and PegIFN was 10% with 48 week's treatment [Ren, 2019; Lee, 2018]. The lower bounds of 95% credible intervals will exclude the RR of 10% if observed RR is greater than or equal to 20% (10 responders out of 50 participants) in an arm.

The posterior probabilities that the true sustained virologic RR is greater than a range of RRs will be calculated from the implied Beta posterior, given the actual number of responders observed.

The operating characteristics based on at least 65% posterior confidence that the true rate exceeds a threshold of interest, are shown in Table 12 for various sample sizes and true

cure rates. The operating characteristics shown are based on a Bayesian inference without consideration of baseline stratification factors.

Table 12 End of study (EoT+24wks) Operating Characteristics by Sample Size

Criterion	Sample Size per Arm	Minimum Number (%) or Responders Required to Meet Criterion	Probability of Meeting Criterion under Various Assumptions			
			True SVR rate = 20%	True SVR rate = 30%	True SVR rate = 35%	True SVR rate = 40%
Probability (true response rate > 20%) > 65%	30	7 (23%)	39%	84%	94%	98%
	40	9 (23%)	41%	89%	97%	99%
	50	12 (24%)	29%	86%	97%	99%
	60	14 (23%)	31%	90%	98%	100%
Probability (true response rate > 30%) > 65%	30	10 (33%)	6%	41%	64%	82%
	40	14 (35%)	2%	30%	56%	79%
	50	17 (34%)	1%	32%	61%	84%
	60	20 (33%)	1%	33%	65%	88%
Probability (true response rate > 40%) > 65%	30	14 (47%)	0%	4%	12%	29%
	40	18 (45%)	0%	3%	12%	31%
	50	22 (44%)	0%	3%	12%	33%
	60	26 (43%)	0%	2%	11%	34%

Based on these operating characteristics, for a true RR of 30%, the proposed sample size of n=50 for each arm has ~86% probability of confirming a true response of at least 20%, and if the true rate is 40%, there is an 84% chance of confirming a true response of at least 30%. There are no plans for sample size re-estimation.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Enrolled Analysis Set. A summary of the number and percentage of participants in each of the participant level analysis set will be provided. Participants excluded from various study populations will be presented in a listing.

Subject enrolment will be presented by country and site ID.

For the interim analysis, a table showing the amount of pending data will be produced for participants with SVR status unknown due to them not having reached the end of off-treatment follow-up (EoT+24wks) at the time of IA. Assessment of pending data should be performed based on occurrence of endpoint analysis window visits.

6.1.1. Participant Disposition

A summary of the number of participants who were screened including number and percentage of screen failures will be provided. In addition, reasons for screen failure will be presented.

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study discontinuation will be summarized.

A summary of study intervention status will be provided. This display will show the number and percentage of participants who have completed the scheduled study intervention or have discontinued study intervention prematurely, as well as primary reasons for discontinuation of study intervention.

Reasons for screen failures, study withdrawal and study treatment discontinuation will also be presented in listings.

6.1.2. Demographic and Baseline Characteristics

Unless otherwise stated, study population analyses will be based on the Enrolled population.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, nucleos(t)ide treatment ongoing at randomization, medical history and exposure and treatment compliance will be presented.

Demographic characteristics including sex, age, ethnicity, race, height, weight will be summarized with descriptive statistics.

Baseline characteristics including Body Mass Index (BMI), hypertension, non-steroidal anti-inflammatory drugs (NSAIDs), tenofovir disoproxil fumarate (TDF)/tenofovir alafenamide (TAF) containing medications use, ADV containing medications use, diabetes, eGFR, serum creatinine, urine ACR, platelets, ANC, complement C3, complement C4, complement C5a, complement Bb, CRP, MCP-1, c-ANCA, p-ANCA, and subgroup categories (listed in Section 4.6) will be summarized with descriptive statistics.

