# Statistical Analysis Plan

**Study ID:** 209668

**Official Title of Study:** Reporting and Analysis Plan for Phase IIb Multi-Center, Randomised, Partial-Blind Parallel Cohort Study to Assess the Efficacy and Safety of Treatment with GSK3228836 in Participants with Chronic Hepatitis B Virus (B-Clear)

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# TITLE PAGE

**Protocol Title:** Reporting and Analysis Plan for Phase IIb Multi-Center, Randomised, Partial-Blind Parallel Cohort Study to Assess the Efficacy and Safety of Treatment with GSK3228836 in Participants with Chronic Hepatitis B Virus (B-Clear)

**Study Number:** 209668

**Compound Number:** GSK3228836

**Abbreviated Title:** Phase IIb study of GSK3228836 in Participants with Chronic Hepatitis B (B-Clear)

**Acronym:** B-Clear

**Sponsor Name:** GlaxoSmithKline Research & Development Limited

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# Version history

| SAP Version | Approval Date | Protocol Version (Date) on which SAP is Based | Change | Rationale |
|---|---|---|---|---|
| SAP amendment 02 | 14 Apr 2022 | 209668 / Amendment 1 (10-May-2021) | Section 4.4.1.1: Replaced text "The same model as specified in Section 4.2.2 will be used, but θg will be defined as the log odds ratio of treatment effect comparing one treatment arm to another treatment arm." with "Comparisons between arms will be made by calculating differences 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 (e.g. Pr(Arm 1 – Arm 2 > -5% \| Data))." | Correction |
| | | | Section 4.4.5: Included references for HBQoL and EQ-5D scoring procedures. | Clarification |
| | | | Section 4.6.1 (Table 7): Added additional HBsAg subgroup.<br><br>Defined HBV RNA and HBcrAg subgroup categories. | Addition/ Clarification |
| | | | Section 4.5.3.1: Corrected repeated text "negative to post-baseline Positive, baseline value no change, and baseline Negative to post-baseline Positive" | Correction |
| | | | Section 4.6.1: Removed text describing statistical analysis of subgroups. Only descriptive stats will be presented for subgroup analyses. | Correction |
| SAP amendment 01 | 11-Feb-2022 | 209668 / Amendment 1 (10-May-2021) | Sections 4.1.1: Added parameters HBV DNA and HBcrAg | Omission - Parameters HBV DNA and HBcrAg were not previously included in the raw data but will be presented at end of study. |
| | | | Sections 4.4.1.3: Added parameters HBV DNA and HBcrAg | Omission - Parameters HBV DNA and HBcrAg were not |

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| | | | | previously included in the raw data but will be presented at end of study. |
| | | | Section 4.2.2 Updated format of formulae | Formatting only |
| | | | Section 4.2.2.1 Updated visit windowing for the end of treatment analysis timepoint | To ensure that on-treatment values are not used when there is a more appropriate end of treatment value available. |
| | | | Section 4.2.4.4 Added clarifying text "Subjects 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 non-responders." | Clarification |
| | | | Section 4.3.1.1: clarifying text added to population section. | Clarification, |
| | | | Section 4.3.1.1: Update to deal with intercurrent events for the proportion of participants achieving HBsAg <LLOQ and HBV DNA <LLOQ in the absence of rescue medication at the end of treatment analysis window in the same way as for the primary efficacy endpoint.<br><br>Included text to state outputs that will be presented by subgroups/ strata. | Update for consistency |
| | | | Section 4.3.1.1: Added HBs antibody variable, which was omitted from the previous version. | Omission |
| | | | Section 4.3.1.1: modified text for censoring | Omission |
| | | | Section 4.3.1.2: Replaced text "The same model as specified in Section 4.2.2 will be used, but θg will be defined as the log odds ratio of treatment effect comparing one treatment arm to another treatment arm." with "Comparisons | Correction |

| SAP Version | Approval Date | Protocol Version (Date) on which SAP is Based | Change | Rationale |
|---|---|---|---|---|
| | | | between arms will be made by calculating differences 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 (e.g. Pr(Arm 1 – Arm 2 > -5% \| Data)).” | |
| | | | Section 4.3.3.4: Added text “(separately for tenofovir disoproxil fumarate and tenofovir alafenamide)” | Clarification |
| | | | Section 4.4.3: Updated to state that all virology analyses will be performed using the safety population | Correction |
| | | | Section 4.4.3.1: Reworded section on how final reported genotype will be derived for clarification.<br><br>Amended text to make it clearer when to use visit and when to use analysis window. | Clarification |
| | | | Section 4.4.3.2: Added text to explain how to identify nucleotide changes | This text was omitted from the first version of the SAP as it was not yet finalised |
| | | | Section 4.4.3.2: Amended text to make it clearer when to use visit and when to use analysis window. | Clarification |
| | | | Section 4.4.3.2: Addition of table showing mutation by response for binding site mutations with >=1% allelic frequency | Addition at request of virology expert. |
| | | | Section 4.5: Addition of text “To allow comparison between safety in active treatment vs placebo, and loading dose vs no loading dose, selected safety displays will be presented by study Weeks 1 – 12, Weeks 13 – 24, and Weeks 25 – 48; refer to the OPS for details of which outputs should be | Clarification |

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|---|---|---|---|---|
| | | | presented by Week, and refer to Section 6.2.2.2 for definitions of assessment windows for adverse events." | |
| | | | Section 4.5.2: Addition of summaries Serious, Non-serious and Drug-Related AEs by SOC and PT (number of subjects and occurrences) ). This will be presented for Overall, and for Week 1 – 12, Week 13 – 24, and Week 25 – Week 48.<br><br>And Serious Fatal and Non-Fatal Drug-Related AEs by Overall Frequency | Omission |
| | | | Section 4.5.2.3 Removal of text "Common AEs" | All AEs are presented for this study, not only common AEs. |
| | | | Section 4.5.3.1: Added text "Ang-II will be included in the immunology summaries and listings and additionally a listing of all Ang-II lab values will be presented. Plots showing mean actual and change from baseline values of Ang-II over time will be presented. " | This text was excluded from the original SAP as the data were not expected to be available until after EoS. |
| | | | Section 4.5.3.2: Removed Grade 0 | Correction – there is no Grade 0 in DAIDS |
| | | | Section 4.6.3: Addition of concordance of virologic response & SVR | Additional analysis requested at IA3 |
| | | | Section 4.6.4: Addition of association between HBV DNA TND and relapse | Additional analysis requested at IA3 |
| | | | Section 4.6.5: Addition of cut point analysis | Additional analysis requested at IA3 |

| SAP Version | Approval Date | Protocol Version (Date) on which SAP is Based | Change | Rationale |
|---|---|---|---|---|
| | | | Section 4.6.6: Addition of predictors of response analysis | Additional analysis requested at IA3 |
| | | | Section 4.6.7 Addition of listings 3 | Clinical request |
| | | | Section 4.8: Removal of text to state that we will include a supplementary estimand to measure SVR from the actual end of treatment instead of planned end of treatment | Analysis is included in Protocol Amendment 01 |
| | | | Section 6.1.2: Removed baseline characteristics from demographic characteristics table and added clarification on which summary stats to use for continuous characteristics.<br><br>Added listing of nucleos(t)ide treatment at baseline for the on stable nucleos(t)ide cohort | Correction & omission |
| | | | Section 6.2.2: Added text to describe visit windowing for early termination visits and AEs | Clarification / omission |
| | | | Section 6.2.3: Added text "Off Treatment Day 1 occurs 7 days after the last study treatment dose received, regardless of whether the participant completes treatment as planned or the participant is withdrawn from study treatment." | Clarification |
| | | | Section 6.2.6: "Duration of Hep B infection (years) will be calculated based on year only" | Based on data, only year of diagnosis is known in most cases. |
| SAP | 09-Aug-2021 | 209668 / Amendment 1 (10-May-2021) | Not Applicable | Original version |

# 1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses to be included in the CSR for Study 209668. Details of the final analyses are provided. Details of interim analyses are provided in separate Interim Analysis Reporting and Analysis Plans.

## 1.1. Objectives, Estimands and Endpoints

| Objectives | Endpoints |
|---|---|
| Primary | |
| **Efficacy**: To assess the efficacy of the three dosing regimens of GSK3228836 in participants with CHB | Primary estimands supporting the primary objective are defined as:<br>- **Population**: separate assessment for the following:<br>• participants with CHB on stable nucleos(t)ide therapy<br>• participants with CHB not currently on nucleos(t)ide therapy<br>- **Variable**: Participants achieving sustained virologic response (SVR, described in Section 4.2) for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication.<br>- **Treatments**: arms 1, 2, and 3. Estimation of the within-arm response rate.<br>- **Intercurrent events**: use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication has been incorporated into the definition of variable (composite strategy). Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption of, and non-adherence to GSK3228836 will be handled assuming they had not happened (hypothetical strategy).<br>- **Population summary**: proportion of participants who achieve SVR for each treatment arm.<br><br>The primary estimands for each sub-population is the proportion of participants in each treatment arm 1, 2, and 3 who achieve SVR for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication regardless of completing IP, interruptions in IP or adherence to IP had they not been affected by wide disruptive events.<br>A supplementary estimand is defined to support the primary objective: |