Hepatitis B characteristics, as collected on the Hepatitis B Disease Characteristics eCRF, will be summarized using descriptive statistics and will be listed.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using the GSK Drug dictionary. The summary of concomitant medications will be provided by ingredient, i.e., multi-ingredient medications will be summarized for each individual ingredient rather than a combination of ingredients. The summary will be created using ingredient base names, i.e., ingredients with the same base name but different salt will appear under one base name in the summary. Anatomical Therapeutic Chemical (ATC) classifications will not appear in the summary.

A prior medication is defined as any medications that is ended prior to the date of first dose of study drug.

Medications initiated after the first dose of study drug or initiated prior to the first dose of study drug and continued after the first dose of study drug will be counted as concomitant medications. A medication that cannot be determined as prior or concomitant medication due to partially or completely missing start/stop date will be counted as both prior and concomitant medication.

6.1.5. Study Intervention Compliance

A summary of overall compliance for GSK3228836 and PegIFN based on the exposure data will be produced. Overall compliance will be summarized using descriptive statistics as well as the categories <80%, 80%-100%, and >100%.

Compliance will be summarized both in terms of number of injections administered and total dose received during the planned on-treatment period.

Percentage of compliance will be calculated as follows:

$$\textit{Study intervention Compliance (\%)} = \textit{(Number of actual doses}^{[1]} \textit{ / Number of planned doses) *100}$$

$$\textit{Study dose Compliance (\%)} = \textit{(Total Cumulative Actual Dose}^{[2]} \textit{ / Total Cumulative Planned Dose) * 100}$$

1) GSK3228836 :- The planned number of doses are 26 or 14 for Arm 1 & Arm 2 respectively. The Planned Total Cumulative Dose is calculated by multiplying number of planned doses and dose that is, 300 mg.

*Planned Total Cumulative Dose = Number of planned doses * 300 mg*

2) PegIFN: - The planned number of doses are 24 if subject becomes eligible for PegIFN Week 1. If subject becomes eligible after PegIFN Week 1, then follow Protocol table 6 to identify number of planned doses –

Table 6 PegIFN Dosing for Participants becoming Eligible for PegIFN after Week 1

Become Eligible for PegIFN at PegIFN Eligibility Week (Table 5)	PegIFN Dosing (Table 4) should continue until PegIFN Dosing Week
2	23
3	22
4	21
6	19
8	17
10	15
13	12

The Planned Total Cumulative Dose is calculated by multiplying number of planned doses and dose that is, 180 mcg.

*Planned Total Cumulative Dose = Number of planned doses * 180 mcg*

[1] : Subject might receive reduced dose that is smaller than the number of injections. Reduced dose should be still counted as 'one' dose for *Number of actual doses* calculations.

[2] : Refer to SAP Section 4.5.1

6.1.6. Additional Analyses Due to the COVID-19 Pandemic

A participant is defined as having a suspected, probable, or confirmed COVID-19 infection during the study if the answer is 'Confirmed', 'Probable', or 'Suspected' to the case diagnosis question from the COVID-19 coronavirus infection assessment eCRF. Numbers of participants with a suspected, probable, or confirmed COVID-19 infection, and of COVID-19 test results will be summarized.

If a high proportion (>5% overall) of participants have a suspected, probable, or confirmed COVID-19 infection, the following data displays will be produced:

- Summary of current (and/or past) medical conditions for participants with COVID-19 adverse events.
- Summary of baseline characteristics for participants with COVID-19 adverse events.

6.2. Appendix 2: Data Derivation Rules

6.2.1. Criteria for Potential Clinical Importance

Grading categories for laboratory tests are determined using the DAIDS grading system Version 2.1 [National Institute of Allergy and Infectious Diseases. Division of AIDS, 2017].

No Laboratory tests values of potential clinical importance (PCI) are defined. Laboratory values outside of normal range will be summarized and listed.

6.2.2. Study Phase and Period

Safety assessments and events will be classified according to the time of occurrence relative to the study intervention period.