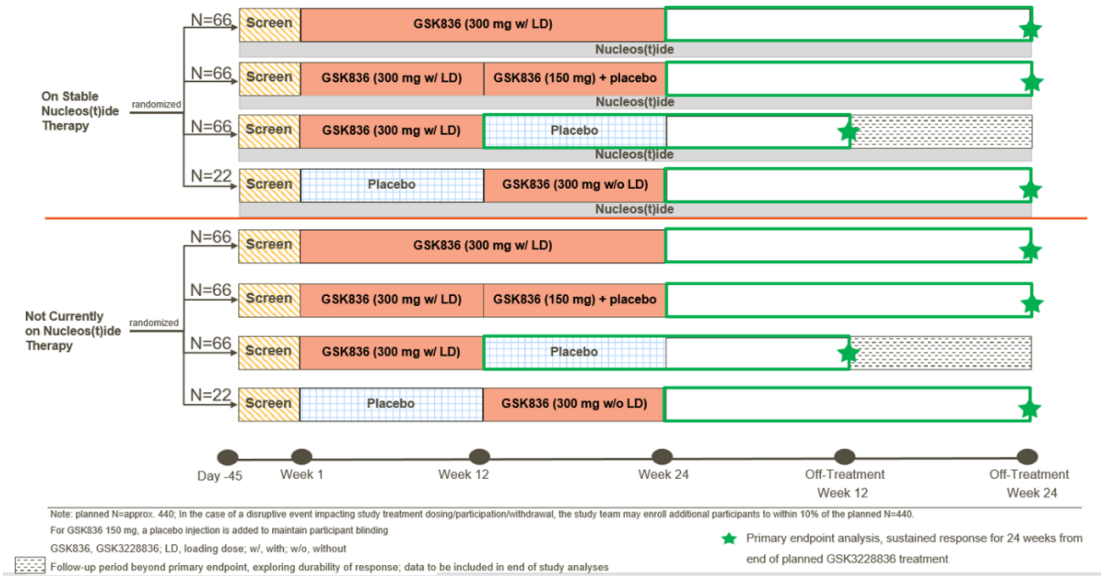
| Objectives | Endpoints |
|---|---|
| | - the supplementary estimand is defined in the same way as the main estimand, except the assessment time frame for participants achieving SVR will be 24 weeks after the actual end of treatment. Therefore, the strategy for intercurrent events of treatment discontinuation will be while-on-treatment. This supplementary estimand supporting the primary objective in participants with CHB on stable nucloes(t)ide therapy and participants with CHB not currently on nucleos(t)ide therapy is the proportion of participants in each treatment arm 1, 2, and 3 who achieve SVR for 24 weeks after the actual end of GSK3228836 treatment in the absence of rescue medication, regardless of completing IP, interruptions in IP or adherence to IP, had they not been affected by wide disruptive events. |
| Secondary | |
| **Efficacy**: To assess the efficacy of GSK3228836 on biomarkers and virus-specific antibody responses | The estimands supporting this secondary objective are defined as follows:<br>- **Population**: separate assessment for the following:<br>• participants with CHB on stable nucleos(t)ide therapy<br>• participants with CHB not currently on nucleos(t)ide therapy.<br>- **Treatments**: arms 1-4. Estimation within each arm.<br>- **Intercurrent events**: use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication will be ignored (treatment policy strategy). Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy)<br>**1) Categorical Variables:**<br>• Achieving HBsAg <LLOQ and HBV DNA <LLOQ at the end of treatment.<br>• 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 log IU/mL)<br>• ALT normalization (ALT≤ULN) over time in absence of rescue medication in participants with baseline ALT>ULN<br>• HBe antibody (anti-HBeAg) levels<br>- Population summary: proportion of participants in each category for each treatment arm.<br><br>**2) Continuous Variables:** Actual values and change from baseline over time of HBsAg and HBV DNA and actual values |

| Objectives | Endpoints |
|---|---|
| | and change from baseline of HBeAg levels; HBs antibody (anti-HBsAg) levels<br>- **Population summary**: mean values and mean changes from baseline for each variable in each treatment arm<br><br>**3) Time to Event Variable:** Time to ALT normalization in absence of rescue medication in participants with baseline ALT>ULN<br>- **Population summary**: Turnbull's estimate for non-parametric estimation of time to ALT normalization in each treatment arm<br>The group of estimands supporting this objective for each sub-population is the population summary for each variable in each treatment arm 1-4 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) |
| **Efficacy**: To compare the efficacy between 12 weeks, 12 weeks + 12 weeks step-down, and 24 weeks of GSK3228836 treatment | The same definition as the primary estimand except treatments and population summary are defined as:<br>-**Treatments**: arms 1, 2, and 3. Three treatment comparisons between: arms 1 & 2, arms 1 & 3, and arms 2 & 3<br>- **Population summary**: difference in proportion of participants who achieve SVR between treatment arms<br><br>The group of estimands supporting this objective for each sub-population are the difference in each treatment comparisons in the proportion of participants who achieve SVR for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication regardless of completing IP, interruptions in IP or adherence to IP had they not been affected by wide disruptive events. |
| **Pharmacokinetics (PK)**: To characterize GSK3228836 and nucleos(t)ide PK in participants with CHB | • In a subset of participants with intensive PK sampling: Derived GSK3228836 and nucleos(t)ide plasma PK parameters including, but not limited to, area under the concentration-time curve (AUC), concentration at the end of the dosing interval ($C\tau$), maximum observed concentration (Cmax), time of maximum observed concentration (tmax).<br>• In all participants: $C\tau$ and terminal half-life ($t_{1/2}$) of GSK3228836. |

| Objectives | Endpoints |
|---|---|
| Safety | |
| **Safety**: To assess the safety and tolerability of GSK3228836 when dosed for 12 weeks, 12 weeks + 12 weeks step-down, and 24 weeks duration in participants with CHB | Clinical assessments including, but not limited to vital signs, laboratory measurements and adverse events. |
| Exploratory | |
| **PK-PD relationships**: To evaluate PK-efficacy relationship and PK-safety relationship | Exploratory graphical analyses will be initially performed for efficacy (e.g., HBsAg) and safety endpoints. If a relationship between exposure and efficacy and/or safety endpoints is present, population PK-PD modelling will be conducted using nonlinear mixed effect methods.<br>The model will assess the effect of various factors (covariates) of the modelled efficacy or safety endpoints. Relevant PK-PD model endpoints for example:<br>• apparent clearance<br>• apparent volume of distribution<br>• IC50<br>• random variability |
| **Efficacy**: To compare the efficacy between 12 weeks of GSK3228836 treatment with a loading dose or without a loading dose | The same definition as the primary Estimand except treatments and population summary are defined as:<br>- **Treatments**: arm 3 & 4. Treatment comparison between arms 3&4.<br>- **Population summary**: difference in proportion of participants who achieve SVR between treatment arms 3 & 4.<br>The group of estimands supporting this objective for each sub-population are the differences between arms 3 & 4 in the proportion of participants who achieve SVR for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication regardless of completing IP, interruptions in IP or adherence to IP had they not been affected by wide disruptive events. |
| **Efficacy**: To assess the pharmacodynamic effect of GSK3228836 on exploratory viral biomarkers | HBV core related antigen (HBcrAg), HBV RNA |
| **Virology**: To assess the effect of genotype/phenotype | Sequencing of the viral HBV DNA and/or HBV RNA prior to treatment, during treatment and post treatment visits |

| Objectives | Endpoints |
|---|---|
| and presence of baseline polymorphisms within the GSK3228836 binding site to assess the effect on treatment response.<br>To assess the emergence of mutations within the GSK binding site, and elsewhere in the hepatitis B genome, during and after treatment. | |
| **Immunology**: To assess the effect of 12 weeks, 12 weeks + 12 weeks step-down or 24 weeks treatment with GSK3228836 on immunological biomarkers.<br>To describe the relationship(s) between virology biomarkers, including but not limited to HBsAg, and immunological biomarkers. | Laboratory measurements of and correlation between the following<br>Virological biomarkers, as determined by (but not limited to) specific viral parameters (HBeAg, HBV DNA, HBV RNA, HBcrAg).<br>Soluble immunological biomarkers, as determined by (but not limited to) levels of circulating cytokines and chemokines.<br>Markers of immune cell function, as measured by (but not limited to) relative frequencies of immune cell subsets among PBMCs, activation status as determined by phenotyping and gene expression patterns, and functional assays including HBV-specific cytokine and/or antibody production. |
| **Patient Reported Outcomes**: To assess changes from baseline in patient reported outcomes following 12 weeks, 12 weeks + 12 weeks step-down, and 24 weeks of treatment with GSK3228836. | Change from baseline of HBQOL and EQ-5D. |

## 1.2. Study Design

| **Overview of Study Design and Key Features** | |
|---|---|
|  | |
| **Design Features** | • Phase IIb, multi-center, randomized, partial-blind, parallel cohort study to assess efficacy and safety of treatment with GSK3228836 in two populations of patients with CHB (1) participants on stable nucleos(t)ide treatment and (2) participants not currently on nucleos(t)ide therapy. |
| **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).<br>• 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 step-down in dose of 150 mg (plus placebo to match to maintain participant blinding) GSK3228836 once/week for 12 weeks.<br>• Arm 3. 300 mg GSK3228836 once/week for 12 weeks (plus loading doses of 300 mg GSK3228836 on Day 4 and Day 11) followed by placebo once/week for 12 weeks.<br>• Arm 4. Placebo once/week for 12 weeks followed by 300 mg GSK3228836 once/week for 12 weeks (plus placebo loading doses to match on Day 4 and Day 11, no loading dose for GSK3228836 treatment). |
| **Study Intervention Assignment** | • Participants will be randomized in a 3:3:3:1 ratio to receive study intervention. |
| **Interim Analysis** | • Separately for participants on stable nucleos(t)ide treatment and participants currently not on nucleos(t)ide treatment, there are 3 interim analyses planned for the study.<br>• Interim 1: approximately 30% participants complete Week 12 to assess safety and futility.<br>• Interim 2: approximately 50% participants complete Week 24 to assess safety and futility. |

| Overview of Study Design and Key Features | |
|---|---|
| | • Interim 3: all participants complete Week 24 and 50% of the on stable nucleos(t)ide treatment participants complete 24 weeks post-GSK3228836 planned end of treatment, to assess safety and efficacy.<br>• IDMC safety review: periodic safety review (approximately every 3 months). |

# 2. STATISTICAL HYPOTHESES

The primary objective of the study is to assess the efficacy of three dosing regimens (arms 1, 2, and 3) of GSK3228836 in participants with CHB as described in Section 4.1. Note that loading vs. no loading dose (arm 3 vs. arm 4) is assessed in an exploratory objective. The primary endpoint is achieving a sustained virologic response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication. Rescue medication is defined as any medication initiated for the purpose of antiviral suppression.

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 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.

## 2.1. Multiplicity Adjustment

Not Applicable.

# 3. ANALYSIS SETS

| Analysis Set | Definition / Criteria | Analyses Evaluated |
|---|---|---|
| Screened | All participants who were screened for eligibility. | • Study Population |
| Enrolled | • All participants who passed screening and entered the study.<br>• Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study are excluded from the Enrolled analysis set as they did not enter the study. | • Study Population |
| ITT | • All randomized participants<br>• This population will be based on the treatment the participant was randomized to. | • Efficacy<br>• PRO |

| Analysis Set | Definition / Criteria | Analyses Evaluated |
|---|---|---|
| | • Any participant who receives a treatment randomization number will be considered to have been randomized.<br>• Data will be reported according to the randomized study intervention. | |
| Safety | • All participants who received at least one dose of study treatment.<br>• This population will be based on the treatment the participant received.<br>• Note participants who were randomized but received at least one dose of study treatment will be listed. | • Safety<br>• 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)<br>• Note: PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not 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 separately for the following populations:

- Participants with CHB on stable nucleos(t)ide therapy.
- Participants with CHB not currently on nucleos(t)ide therapy.