Table 13 Study Phase Definitions

Study Intervention Phase	Definition
Pre-Treatment	For Assessments – Date[1] ≤ Study Treatment Start Date For Events – Date[1] < Study Treatment Start Date
On-Treatment	For Assessments – Study Treatment Start Date < Date[1] < Last Treatment Stop Date + 7 days For Events – Study Treatment Start Date ≤ Date[1] < Last Treatment Stop Date + 7 days
Post-Treatment	Date[1] ≥ Last Treatment Stop Date + 7 days

[1] Date is the start date of the assessment/event.

Table 14 Study Period Definitions

Study Intervention Period	Definition
GSK3228836 Treatment Period	For Assessments – All Analysis Timepoints within : WK 1 DAY 1 to a day prior PEGIFN ELIGIBILITY WK 1 DAY 1* For Events – Study Treatment Start Date ≤ Date[1] < GSK836 Last Treatment Date + 7 days
PegIFN Eligibility Period	For Assessments – All Analysis Timepoints within : 1) PEGIFN ELIGIBILITY WK 1 DAY 1 to a day prior PEGIFN DOSING WK 1 DAY 1* and 2) PEGIFN ASSESSMENT WK 14 to a day prior OT-W1 OT-DAY 1*

Study Intervention Period	Definition
	For Events – GSK836 Last Treatment Date + 7 days ≤ Date[1] < PegIFN Treatment Start Date *if subject withdrew or never received PegIFN dosing before PegIFN Dosing Visit then end of period would be 'Last PegIFN Assessment Week Stop Date + 7 days'
PegIFN Treatment Period	For Assessments – All Analysis Timepoints within : PEGIFN DOSING WK 1 DAY 1 to a day prior OT-W1 OT-DAY 1* For Events – PegIFN Treatment Start Date ≤ Date[1] < PegIFN Treatment Stop Date + 7 days
Follow-up Period	For Assessments – All Analysis Timepoints within : OT-W1 OT-DAY 1* onwards For Events – If subject never received PegIFN dosing and did not discontinue on-treatment - Date1 ≥ Last PegIFN Assessment Week Stop Date + 7 days Else Date1 ≥ Last Treatment Stop Date + 7 days

[1] Date is the start date of the assessment/event.
* If a subject withdrew early or skipped period(s), consider start of next period analysis timepoint. If analysis timepoint is not collected, use corresponding planned start visit day in Section 6.2.8.

6.2.3. Study Day and Reference Dates

The study reference date is the study treatment start date and will be used to calculate study day for safety and efficacy measures.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Reference Date
- Assessment Date ≥ Reference Date → Study Day = Assessment Date – Reference Date + 1

6.2.4. Multiple Measurements at One Analysis Time Point

Table 15 Multiple Measurements at One Analysis Time Point

Definition
• Handling of multiple measurements within an analysis window for primary endpoint is described in Section 4.2.2 • Assessments on unscheduled visit will not be included in the tables of summary statistics by visit but will be included in the associated listings. Also, such assessments on unscheduled visit will be used for the "any time on-treatment" or "Any visit post-baseline" time point. • If there are multiple assessments on scheduled visit within visit window, will query the site to identify the valid assessment as the assessment for the scheduled visit. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. • If after window assignment of Early Termination visits there are multiple valid assessments of a parameter within the same window (see Section 6.2.8), then the following hierarchy will be used to determine the value to be used for summary statistics of observed values: o the assessment closest to the window target Study Day. o if there are multiple assessments equidistant from the target Study Day, then the mean of these values will be used. • If normal LAB ranges are collected and there are duplicate LAB records at the same date/timepoint, the the "worst-case" value will be selected. Specifically: o For LAB result > Lower Normal range, select Maximum of Lab result (AVAL). o For LAB result <= Lower Normal range, select minimum of Lab result (AVAL).

6.2.5. Study Phases for Concomitant Medication

Please refer to Section 6.2.9 for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

Table 16 Definition of Prior and Concomitant Medications

Study Phase	Definition
Prior	A prior medication is defined as any medication that has ended prior to the date of first dose of study drug.
Concomitant	Medications initiated after the first dose of study drug or initiated prior to the first dose of study drug and continued after the first dose of study drug will be counted as concomitant medications. A medication cannot be determined as prior or concomitant medication due to partially or completely missing start/stop date will be counted as both prior and concomitant medication.

6.2.6. Treatment Emergent Flag for Adverse Events

If the study treatment stop date is missing, then the AE will be classified as on-treatment.

Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

Table 17 Definition of Treatment Emergent Adverse Events

Flag	Definition
Treatment Emergent	• Study Treatment Start Date ≤ AE Start Date

6.2.7. METAVIR Fibrosis Score

The METAVIR score determined from the Fibrosis score is presented in table below.

Table 18 METAVIR Fibrosis Score

Fibrosis Score	METAVIR	Comment
≤0.21	Stage F0	No fibrosis
>0.21 – 0.27	F0-F1	
>0.27 – 0.31	F1	Portal Fibrosis
>0.31 – 0.48	Stage F1 – F2	
>0.48 – 0.58	Stage F2	Bridging fibrosis with few septa
>0.58 – 0.72	Stage F3	Bridging fibrosis with many septa
>0.72 – 0.74	Stage F3 – F4	
>0.74	Stage F4	Cirrhosis
https://www.labcorp.com/tests/related-documents/L9465, accessed 11Jan2022.		

6.2.8. Assessment Windows for Early Termination

Unless otherwise specified, no windowing will be applied to unscheduled visits. Planned time relative to dosing will be used in figures, summaries, statistical analyses, and calculation of any derived parameters, unless otherwise stated. Unscheduled visits will not be included in summary tables and/or figures except from determining response for primary endpoint as described in Section 4.2.2 and summaries over "any time on treatment" or "any visit post-baseline". Unscheduled visits will be included in listings.

Laboratory and vital signs data collected at Early Termination Visits will be assigned to assessment windows, according to the actual date.

Table 19 Early Termination Visit Windowing

Analysis Set / Domain	Target study day	Analysis Window		Analysis Timepoint
		Start day	End day	
GSK3228836 Arm 1 and Arm 2				
Lab, Vital Signs	1	1	2	Week 1 Day 1
	4	3	6	Week 1 Day 4
	8	7	9	Week 2 Day 8
	11	10	12	Week 2 Day 11
	15	13	18	Week 3 Day 15
	22	19	25	Week 4 Day 22
	1+7*(x-1)	1+7*(x-1)-3	1+7*(x-1)+3	Week x Day 1+7*(x-1)
PegIFN Arm 1 Dosing Weeks*				
Lab Vital Signs	1+7*(23+y+z)	1+7*(23+y+z)-3	1+7*(23+y+z)+3	PegIFN Dosing Week y Day 1
PegIFN Arm 2 Dosing Weeks*				
Lab Vital Signs	1+7*(11+y+z)	1+7*(11+y+z)-3	1+7*(11+y+z)+3	PegIFN Dosing Week y Day 1
PegIFN Arm 1 Eligibility (No Dosing) Weeks (up to 13)				
Lab Vital Signs	1+7*(23+u)	1+7*(23+u)-3	1+7*(23+u)+3	PegIFN Eligibility Week u Day 1
PegIFN Arm 2 Eligibility (No Dosing) Weeks (up to 13)				
Lab Vital Signs	1+7*(11+u)	1+7*(11+u)-3	1+7*(11+u)+3	PegIFN Eligibility Week u Day 1