### 4.1.1. General Methodology

Participants who prematurely withdrew from study will not be replaced.

In the case of wrong randomization stratification assigned at the time of randomization, the analyses will be performed based on the actual stratum per data collected in the baseline lab eCRF. In the case of randomization to the incorrect cohort (i.e., if a naïve participant is randomised to the on stable nucleos(t)ide treatment cohort, or vice versa), analysis will be performed based on the actual cohort the subject should have been assigned to.

Confidence intervals will use 95% confidence levels unless otherwise specified.

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.

HBV DNA (as appropriate), HBV RNA, HBcrAg, HBsAg, HBeAg levels that are below the LLOQ will be imputed for summaries of actual values and change from baseline.

The number of significant digits in the LLOQ will be used to determine how much to add or subtract in order to impute the corresponding numeric value.

- Example 1: 2 Significant Digits = '< x' becomes x – 0.01
- Example 2: 1 Significant Digit = '< x' becomes x - 0.1
- Example 3: 0 Significant Digit = '< x' becomes x – 1

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.

### 4.1.2. Baseline Definition

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose (GSK or placebo) assessment with a non-missing value, including those from unscheduled visits. If time is not collected or time of assessment equals that of the first dose, 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 eGFR and serum creatinine is defined as the mean of all pre-dose values, from screening to Day 1 pre-dose assessment.

## 4.2. Primary Endpoint(s) Analyses

The primary analysis for the primary endpoint will be conducted once the last participant has completed the Week 48 visit and database lock has been achieved.

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.

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

HBsAg and HBV DNA from Week 24 to Off-Treatment Week 24 will be used to assess the primary endpoint for arms 1 and 2, and the exploratory endpoint for arm 4. For dosing schedule of arms 1, 2, and 4, see Section 1.2.

For arm 3, because of the shortened time on GSK3228836 treatment (12 weeks instead of 24 weeks), post-treatment visit schedules will not match those of arms 1 and 2. To avoid risk of bias the following visits have been selected for arm 3 to match the number and timing of visit windows for measuring off-treatment virologic responses in arms 1 and 2 to evaluate the primary endpoint:

- Week 12, 13, 14, 16, 20, 24, off-treatment Week 4, 8, 12.

### 4.2.1. Definition of estimands

Primary Estimands supporting the primary objective are defined as:
- **Population**: separate assessment for the following:
  - participants with CHB on stable nucleos(t)ide therapy
  - participants with CHB not currently on nucleos(t)ide therapy
- **Variable**: Sustained virologic response (SVR) for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication.
- **Treatments**: arms 1, 2, and 3. Estimation of the within-arm response rate. Note: arm 4 is described in Section 4.4.1
- **Intercurrent events**: use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication has been incorporated into the definition of variable (composite strategy). Discontinuation of, interruption of, and adherence to IP not due to wide disruptive event will be ignored (treatment policy). Wide disruptive events

(such as COVID-19 pandemic) leading to discontinuation of, interruption of, and non-adherence to GSK3228836 will be handled assuming they had not happened (hypothetical strategy).

- **Population summary**: proportion of participants who achieve SVR for each treatment arm.

The primary estimands for each sub-population is the proportion of participants in each treatment arm 1, 2, and 3 who achieve SVR for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication regardless of completing IP, interruptions in IP or adherence to IP had they not been affected by wide disruptive events.

### 4.2.2. Main analytical approach

The participant population (on nucelos(t)ide treatment or not currently on nucleos(t)ide treatment) will not be included as a stratification factor in the analysis model, as each population will be analyzed separately.

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

Model for each arm:

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

$$\theta_g = logit(P_g) = \log\left(\frac{P_g}{1-P_g}\right) = \gamma_0 + \gamma_1 I_{\{B1+\}} + \gamma_2 I_{\{B2+\}} + \psi_g, \qquad g = 1,2,3,4$$

Where $\gamma_0, \gamma_1, \gamma_2, \psi_g$ are all parameters. Thus,

$\theta_1 = \gamma_0 + \psi_1$

$\theta_2 = \gamma_0 + \gamma_1 + \psi_2$

$\theta_3 = \gamma_0 + \gamma_2 + \psi_3$

$\theta_4 = \gamma_0 + \gamma_1 + \gamma_2 + \psi_4$

Priors:

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

$\psi_g \sim Normal(0, \omega^2), g = 1,2,3,4$

$\omega \sim Half - normal(1)$

Where we define $r_g$ as the number of SVR responders among $n_g$ participants, $p_g$ as SVR rate $\frac{r_g}{n_g}$, $\theta_g$ as the log odds of treatment response $\log(\frac{p_g}{1-p_g})$, index g =1,...,4 refers to the analysis stratum number, $\gamma_k$ represent fixed effects of baseline analysis stratification factors (see below), and $\psi_g$ denotes a random effect in analysis stratum g.

The four analysis strata and representation of the two baseline analysis stratification factors $B_1$ and $B_2$ in the model are shown in Table 1.

**Table 1 Baseline Analysis Strata**

| Stratum | $B_1$: HBsAg ($I_{\{B1+\}}$) | $B_2$: HBeAg ($I_{\{B2+\}}$) |
|---|---|---|
| 1: HBsAg ≤3 log IU/mL and Negative HBeAg | $B_{1-}$ (≤3 log IU/mL) (0) | $B_{2-}$ (Negative) (0) |
| 2: HBsAg >3 log IU/mL and Negative HBeAg | $B_{1+}$ (>3 log IU/mL) (1) | $B_{2-}$ (Negative) (0) |
| 3: HBsAg ≤3 log IU/mL and Positive HBeAg | $B_{1-}$ (≤3 log IU/mL) (0) | $B_{2+}$ (Positive) (1) |
| 4: HBsAg >3 log IU/mL and Positive HBeAg | $B_{1+}$ (>3 log IU/mL) (1) | $B_{2+}$ (Positive) (1) |

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.

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

Posterior probability of SVR rate exceeding a range of clinically meaningful response rates, e.g., 10%, 15%, 20%, will be generated using the approach specified above for each arm.

#### 4.2.2.1. Visit windowing and multiple measurements at one analysis timepoint

Visit windowing for the primary endpoint 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 '836 Treatment Analysis Timepoint:

1. The latest available assessment in the window will be selected.

For Post '836 Treatment Analysis Timepoints:

1. Worst non-missing value in the analysis window will be selected, 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. 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.

**Table 2 Primary endpoint analysis windows for Arms 1, 2 and 4**

| Analysis Set / Domain | Parameter (if applicable) | Target Study Day | Analysis Window | | Analysis Timepoint | Protocol Visit |
|---|---|---|---|---|---|---|
| | | | Beginning Timepoint | Ending Timepoint | | |
| Efficacy | HBsAg and HBV DNA | 162 | 148 | 182 | End of '836 Treatment | Week 24 |
| | | 218 | 183 | 238 | Post '836 treatment Week 8 | Off treatment Week 8 |
| | | 274 | 239 | 294 | Post '836 treatment Week 16 | Off treatment Week 16 |
| | | 330 | 295 | 350 | Post '836 treatment Week 24 | Off treatment Week 24 |

**Table 3 Primary endpoint analysis windows for Arm 3**

| Analysis Set / Domain | Parameter (if applicable) | Target Study Day | Analysis Window | | Analysis Timepoint | Protocol Visit |
|---|---|---|---|---|---|---|
| | | | Beginning Timepoint | Ending Timepoint | | |
| Efficacy | HBsAg and HBV DNA | 78 | 64 | 98 | End of '836 Treatment | Week 12 |
| | | 134 | 99 | 154 | Post '836 treatment Week 8 | Week 20 |
| | | 190 | 155 | 210 | Post '836 treatment Week 16 | Off treatment Week 4 |
| | | 246 | 211 | 266 | Post '836 treatment Week 24 | Off treatment Week 12 |

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

For the second supplementary estimand described in 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 this estimand, 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 windows Arms 1, 2, 3 and 4**

| Analysis Set / Domain | Parameter (if applicable) | Reference day | Analysis Window | | Analysis Timepoint |
|---|---|---|---|---|---|
| | | | Beginning Timepoint | Ending Timepoint | |
| Efficacy | HBsAg and HBV DNA | Reference date | Reference date - 14 | Reference date + 20 | End of '836 Treatment |
| | | Reference date + 56 | Reference date + 21 | Reference date + 76 | Post '836 treatment Week 8 |
| | | Reference date + 112 | Reference date + 77 | Reference date + 132 | Post '836 treatment Week 16 |
| | | Reference date + 168 | Reference date + 133 | Reference date + 188 | Post '836 treatment Week 24 |

#### 4.2.2.2. Intercurrent Events and Missing data

The intercurrent event of use of rescue medication has been incorporated into the definition of variable (composite strategy). The intercurrent event of discontinuation of, interruption of, and adherence to IP not due to wide disruptive event will be ignored (treatment policy).

To prevent the efficacy of GSK3228836 being penalized for uncontrollable and unusual events (i.e. wide disruptive events such as the COVID-19 pandemic), if a wide disruptive event leads to discontinuation of GSK3228836 or significant interruption/non-adherence to GSK3228836, this will be handled assuming the intercurrent event had not happened (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. According the hypothetical strategy, any data collected after the intercurrent event will be set to missing.

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, then the participant is a non-responder.
2. If HBsAg <LLOQ and HBV DNA <LLOQ in each of the analysis window, then the participant is a Responder, otherwise the participant is non-responder. Note: A result of TND is considered as <LLOQ.

The following approach will be used to determine a participant's response when HBsAg and HBV DNA data are missing from visits required to derive the primary endpoint:

For participants where wide disruptive events (such as COVID-19 pandemic) prevent assessment of the primary outcome, SVR will be imputed using all available data for

participants for whom SVR can be assessed. The final inference from the hierarchical Bayesian model will account for the missing data assuming MAR. For other participants where SVR in the absence of rescue medication cannot be ascertained due to missing data (withdrawal from the study or missing due to other reasons, but not due to a wide disruptive event), the participant will be assumed not to have achieved SVR (non-responder imputation).

After the imputation above, if there is missing data in at least one analysis window then the participant is a non-responder.

#### 4.2.2.3. Model Checking & 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 above 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 SP, 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, 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.