Analysis Set / Domain	Target study day	Analysis Window		Analysis Timepoint
		Start day	End day	
PegIFN Arm 1 No Dosing Assessment Weeks (week 14 onwards)				
Lab Vital Signs	1+7*(23+v)	1+7*(23+v)-3	1+7*(23+v)+3	PegIFN Asessment Week v
PegIFN Arm 2 No Dosing Assessment Weeks (week 14 onwards)				
Lab Vital Signs	1+7*(11+v)	1+7*(11+v)-3	1+7*(11+v)+3	PegIFN Assessment Week v
Off-Treatment Week (OTW) Follow-up Arm 1				
Lab Vital Signs	337	334	340	Off-Treatment Week 1
	344	341	347	Off-Treatment Week 2
	358	348	372	Off-Treatment Week 4
	386	373	400	Off-Treatment Week 8
	414	401	435	Off-Treatment Week 12
	456	436	477	Off-Treatment Week 18
	498	478	518	Off-Treatment Week 24
Off-Treatment Week (OTW) Follow-up Arm 2				
Lab Vital Signs	253	250	256	Off-Treatment Week 1
	260	257	263	Off-Treatment Week 2
	274	264	288	Off-Treatment Week 4
	302	289	316	Off-Treatment Week 8
	330	317	351	Off-Treatment Week 12
	372	352	393	Off-Treatment Week 18

Analysis Set / Domain	Target study day	Analysis Window		Analysis Timepoint
		Start day	End day	
	414	394	435	Off-Treatment Week 24
	456	436	477	Off-Treatment Week 30
	498	478	518	Off-Treatment Week 36

* Only if subject started PegIFN treatment.

1. Week x includes on-treatment weeks 5 – 24 for treatment with GSK3228836.
2. Week y includes on-treatment weeks 1 – 24 for treatment with PegIFN.
3. Week u includes PegIFN Eligibility weeks 1 – 13.
4. Week v includes PegIFN Eligibility weeks 14 – 24.
5. z is the total number of PegIFN ineligibility weeks prior to PegIFN treatment.
6. Visit windows are to be used for windowing of Early Termination visits only.

6.2.9. Handling of Missing and Partial Dates

Table 20 Rules for Handling Missing and Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>• Partial dates will be displayed as captured in participant listing displays.
• However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below.
• Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.</td></tr>
<tr><td>Adverse Events</td><td>• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table><tr><td>Missing start day</td><td>• If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = 1st of month.
• Else if study intervention start date is not missing:
o If month and year of start date = month and year of study intervention start date, then
▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
▪ Else set start date = study intervention start date.</td></tr></table></td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>o Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>• If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = January 1.
• Else if study intervention start date is not missing:
o If year of start date = year of study intervention start date, then
▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
▪ Else set start date = study intervention start date.
o Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>No Imputation.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation.</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>• If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = 1st of month.
• Else if study intervention start date is not missing:
o If month and year of start date = month and year of study intervention start date, then
▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail	
		▪ Else set start date = study intervention start date. o Else set start date = 1st of month.
	Missing start day and month	• If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = January 1. • Else if study intervention start date is not missing: o If year of start date = year of study intervention start date, then ▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. ▪ Else set start date = study. intervention start date. o Else set start date = January 1.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.
	Completely missing start/end date	No imputation

6.3. Appendix 3: Abbreviations

Table 21 List of Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
ADRG	Analysis Data Reviewer's Guide
ACR	Albumin to creatinine ratio
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike Information Criteria
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCA	Anti-neutrophil cytoplasmic antibody
APRI	Aspartate aminotransferase to platelet ratio index
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
Bb	Fragment of complement factor B
BDI-II	Beck Depression Inventory-II
BGR	Brooks-Gelman ratio
BMI	Body Mass Index
C2P3	Commit to Phase 3
C3	Complement component 3
C4	Complement component 4
C5a	Complement component 5a
c-ANCA	Cytoplasmic ANCA
p-ANCA	Perinuclear ANCA

Abbreviation	Description
CDISC	Clinical Data Interchange Standards Consortium
CHB	Chronic Hepatitis B
CI	Confidence interval
COVID19	Coronavirus disease 2019
CPMS	Clinical Pharmacology Modelling and Simulation
C_T	Concentration at the end of the dosing interval
CSR	Clinical Study Report
C-SVRRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
$\%CV_b$	Coefficient of variation (between)
DAIDS	Division of Acquired Immune Deficiency Syndrome
DBP	Diastolic blood pressure
DBR	Database release
DP	Decimal place
DRB	Development Review Board
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Amendments Act
EMA	European Medicines Agency
EoT	End of sequential treatment of GSK3228836 and Peginterferon
EoT+24wks	End of 24 weeks of off-treatment follow-up after end of treatment
EoS	End of study, i.e. final study visit per protocol

Abbreviation	Description
FP	False positive
GSK	GlaxoSmithKline
HBcrAg	Hepatitis b core-related antigen
Anti-HBeAg	Hepatitis B virus e-antibody
HBeAg	Hepatitis B virus e-antigen
Anti-HBsAg	Hepatitis B virus surface antibody
HBsAg	Hepatitis B virus surface antigen
HBV DNA	Hepatitis B virus deoxyribonucleic acid
HBV RNA	Hepatitis B virus ribonucleic acid
HLT	High level term
hs-CRP	High-sensitivity C-reactive protein
IA	Pre-specified Interim Analysis
IDMC	Independent Data Monitoring Committee
IP	Investigational product
INR	International normalized ratio
ITT	Intent-to-treat
LLOQ	Lower limit of Quantification
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MCP-1	Monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Authorities
MMRM	Mixed Model Repeated Measures
NA	Nucleos(t)ide analogue
Neg	Negative

Abbreviation	Description
NI	Non-inferiority
NSAID	Non-steroidal anti-inflammatory drug
NUC	Nucleos(t)ide
NVR	Number of virologic responses
NSVR	Number of sustained virologic responses
OCs	Operating Characteristics
OPS	Output and Programming Specification
PBMCs	Peripheral blood mononuclear cells
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PegIFN	Pegylated interferon
PK	Pharmacokinetic
Pos	Positive
PT	Preferred term
PT_{test}	Prothrombin time
RBC	Red blood cells
ROC	Receiver operating characteristic
RR	Response rate
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SD	Standard deviation
SDTM	Study Data Tabulation Model
SVR	Sustained virologic response
SMQ	Standardised MedDRA Query

Abbreviation	Description
SoA	Schedule of assessments
SOC	System Organ Class
t½	Terminal half-life
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
TN	True negative
TND	Target not detected
TP	True positive
ULN	Upper limit of normal
VR	Virologic response

6.3.1. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies	Trademarks not owned by the GlaxoSmithKline Group of Companies
None	WinNonlin

7. REFERENCES

Brooks, S. P. and Gelman, A. (1998) Alternative Methods for Monitoring Convergence of Iterative Simulations. Journal of Computational and Graphical Statistics 7, 434–455.

Heinze G, Schemper M. A solution to the problem of separation in logistic regression. Statist. Med. 2002;21:2409–2419

Jones HE, Ohlssen DI, Neuenschwander B, Racine A, Branson M. Bayesian models for subgroup analysis in clinical trials. Clin Trials. 2011; 8:129–143.

Lee IC, Yang SVR, Lee CJ, Su CW, Wang YJ, Lan KH, et al. 2018. 'Incidence and Predictors of HBsAg Loss After Peginterferon Therapy in HBeAg-Negative Chronic Hepatitis B: A Multicenter, Long-term Follow-up Study', *J Infect Dis*, 2018: 1075-84.

National Institute of Allergy and Infectious Diseases. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, JULY 2017.

Ren H, Huang Y. 2019. 'Effects of pegylated interferon-alpha based therapies on functional cure and the risk of hepatocellular carcinoma development in patients with chronic hepatitis B', *J Viral Hepat*, 26 Suppl 1: 5-31.

Wicklin, Rick. (2013). *Simulating Data with SAS®*. Cary, NC: SAS Institute Inc.