### 4.2.4. Additional estimands

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

#### 4.2.4.1. Using Hypothetical Strategy to Deal with ICE of Discontinuation of, Interruption of, and Adherence to IP

The first supplementary estimand is defined in the same way as the primary estimand, except the intercurrent event of discontinuation of, interruption of, and adherence to IP will be handled assuming they had not happened (hypothetical strategy). Discontinuation of GSK3228836 or significant interruption/non-adherence to GSK3228836 will be handled assuming the intercurrent event had not happened (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. According the hypothetical strategy, any data collected after the intercurrent event will be set to missing.

This supplementary estimand supporting the primary objective in participants with CHB on stable nucloes(t)ide therapy and participants with CHB not currently on nucleos(t)ide therapy is the proportion of participants in each treatment arm 1, 2, 3 and 4 who achieve SVR for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication, had they not been affected by discontinuation of IP, interruptions in IP, adherence to IP, or wide disruptive events.

#### 4.2.4.2. Measuring SVR from Actual End of Treatment instead of Planned End of Treatment

The second 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. 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 nucleos(t)ide therapy and participants with CHB not currently on nucleos(t)ide therapy is the proportion of participants in each treatment arm 1, 2, 3 and 4 who achieve SVR for 24 weeks after the actual end of GSK3228836 treatment in the absence of rescue medication, regardless of completing IP, interruptions in IP or adherence to IP, had they not been affected by wide disruptive events.

#### 4.2.4.3. Using Principal Stratum Strategy to Deal with Protocol Deviations

The third supplementary estimand is defined in the same way as the primary estimand, except for the population, variable and intercurrent events definitions. The population is participants with CHB not currently on nucleos(t)ide therapy. The variable for this estimand will be defined as sustained virologic response (SVR) for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication for medical reasons. The intercurrent event of use of rescue medication will be separated into two:

1. Use of rescue medication for medical reasons
2. Use of rescue medication because of a protocol deviation

The use of rescue medication for medical reasons has been incorporated into the definition of variable (composite strategy). The use of rescue medication because of a protocol deviation will be handled by excluding these participants from the analysis (principal stratum strategy). This supplementary estimand supporting the primary objective in participants with CHB not currently on nucleos(t)ide therapy is the proportion of participants in each treatment arm 1, 2, 3 and 4 who achieve SVR for 24 weeks after the planned end of GSK3228836 treatment in the stratum of participants who did not use rescue medication in error, in the absence of rescue medication for medical reasons, regardless of completing IP, interruptions in IP or adherence to IP, had they not been affected by wide disruptive events.

#### 4.2.4.4. Using a Modified Definition of SVR

The fourth supplementary estimand is defined in the same way as the primary estimand, except the variable is defined using a modified definition of sustained virologic response (SVR) for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication. The modified definition of sustained virologic response is defined as

observing HBsAg <LLOQ and HBV DNA <LLOQ at each analysis window in the 24 weeks after the end of GSK3228836 treatment. Any observation of HBsAg ≥LLOQ or HBV DNA ≥LLOQ must be confirmed at a consecutive visit (including unscheduled visits) for the patient to be classed as having lost their SVR.

Subjects 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 non-responders.

This supplementary estimand supporting the primary objective in participants with CHB on stable nucloes(t)ide therapy and participants with CHB not currently on nucleos(t)ide therapy is the proportion of participants in each treatment arm 1, 2, 3 and 4 who achieve the modified definition of SVR for 24 weeks after the planned end of GSK3228836 treatment in the absence of rescue medication, regardless of completing IP, interruptions in IP or adherence to IP, had they not been affected by wide disruptive events.

## 4.3. Secondary Endpoint(s) Analyses

### 4.3.1. Key secondary endpoint(s)

#### 4.3.1.1. Efficacy of GSK3228836 on biomarkers and virus-specific antibody response

The group of estimands supporting the secondary objective of assessing the efficacy of GSK3228836 on biomarkers and virus-specific antibody responses for each sub-population are the population summary for each variable in each treatment arm 1-4.

Missing data for variables defined above (except for Time to ALT normalization) will be ignored, only available data will be summarized. No sensitivity analysis is planned for the group of estimands supporting this objective.

Estimands supporting this objective are defined as follows:

**- Population**: one subpopulation of participants with CHB on stable nucleos(t)ide therapy and a second subpopulation of participants with CHB not currently on nucleos(t)ide therapy. For the time to ALT normalization endpoint, only subjects with ALT>ULN at baseline will be included. For summaries of HBe antibody (anti-HBeAg) levels, only participants who are HBeAg Positive at baseline will be included.

**- Treatments**: arms 1-4. Estimation within each arm.

- **Intercurrent events**: For the proportion of participants achieving HBsAg <LLOQ and HBV DNA <LLOQ in the absence of rescue medication at the end of treatment analysis window, end of treatment will be determined using the end of treatment analysis window defined in Section 4.2.2. In line with the primary endpoint, missing data not due to wide disruptive events will be imputed as non-response. Missing data due to wide disruptive events will be ignored without any imputation.

Other endpoints will be summarized regardless of completing IP, interruptions in IP or adherence to IP (treatment policy strategy) and regardless of rescue medication (except

for ALT normalization which can only be achieved in the absence of rescue medication). HBV DNA, HBsAg, HBeAg levels that are below the LLOQ will be imputed for summaries of actual values and change from baseline following the rules in Section 4.1.1.

**1) Categorical Variables**:

- Achieving HBsAg <LLOQ and HBV DNA <LLOQ at the end of treatment analysis window. Data will be presented overall and by baseline stratification factors (HBsAg <3 log IU/mL and Negative HBeAg; BsAg >3 log IU/mL and Negative HBeAg; HBsAg <3 log IU/mL and Positive HBeAg; HBsAg >3 log IU/mL and Positive HBeAg; HBsAg <3 log IU/mL and All HBeAg; All HBsAg and Negative HBeAg; HBsAg <3 log IU/mL and All HBeAg; All HBsAg and Positive HBeAg)

- Categorical changes from baseline in HBsAg (e.g., <0.5, ≥0.5, ≥1, ≥1.5, ≥3 $\log_{10}$ IU/mL) and in HBV DNA (e.g., <1, ≥1, ≥2, ≥3 log 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 baseline stratification factors (HBsAg <3 log IU/mL and Negative HBeAg; BsAg >3 log IU/mL and Negative HBeAg; HBsAg <3 log IU/mL and Positive HBeAg; HBsAg >3 log IU/mL and Positive HBeAg; HBsAg <3 log IU/mL and All HBeAg; All HBsAg and Negative HBeAg; HBsAg <3 log IU/mL and All HBeAg; All HBsAg and Positive HBeAg)

- ALT normalization (ALT≤ULN) over time in absence of rescue medication in participants with baseline ALT>ULN

- HBe antibody (anti-HBeAg) levels in HBeAg Positive patients

- HBs antibody (anti-HBsAg) levels (HBs Antibody >=11.5 IU/L is HBs antibody positive and HBs Antibody <11.5 IU/L is HBs antibody negative)

- **Population summary:** proportion of participants in each category for each treatment arm.

**2) Continuous Variables**:

- Actual values and change from baseline over time of HBsAg and HBV DNA

- Actual values and change from baseline of HBeAg levels

- HBs antibody (anti-HBsAg) levels

- **Population summary**: mean values and mean changes from baseline for each variable in each treatment arm.

**3) Time to Event Variable**:

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

- **Population summary**: Turnbull's estimator for the non-parametric estimation of time to ALT normalization in each treatment arm.

ALT normalization is defined in subjects 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, time to ALT normalization will be censored at the time of 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.

#### 4.3.1.2. Comparison of efficacy between arms 1, 2 and 3

***Definition of Estimands***

Estimands supporting secondary objective of comparing the efficacy between arms 1, 2, and 3 are defined as follows:

- **Population**: separate assessment for the following:

  - participants with CHB on stable nucleos(t)ide therapy
  - participants with CHB not currently on nucleos(t)ide therapy

- **Variable**: Sustained virologic response (SVR) for 24 weeks after the end of GSK3228836 treatment in the absence of rescue medication.

- **Treatments**: arms 1, 2, and 3. Three treatment comparisons between: arms 1 and 2, arms 1 and 3, and arms 2 and 3.

- **Intercurrent events**: use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication has been incorporated into the definition of variable (composite strategy). Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption of, and non-adherence to GSK3228836 will be handled assuming they had not happened (hypothetical strategy).

- **Population summary**: difference in proportion of participants who achieve SVR between treatment arms.

The group of estimands supporting this objective for each sub-population are the difference in each treatment comparisons in the proportion of participants who achieve SVR for 24 weeks after the end of GSK3228836 treatment in the absence of rescue medication regardless of completing IP, interruptions in IP or adherence to IP had they not been affected by wide disruptive events.

The non-responder imputation described in Section 4.2.2 will be used when HBsAg and HBV DNA data are missing from visits required to derive the endpoint.

***Main analytical approach***

Comparisons between arms will be made by calculating differences 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 (e.g. Pr(Arm 1 – Arm 2 > -5% | Data)).The point estimates of differences in sustained virologic response rate with 95% credible intervals will be calculated for the treatment comparisons described in the estimands.

Posterior probability for the differences of following comparisons will also be reported;

1. Arm 1 vs. Arm 2
2. Arm 1 vs. Arm 3
3. Arm 2 vs. Arm 3

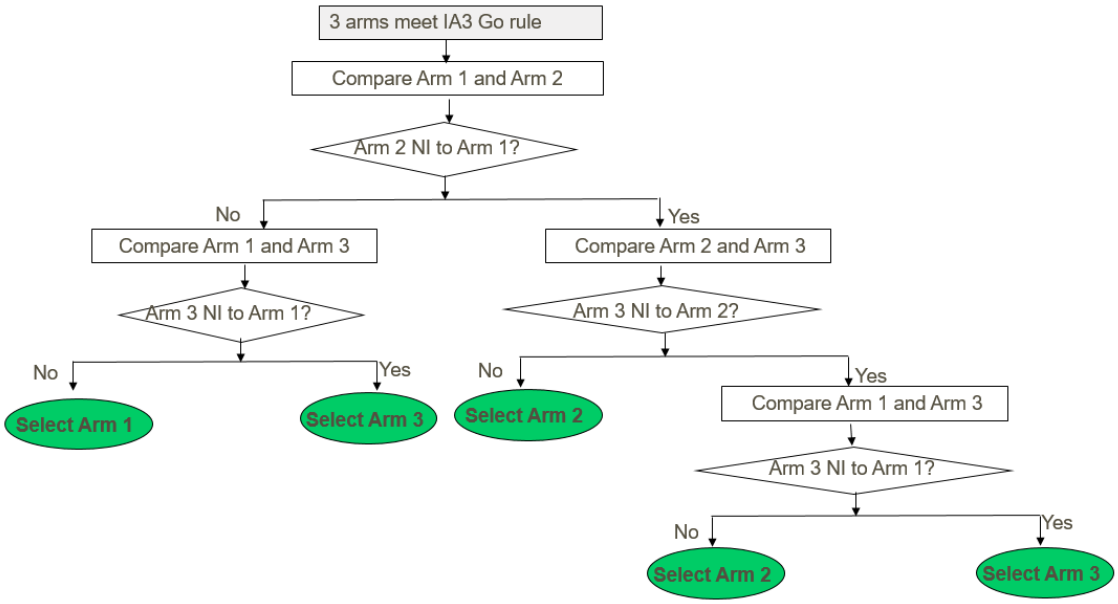
***Regimen Selection Approach***

If success criteria is met for more than one arm, regimen selection will be conducted. The non-inferiority (NI) decision rules for two-treatment comparison is Posterior Prob(less intensive arm SVR rate – more intensive arm SVR rate > -5%) > 65%. The arms are ordered in intensity from 1 (most intensive) to 4 (least intensive).

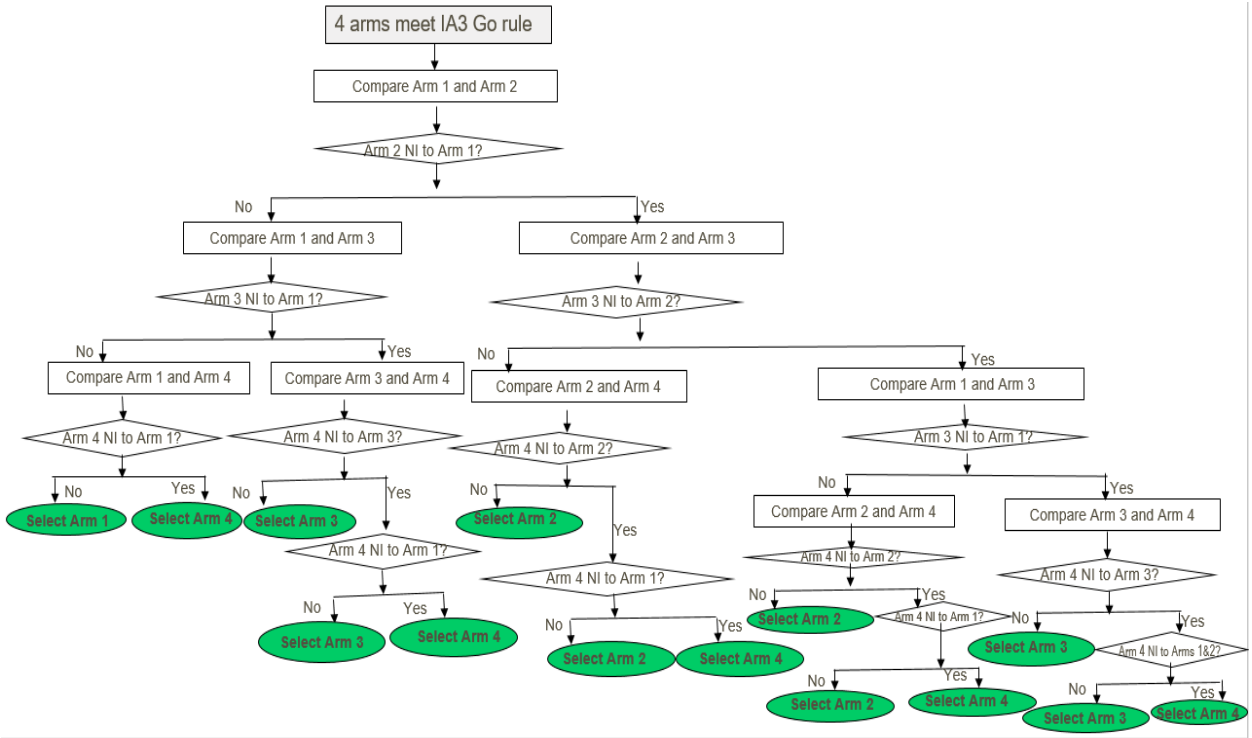
For each comparison, the posterior distribution of difference in SVR rate will be derived and the posterior probability (less intensive arm SVR rate – more intensive arm SVR rate > -5%) will be obtained based on the model described in Main analytical approach present under Section 4.3.1.2. If posterior probability is >65%, EoS NI rule is met.

If 2 arms meet the success rule, NI comparison between the 2 arms will be conducted. If the NI rule is met, then select the less intensive arm, otherwise select the more intensive arm.

If 3 arms meet the success rule, sequential two-treatment comparisons will be conducted for the 3 arms. The regimen selection follows the decision tree below.




If 4 arms meet the success rule, sequential two-treatment comparisons will be conducted for the 4 arms. The regimen selection follows the decision tree below.




### *Operating Characteristics for Regimen Selection*

The Operating characteristics of regimen selection are summarized in Table 5 for a range of scenarios.

**Table 5 Operating Characteristics for Regimen Selection**

| Arm 1 True rate | Arm 2 True rate | Arm 3 True rate | Arm 4 True rate | Prob of selecting arm 1 | Prob of selecting arm 2 | Prob of selecting arm 3 | Prob of selecting arm 4 | Prob of selecting none |
|---|---|---|---|---|---|---|---|---|
| 30% | 30% | 30% | 30% | 16% | 21% | 28% | 35% | 0% |
| 30% | 30% | 30% | 25% | 19% | 26% | 36% | 19% | 0% |
| 30% | 30% | 25% | 30% | 21% | 29% | 11% | 39% | 0% |
| 30% | 25% | 30% | 30% | 21% | 7% | 33% | 39% | 0% |
| 25% | 30% | 30% | 30% | 4% | 23% | 33% | 39% | 0% |
| 30% | 30% | 25% | 25% | 26% | 37% | 15% | 22% | 0% |
| 30% | 25% | 30% | 25% | 26% | 9% | 43% | 22% | 0% |
| 25% | 30% | 30% | 25% | 6% | 30% | 43% | 22% | 0% |
| 30% | 25% | 25% | 30% | 30% | 11% | 14% | 44% | 1% |
| 25% | 30% | 25% | 30% | 7% | 34% | 14% | 44% | 1% |
| 25% | 25% | 30% | 30% | 7% | 8% | 40% | 44% | 1% |
| 30% | 25% | 25% | 25% | 38% | 15% | 19% | 26% | 1% |
| 25% | 30% | 25% | 25% | 9% | 44% | 19% | 27% | 1% |
| 25% | 25% | 30% | 25% | 9% | 11% | 52% | 27% | 1% |
| 25% | 25% | 25% | 30% | 11% | 15% | 19% | 53% | 2% |

### 4.3.2. Supportive secondary endpoint(s)

**Historical placebo control**

If historical individual patient-level data are available, a longitudinal model including historical response at 12, 24 and 48 weeks of placebo treatment will be constructed. For the first 12-week period, the model will allow dynamic borrowing from historical placebo data to the concurrent placebo in Weeks 1-12 in arm 4. Furthermore, the model will provide longitudinal prediction of response at Week 24 and Week 48 for participants in arm 4 (had they continued on Placebo rather than switching to GSK3228836 treatment).

### 4.3.3. Pharmacokinetic Secondary Endpoints

#### 4.3.3.1. Endpoint / Variables

Pharmacokinetics (PK) of GSK3228836 and nucleos(t)ide will be characterized. In all participants, GSK3228836 $C\tau$ and terminal half-life ($t_{½}$) will be estimated. In participants with intensive PK sampling, GSK3228836 and nucleos(t)ide plasma PK parameters will be derived, including but not limited to AUC, $C\tau$, Cmax and tmax.

#### 4.3.3.2. Derived Pharmacokinetic Parameters

Pharmacokinetic 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. Pharmacokinetic

parameters listed will be determined from the plasma concentration-time data, as data permits.

**Table 6 Pharmacokinetic Parameters and Parameter Description**

| Parameter | Data | Analyte | Parameter Description |
|---|---|---|---|
| AUC(0-24) | Intensive PK | GSK3228836 Nucleos(t)ide | Area under the concentration-time curve from time zero up to 24 hours post-dose. |
| AUC(0-168) | Intensive PK | GSK3228836 | Area under the concentration-time curve from time zero up to 168 hours post-dose. |
| Cτ | Intensive PK | Nucleos(t)ide | Concentration at the end of the dosing interval |
| Cτ | Sparse PK – All Subjects | GSK3228836 | Concentration at the end of the dosing interval |
| Cmax | Intensive PK | GSK3228836 Nucleos(t)ide | Maximum observed concentration |
| tmax | Intensive PK | GSK3228836 Nucleos(t)ide | Time of maximum observed concentration |
| t½ | Sparse PK – All Subjects | GSK3228836 | Terminal half-life determined using concentrations collected during the off-treatment period |

Sparse PK is collected weekly during the dosing period and at certain pre-specified visits during the off-treatment period. Intensive PK is collected at one visit between Week 14 (inclusive) and week 24 (inclusive).

#### 4.3.3.3. Population of Interest

The secondary pharmacokinetic analyses will be based on the Pharmacokinetic (PK) population, unless otherwise specified.

#### 4.3.3.4. 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 (%CVb) for the geometric mean. For sparse PK summary of Cτ and t1/2, additionally present 5th and 95th percentile.

Sparse PK parameters (Cτ and t1/2) of GSK3228836 will be summarised and listed by treatment arm, study visit (only applies to Cτ), geographic region (All participants, China, Japan and East Asia). Sparse Cτ-time plots will be created and compared by the same factors.

Intensive PK parameters (AUC(0-24), AUC(0-168), Cmax and tmax) of GSK3228836 will be summarised and listed by dose level (150mg and 300mg). Intensive concentration-time plots will be created and compared by the same factors.

Intensive PK parameters (AUC(0-24), Cτ, Cmax and tmax) of nucleos(t)ide will be summarised and listed separately for tenofovir (separately for tenofovir disoproxil fumarate and tenofovir alafenamide) and entecavir. Intensive concentration-time plots will be created separately for tenofovir (separately for tenofovir disoproxil fumarate and tenofovir alafenamide) and entecavir.

Refer to Section 4.6 for more information on geographic region subpopulations.

## 4.4. Exploratory Endpoints Analyses

### 4.4.1. Exploratory Efficacy Endpoints

In addition to the exploratory analyses described in this section, all primary and secondary endpoints assessed for Arms 1, 2, and 3 will also be assessed as exploratory analyses in Arm 4.

#### 4.4.1.1. Comparison of efficacy between 12 weeks of GSK3228836 treatment with a loading dose or without a loading dose

Estimands supporting exploratory objective of comparing the efficacy between 12 weeks of GSK3228836 treatment with a loading dose or without a loading dose are defined as follows:

- **Population**: separate assessment for the following:
  - participants with CHB on stable nucleos(t)ide therapy.
  - participants with CHB not currently on nucleos(t)ide therapy.

- **Variable**: Sustained virologic response (SVR) for 24 weeks after the end of GSK3228836 treatment in the absence of rescue medication.
- **Treatments**: arm 3 and 4. Treatment comparison between arms 3 and 4.
- **Intercurrent events**: use of rescue medication, and discontinuation of/interruption of/adherence to IP. The use of rescue medication has been incorporated into the definition of variable (composite strategy). Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). Wide disruptive events (such as COVID-19 pandemic) leading to discontinuation of, interruption of, and non-adherence to GSK3228836 will be handled assuming they had not happened (hypothetical strategy).
- **Population summary**: difference in proportion of participants who achieve SVR between treatment arms 3 and 4.

The group of estimands supporting this objective for each sub-population are the differences between arms 3 and 4 in the proportion of participants who achieve SVR for 24 weeks after the end of GSK3228836 treatment in the absence of rescue medication regardless of completing IP, interruptions in IP or adherence to IP had they not been affected by wide disruptive events.
The non-responder imputation described in Section 4.2.2 will be used when HBsAg and HBV DNA data are missing from visits required to derive the endpoint.

Comparisons between arms will be made by calculating differences 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 (e.g. Pr(Arm 1 – Arm 2 > -5% | Data)).The point estimates of differences in sustained virologic response rate with 95% credible intervals will be calculated for the treatment comparisons described in the estimands.

#### 4.4.1.2. Concordance of virologic response at Week 6, Week 12 and Week 24 and achieving SVR

The concordance of virologic response (HBV DNA < LLOQ and HBsAg < LLOQ) at on-treatment timepoints of interest with achieving SVR will be explored. Number of subjects with an early response (Yes or No) will be cross tabulated with SVR (Yes or No) for on-treatment visits Week 6, Week 12 and Week 24 separately. Positive Predictive Value and Negative Predictive Value will be presented.

#### 4.4.1.3. Pharmacodynamic effect of GSK3228836 on exploratory biomarkers

The pharmacodynamic effect of GSK3228836 on exploratory biomarkers (HBcrAg, HBV RNA) will be assessed.

Summary tables and figures will be created to show HBcrAg and HBV RNA (for units copies/mL and log10 copies/mL) over time. Additionally, summaries of HBcrAg by HBeAg status, and HBV RNA for RoW (excluding China) and China population will be presented.

For end of treatment visit only, a summary of HBcrAg and HBV RNA for subjects with/or without HBsAg < LLOQ at end of treatment will be presented, by SVR status.

Further details will be described in a separate PK-PD analysis plan developed by CPMS.

### 4.4.2. Exploratory PK-PD Endpoints

To evaluate PK-efficacy relationship and PK-safety relationship, exploratory graphical analyses will be initially performed for efficacy (e.g., HBsAg) and safety endpoints. If a relationship between exposure and efficacy and/or safety endpoints is present, population PK-PD modelling will be conducted using nonlinear mixed effect methods.

The model will assess the effect of various factors (covariates) of the modelled efficacy or safety endpoints. Relevant PK-PD model endpoints for example:

- apparent clearance
- apparent volume of distribution
- IC50
- random variability

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

### 4.4.3. Exploratory Virology Endpoints

The virology analyses will be based on the "Safety" population.

Missing data for the endpoints in this section will be ignored without any imputation.

#### 4.4.3.1. HBV Genotype

HBV Genotype will be collected in the eCRF as well as identified by HBV Sequence. HBV Genotype from both data sources will be listed and the listing will include the final reported genotype.

For subjects with genotype both collected in the eCRF and determined by HBV Sequence the final reported genotype will be determined as follows:

For participants on stable nucleos(t)ide treatment:

- Genotype reported in the eCRF will take precedence

For participants currently not on nucleos(t)ide treatment:

- If the if the sequence genotype was derived from DNA, the HBV Sequence genotype will take precedence.

- If the if the sequence genotype was derived from RNA (i.e. rather than DNA due to low DNA levels hence RNA sequencing was employed), the genotype reported in the eCRF will take precedence – similar to the participants on stable nucleos(t)ide.

Data from the Week 1 Day 1 visit will be used to determine HBV genotype by HBV DNA or RNA sequencing. However, as HBV genotype should not change over time, if a participant missed the Week 1 Day 1 visit, HBV genotype can be determined from a later sample if available.

The number of participants with each final reported genotype will be presented by arm and overall.

Baseline log HBsAg, change from baseline in log HBsAg at End of GSK836 Treatment visit (Week 12 / Week 24) and Off GSK836 Treatment Week 24 visit (Week 36 / Week 48), number of subjects achieving HBsAg < LLOQ at any time up to End of GSK836 Treatment visit (Week 12 / Week 24) or Off GSK836 Treatment Week 24 visit (Week 36 / Week 48), and mean time to achieving HBsAg < LLOQ will be presented for each arm separately. Results will be summarized by baseline final reported genotype.

For participants currently not on nucleos(t)ide treatment only, baseline log HBV DNA, change from baseline in log HBV DNA at End of GSK836 Treatment visit (Week 12 /

Week 24) and Off GSK836 Treatment Week 24 visit (Week 36 / Week 48), number of subjects achieving HBV DNA < LLOQ at any time up to End of GSK836 Treatment visit (Week 12 / Week 24) and Off GSK836 Treatment Week 24 visit (Week 36 / Week 48), and mean time to achieving HBV DNA < LLOQ will be presented for each arm separately. Results will be summarized by baseline final reported genotype.

#### 4.4.3.2. HBV Sequences

Baseline and treatment emergent nucleotide changes both within HBV binding site and outside of the HBV binding site will be summarized by number of subjects for each arm and overall and data will be listed.

The following steps can be followed to identify nucleotide changes within the HBV binding site:

1. Identify nucleotide sequence records
2. Identify the 20ntd binding site of HBV at the following locations: 1581 – 1600
3. If the allelic frequency meets the threshold for a mutation flag as a mutation

Participants who have data in the PF dataset but have no binding site mutations will be considered Wild Type for the binding site.

Mutations that are reported for >1 genetic location of interest will only be reported once.

Unless otherwise specified, a >=5% threshold of allelic frequency will be used to report a mutation vs wild type and only observations meeting this threshold will be included in summary tables. However, mutations >=1% and <5% will be reported in the Listing of Mutations in the Binding Site in Participants with Mutation at Any Time for full transparency. Mutations will be reported as “variant” if >=15% and “minority species”, >=5% and <15%.

Development of a mutation during therapy (i.e. treatment emergent) will be defined as a substitution present at <5% at baseline but detected at >=5% post baseline.

Baseline log HBsAg, change from baseline in log HbsAg at End of GSK836 Treatment visit (Week 12 / Week 24) and Off GSK836 Treatment Week 24 visit (Week 36 / Week 48), number of subjects achieving HbsAg < LLOQ at any time up to End of GSK836 Treatment visit (Week 12 / Week 24) and Off GSK836 Treatment Week 24 visit (Week 36 / Week 48), and mean time to achieving HbsAg < LLOQ will be presented for each arm separately. Results will be summarized by baseline binding site polymorphism.

For participants currently not on nucleos(t)ide treatment only, baseline log HBV DNA, change from baseline in log HBV DNA at End of GSK836 Treatment visit (Week 12 / Week 24) and Off GSK836 Treatment Week 24 visit (Week 36 / Week 48), number of subjects achieving HBV DNA < LLOQ at any time up to End of GSK836 Treatment visit (Week 12 / Week 24) and Off GSK836 Treatment Week 24 visit (Week 36 / Week 48), and mean time to achieving HBV DNA < LLOQ will be presented for each arm separately. Results will be summarized by baseline binding site polymorphism.

For all observed mutations in the binding site at baseline and for frequently (e.g. in >=5% subjects) observed mutations outside of the binding site at baseline, a 2x2 contingency table of mutation (present / absent) vs. response at end of GSK836 treatment (Yes / No) and response at Off GSK836 Treatment Week 24 (Yes / No) will be presented. Response at end of GSK836 treatment will be defined as HBV DNA < LLOQ, HBsAg < LLOQ and no rescue medication at the end of treatment analysis window. Response at 24 weeks off GSK836 treatment will be defined as SVR. The table will be repeated using a >=1% threshold of allelic frequency, for all mutations in the binding site only.

### 4.4.4. Exploratory Immunology Endpoints

Details of the immunology endpoints will be included in a separate biomarker analysis plan.

### 4.4.5. Exploratory PRO Endpoints

Patient reported outcomes, the HBQOL and the EQ-5D, will be analysed using the ITT analysis set.

For HBQOL summary statistics for actual values and changes from baseline in overall score and each of the 6 domains (psychological well-being, anticipation anxiety, vitality, stigma, transmissibility and vulnerability) will be displayed by visit for Arms 1, 2, 3 and 4. HBQoL v1.0 (Spiegel BM, 2007) will be used to derive scores for HBQoL.

The EQ-5D quality of life instrument provides a utility score and thermometer score. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with 3 levels for each dimension from level 1 = no problem to level 3 = extreme problems.

The health state is defined by combining the levels of answers from each of the 5 questions. Each health state is referred to in terms of a 5-digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 11223 indicates no problems walking about, no problems with self-care, some problems with performing usual activities, moderate pain or discomfort and extremely anxious or depressed.

The health state 5-digit code is translated into the utility score, which is valued up to one (representing perfect health) with lower values meaning worse state, according to the methodology described in Dolan P., 1997. The UK values set described in Dolan P., 1997 will be used for all subjects regardless of their country origin.

Summary statistics for actual values and changes from baseline in EQ-5D thermometer and utility scores will be presented by visit for Arms 1, 2, 3 and 4.

A listing of the utility score and thermometer values will be produced.

## 4.5. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified. To allow comparison between safety in active treatment vs placebo, and loading dose vs

no loading dose, selected safety displays will be presented by study Weeks 1 – 12, Weeks 13 – 24, and Weeks 25 – 48; refer to the OPS for details of which outputs should be presented by Week, and refer to Section 6.2.2.2 for definitions of assessment windows for adverse events.

### 4.5.1. Extent of Exposure

Extent of exposure will be summarized using summary statistics. Number of subjects with < 6 weeks <= 12 weeks exposure, <= 24 weeks exposure, > 24 weeks exposure will be presented, and the overall duration of exposure (see Output and Programming Specification for deviation of overall duration of exposure) will be summarized. Study intervention compliance will be summarized as described in Section 6.1.5.Adverse Events

Number of days of exposure to study drug will be calculated based on the formula:
Duration of Exposure in Days = Last injection date – First injection date + 1

The cumulative dose will be based on the formula:
Cumulative Dose = Number of Injections of 300mg x 300mg + Number of Injections of 150mg x 150mg

### 4.5.2. Adverse Events

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. All AE summaries will be based on treatment emergent events unless otherwise specified.

Adverse events will be coded using the latest version of MedDRA coding dictionary, to give a preferred term and a system organ class. These preferred terms and system organ classes will be used when summarising the data. The severity of AEs and SAEs will be determined by the investigator according to the DAIDS grading system Version 2.1 [National Institute of Allergy and Infectious Diseases. Division of AIDS, 2017], unless specified otherwise in the protocol.

For AEs by maximum grade summary tables, if a participant reports an AE more than once within an SOC/PT, the AE with 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”. Adverse events with a missing relationship to study treatment will be regarded as “related” to study treatment.

The followingtable AE summaries will be presented:

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. AEs leading to withdrawal from the study by SOC and PT
8. AEs leading to permanent discontinuation of investigational product by SOC and PT
9. AEs leading to withdrawal from the study by SOC and PT and maximum grade
10. AEs leading to permanent discontinuation of investigational product by SOC and PT and maximum grade
11. Fatal AEs by SOC and PT
12. AEs by overall frequency
13. Serious, Non-serious and Drug-Related AEs by SOC and PT (number of subjects and occurrences). This will be presented for Overall, and for Week 1 – 12, Week 13 – 24, and Week 25 – Week 48.
14. Serious Fatal and Non-Fatal Drug-Related AEs by Overall Frequency

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 the rules stated in the Output and Programming Specification.

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
- Injection site reactions

An up to date list of specific MedDRA Queries (SMQs), high level terms (HLTs) or individual preferred terms (PTs) used to identify AESIs is periodically updated and stored in a central location. At the time of DBR, 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 and injection site reactions) 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.

### 4.5.3. 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.

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

Ang-II will be included in the immunology summaries and listings and additionally a listing of all Ang-II lab values will be presented. Plots showing mean actual and change from baseline values of Ang-II over time will be presented.

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 Intl. Normalized Ratio (INR), Prothrombin Time (PT) 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 hematology parameters will be provided.

Increase to Grade 3 or higher lab abnormalities for platelets, ALT, AST, INR, total bilirubin, serum creatinine, eGFR, 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, July 2017].

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

Liver 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.

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

Potential 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 or stopping criteria are described in the protocol Section 7.1.2.

Haematological monitoring/stopping event will be summarized and listed based on laboratory parameters (platelet count and anti-platelet antibodies). The haematological monitoring and stopping criteria are described in the protocol Section 7.1.3.

Potential 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 RBC, serum creatinine, and eGFR). The kidney injury monitoring and stopping criteria are described in the protocol Section 7.1.4.

Hold/stopping event profile 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.

#### 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 summaries will be produced for worst case post baseline only. The DAIDS grading system Version 2.1 [National Institute of Allergy and Infectious Diseases. Division of AIDS, 2017], will be used for grading: The grade definition for 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). DAIDs does not include a Grade 0, please refer to the Output and Programming Specification (OPS) for instruction on how to present values that don't meet the criteria for Grade 1+. Subjects with missing baseline values are assumed to have a normal baseline value.

## 4.6. Other Analyses

### 4.6.1. Subgroup analyses

Descriptive summary by subgroups as defined in Table 7 will be provided. Summary statistics (n (%)) for the number of SVR responders will be reported by subgroups 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.

In addition, selected summaries will be presented by baseline analysis stratification factors and/or subgroups, as detailed in the OPS.

**Table 7 Subgroups & Subgroup Categories**

| Subgroup | Categories |
|---|---|
| HBeAg Status | Positive or Negative |
| Baseline HBsAg (log10 IU/mL) | Low (≤ 3 log10 IU/mL), High (>3log10 IU/mL)<br><=3, >3-3.5, >3.5-4 and >4<br>Low (<=3000 IU/mL), High (3000 IU/mL) |
| Baseline HBV DNA level (log10 IU/mL) | For participants on stable nucleos(t)ide therapy:<br>- Not applicable<br><br>For participants not currently on nucleos(t)ide therapy:<br><=6 ; >6<br><=4, >4 - <=6, >6 |
| Age group | **EMA:** <18; ≥18-64; ≥65 – 84, ≥85<br>**FDAAA:** ≤18; ≥19-64; ≥65<br>**Clinical and Epi (Group 1):** <50, ≥50 |

| Subgroup | Categories |
|---|---|
| Sex | Male, Female |
| Race | American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White<br><br>If enough data are available (≥5 patients per group per arm) Asian may be further categorised as Asian – Central/South Asian Heritage; Asian – Japanese Heritage; Asian – East Asian Heritage; Asian – South East Asian Heritage or a combination of these, and White may be further categorises as White – Arabic/North African Heritage; White – White/Caucasian/European Heritage |
| Baseline viral genotype | For participants with CHB on stable nucleos(t)ide therapy:<br>- B; C; Other, Unknown<br>For participants with CHB not currently on nucleos(t)ide therapy:<br>- B; C; Other; Unknown. If enough data are available (≥5 patients per group per arm), Other may be further categorised into observed genotypes |
| Baseline substitution in the binding site | For participants with CHB not currently on nucleos(t)ide therapy only:<br>Present; Absent |
| Baseline BMI | <30, ≥30 |
| Baseline ALT | <=ULN; >ULN |
| Baseline METAVIR Fibrosis Score | If enough data are available (≥5 patients per group per arm):<br>F0 – F2 ; F3 |
| For on-NUC population only: Time on current NUC | <3 years; >=3 years |
| For on-NUC population only: Type of NUC | TAF&TDF vs Entecavir vs Other |
| For Treatment naïve group only: Immune tolerance | For participants with CHB not currently on nucleos(t)ide therapy:<br>Immune-tolerant; Not immune-tolerant<br><br>Subjects are defined as immune tolerant if they meet all of the following criteria: Treatment naïve (i.e. no prior medications reported on the Prior Medications CRF), HBeAg positive (>=0.09 U/mL), ALT normal (<= 33 IU/mL in females; <=40 IU/mL in males) and HBV DNA >10^6 IU/mL |
| Duration of Hep B Infection | <5 years, ≥ 5 years - <10 years, ≥ 10 years - <20 years, ≥ 20 years |
| 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.<br><br>Phase 1 = HBeAg-positive, ALT <= ULN during screening and at baseline, HBV DNA > 106 IU/ml during screening and at baseline<br>Phase 2 = HBeAg-positive, ALT > ULN either during screening or at baseline, HBV DNA > 104 IU/ml during screening and at baseline<br>Other HBeAg-positive = HBeAg-positive, neither Phase 1 nor Phase 2<br>Phase 3 = HBeAg-negative, ALT <= ULN during screening and at baseline, HBV DNA < 20,000 IU/ml during screening and at baseline<br>Phase 4 = HBeAg-negative, ALT > ULN either during screening or at |

| Subgroup | Categories |
|---|---|
| | baseline, HBV DNA > 2,000 IU/ml during screening and at baseline<br>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.<br><br>Phase 1 loose= HBeAg-positive, ALT <= ULN during screening and at baseline<br>Phase 2 loose = HBeAg-positive, ALT > ULN either during screening or at baseline<br>Phase 3 loose = HBeAg-negative, ALT <= ULN during screening and at baseline<br>Phase 4 loose = HBeAg-negative, ALT > ULN either during screening or at baseline |
| HBV RNA level | Target not detected; Target detected |
| HBcrAg | Low (<= 3 log10 U/mL); High (> 3 log10 U/mL) |

### 4.6.2. Subpopulations to Support Regulatory Consultation

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

**Japan subpopulation:** All subjects of Japanese heritage enrolled at sites in Japan

**China mainland subpopulation:** All subjects enrolled at sites in China Mainland

**East Asia subpopulation:** All subjects of a relevant Asian heritage (Asian – Japanese Heritage, Asian – East Asian Heritage or Asian – South East Asian Heritage) enrolled at sites in Hong Kong, Taiwan, Japan, South Korea, China mainland.

### 4.6.3. Concordance of virologic response at Week 6, Week 12, Week 18 and Week 24 and achieving SVR

The concordance of early virologic response (HBV DNA < LLOQ and HBsAg < LLOQ) at on-treatment timepoints of interest with achieving SVR will be explored. Number of participants with an early virologic response (Yes or No) will be cross tabulated with SVR (Yes or No) for on-treatment visits Week 6, Week 12, Week 18 and Week 24 separately. Positive Predictive Value and Negative Predictive Value will be presented, calculated as:

Positive Predictive Value = Number of True Positives / (Number of True Positives + Number of False Positives)

A true positive is defined as a participant with an early response who goes on to achieve SVR. A False positive is a participant with an early response who does not achieve SVR.

Negative Predictive Value = Number of True Negatives / (Number of True Negatives + Number of False Negatives)

A true negative is defined as a participant without early response who does not achieve SVR. A false negative is a participant without early response who goes on to achieve SVR.

The table will be presented separately for each arm, and also for Arms 1, 2, and 3 combined.

### 4.6.4. Association between HBV DNA TND and relapse

In participants who achieve a virologic response (HBsAg < LLOQ and HBV DNA < LLOQ) in the absence of rescue medication at the End of GSK3228836 Treatment visit (Week 12 / Week 24), a cross tabulation of achieving HBV DNA TND / not achieving HBV DNA TND vs. no relapse / relapse at 8, 16 and 24 weeks after end of treatment will be produced. The Off-Treatment timepoints will be based on the time since planned end of GSK836 treatment visit rather than visit labels in the schedule of assessments. The table will be repeated for each arm and overall. Data will also be listed.

### 4.6.5. Determining the optimal cut point of baseline HBsAg to predict response

ROC analysis will be used to estimate a single cut-point that can best be used to predict SVR. Baseline HBsAg will be plotted against SVR status and a ROC curve will be produced. A table showing the specificity (1-false positive rate), sensitivity (true positive rate) and accuracy for each cut-off will be presented. The optimal cut-off will be determined from the cut-off with the highest accuracy. The outputs will be displayed for each arm separately, and overall.

False Positive Rate, True Positive Rate and Accuracy are calculated as:

False Positive Rate = number of False Positives (FP) / number with Actual Outcome = Negative (Neg)

True Positive Rate = number of True Positives (TP) / number with Actual Outcome = Positive (Pos)

Accuracy = number of True Positives (TP) + Number of True Negatives (TN) / number with Actual Outcome = Positive (Pos) + number with Actual Outcome = Negative (Neg)

Where counts for FP, TP, TN, Neg and Pos are defined as shown in Table 8.

**Table 8 Classification of conditions for ROC analysis**

| | | Predicted Outcome | |
|---|---|---|---|
| | | Positive (PPos) (Predicted SVR) | Negative (PNeg) (Predicted No SVR) |
| Actual Outcome | Positive (Pos) (SVR) | True Positive (TP) | False Negative (FN) |
| | Negative (Neg) (No SVR) | False Positive (FP) | True Negative (TN) |

If the original value <= cut-off then the predicted outcome is positive (i.e. predicted SVR=yes). If original value > cut-off then the predicted outcome is negative (i.e. predicted SVR=no)

### 4.6.6. Predictors of SVR response

If sufficient data are available, an exploratory analysis will be performed to identify predictors of SVR response.

The following continuous baseline variables will be considered for inclusion in the model, additional clinically relevant variables may be considered:

Age (years), BMI, HBsAg (log10 IU/mL), HBV DNA (log10 IU/mL), HBcrAg (log10 U/mL), HBV RNA (copies/mL), ALT (IU/L), Platelet count, APRI Score, eGFR, Urine Albumin (g/dL), Serum Creatinine (umol/L), ACR (g/mol), Length of Diagnosis (Years)

The following categorical baseline variables will be considered for inclusion in the model, additional clinically relevant variables may be considered:

Sex (Male; Female), Race (American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White), HBsAg (<=3 log10 IU/mL; >3 log10 IU/mL), HBeAg Status (Positive; Negative), HBV Genotype (A, B; C; D, E, Other; Unknown), Metavir Score (F0, F0-F1, F1, F1-F2, F2, F2-F3, F3, F3-F4, F4), Prior Interferon Use (Yes, No), Method of Transmission (Vertical, Horizontal, Unknown, Prefer not to Say and Other), Nucleos(t)ide Use (type of Nucleos(t)ide).

If appropriate, continuous variables may be separated into categories, using the subgroup categories from Section 4.6.1 or another appropriate categorisation (e.g. median split). Additional clinically relevant variables may be considered.

The definition of response for the analyses described in this section is SVR as defined for the primary efficacy analysis.

A summary of the number and proportion of SVR successes will be provided for each category of the variables considered as potential predictors of response. For continuous variables a median split will be used to categorise the data in the summary.

Summary statistics (n, Mean (SD) & 95% CI, Median, Min, Max for continuous variables and n (%) for categorical variables) for potential predictors of response in participants with and without SVR will also be presented by arm and overall.

Summaries will be graphically presented using boxplots (for continuous variables) and Forest style plots (for categorical variables). For boxplots, response (responder vs non-responder) will be shown on the x-axis and baseline characteristic value will be shown on the y-axis. The Forest style plot will show the proportion of participants in each category who have a response.

Summary tables and figures will be presented by treatment arm and overall.

A predictive logistic regression model will be built using a forward stepwise selection approach using the Akaike Information Criterion (AIC). The model will use Firth's penalised likelihood approach to avoid the potential issue of separation [Heinze G, 2002]. Analysis stratification values (HBsAg (<=3 log10 IU/mL; >3 log10 IU/mL), HBeAg Status (Positive; Negative)) will be included in the model, regardless of their impact on AIC. The order in which other covariates will be included in the algorithm will be determined prior to fitting the model, and will be based on clinical understanding of the most relevant / readily available predictors of response. Variables with a high proportion of missing data at baseline (e.g. data missing for >10% participants) will not be included in the model selection procedure. The final model will be the model with the minimum AIC. All arms will be included in a single model and arm will be included in the model. If there are enough SVR successes in a single arm (>= 5 SVR success in an arm), the model selection process will be repeated including data from the single arm only.

### 4.6.7. Other variables and/or parameters

Fibrosis Score is collected at baseline and End of Study (or Early Termination). A shift table for Metavir fibrosis score showing baseline score and End of Study (or Early Termination) score will be provided for each arm, overall and by baseline HBeAg status.

A listing of participants who went above and stayed above >=90 IU/mL HBV DNA will be presented. All visits will be presented for these participants.

A listing showing (quantitative) values of HBeAg at Baseline & Day 1 will be presented for subjects who are anti-HBeAg positive at baseline. A listing showing (quantitative) values of HBsAg at Baseline & Day 1 will be presented for subjects who are anti-HBsAg positive (i.e. HBs Antibody >=11.5 IU/L) at baseline.

## 4.7. Interim Analyses

Details of interim analyses are provided in separate Interim Analysis Reporting and Analysis Plans.

## 4.8. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 9.

**Table 9 Changes to Protocol Defined Analysis Plan**

| Protocol Defined Analysis | SAP Defined Analysis | Rationale for Changes |
|---|---|---|
| • NA - addition | • SAP Section 4.2.4.3: Addition of a supplementary estimand that uses a principal stratum strategy to deal with protocol deviations | • A number of subjects in the not currently on nucleos(t)ide therapy population started nucleos(t)ide therapy on day 1 because of a misunderstanding of the protocol. In the main estimand these participants will be treated as failures on day 1. However, as these patients never had the chance to respond because of an |

| Protocol Defined Analysis | SAP Defined Analysis | Rationale for Changes |
|---|---|---|
| | | operational error, this estimand will be used to counter the main estimand, |
| • NA - addition | • SAP Section 4.2.4.4: Addition of a supplementary estimand to assess efficacy using a modified definition of SVR | • There are a number of 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 estimand will be used to support the primary objective. |

# 5. SAMPLE SIZE DETERMINATION

Approximately 440 participants are planned to be randomly assigned to study intervention.

For each population, there will be approximately 66 participants assigned in each of the first three arms. There will be approximately 22 participants assigned in the fourth arm.

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 response rate. The precision for a range of response rates with 95% credible intervals are shown in Table 10.

**Table 10 95% Credible Interval of Response Rate by Sample Size**

| Sample size per arm | Number of responders | Response rate | 95% credible interval* |
|---|---|---|---|
| 22 | 2 | 9% | 1% – 23% |
| | 3 | 14% | 3% - 30% |
| | 4 | 18% | 5% - 36% |
| | 5 | 23% | 8% - 41% |
| | 6 | 27% | 11% - 46% |
| 66 | 6 | 9% | 3% - 17% |
| | 9 | 14% | 6% - 23% |
| | 12 | 18% | 10% - 28% |
| | 15 | 23% | 13% - 33% |
| | 18 | 27% | 17% - 38% |

*95% highest posterior density interval

The lower bounds of 95% credible intervals will exclude the historical placebo response rate of 3% if observed response rate is greater than or equal to 14% in arms 1-3 or 18% in arm 4.

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

The operating characteristics based on at least 75% posterior confidence that the true rate exceeds a threshold of interest, are shown in Table 11, for various sample sizes, and true cure rates. The operating characteristics shown are based on a Bayesian model without consideration of baseline analysis stratification factors and expected to be similar to operating characteristics from the hierarchical model defined in Section 4.2.2.

**Table 11 End of Study Operating Characteristics by Sample Size**

| Criterion | **Sample size per arm** | **Minimum number (%) of responders required to meet Criterion** | **Probability of Meeting Criterion Under Various Assumptions** | | | |
|---|---|---|---|---|---|---|
| | | | **True Resp Rate=5%** | **True Resp Rate=20%** | **True Resp Rate=25%** | **True Resp Rate=30%** |
| Probability (true response rate>15%)>75% | 22 | 5 (23%) | 0% | 46% | 68% | 84% |
| | 44 | 9 (20%) | 0% | 53% | 81% | 91% |
| | **66** | **12 (18%)** | **0%** | **69%** | **93%** | **99%** |
| | 88 | 16 (18%) | 0% | 71% | 95% | 100% |
| Probability (true response rate>20%)>75% | 22 | 6 (27%) | 0% | 27% | 48% | 69% |
| | 44 | 11 (25%) | 0% | 25% | 56% | 81% |
| | **66** | **16 (24%)** | **0%** | **23%** | **60%** | **88%** |
| | 88 | 21 (24%) | 0% | 22% | 64% | 92% |
| Probability (true response rate>25%)>75% | 22 | 7 (32%) | 0% | 13% | 30% | 51% |
| | 44 | 13 (30%) | 0% | 9% | 29% | 58% |
| | **66** | **19 (29%)** | **0%** | **6%** | **28%** | **63%** |
| | 88 | 25 (28%) | 0% | 4% | 27% | 67% |

Note: If the true response rate is 0%, the probability of meeting each criterion is 0% for all sample sizes.

Based on these operating characteristics, for a true response rate of 20%, the proposed sample-size of n = 66 for arms 1 – 3 has ~70% probability of confirming a true response of at least 15%, and if the true rate is 30%, there is an 88% chance of confirming a true response of at least 20%.

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 of participants in each of the participant level analysis set will be provided.

A listing of subjects excluded from any population will be presented.

In this multicentre global study, enrolment will be presented by country and site.

### 6.1.1. Participant Disposition

A summary of the number and percentage of patients who were screened including screen failures will be provided. Reasons for failure will be included.

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 withdrawal will be summarized.

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

Summaries of disposition, adverse events leading to withdrawal and reasons for withdrawal will be presented by Study Period, as defined in the Output and Programming Specification.

Listings of reasons for study withdrawal, screen failure and study treatment discontinuation will be provided.

### 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 starting after randomization, medical history and exposure and treatment compliance will be presented.

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

Baseline characteristics including but not limited to BMI, hypertension, NSAID use, TDF/TAF containing medications use, ADV containing medications use, diabetes, eGFR, serum creatinine, urine ACR, platelets, ANC, complement C3, complement C4,

complement C5a, complement Bb, C Reactive Protein, MCP-1, c-ANCA, p-ANCA and subgroup categories listed in Section 4.6.1 will be summarized with descriptive statistics. Continuous characteristics will be presented using summary statistics (n, Mean (SD), Median, Min, Max) and may also be categorized and summarised using n (%).

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

A table and listing of nucleos(t)ide treatment at baseline will be presented for the on stable nucleos(t)ide cohort.

### 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 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.

Study intervention Compliance (%) = [Number of actual doses / Number of planned doses] *100.

Study dose Compliance (%) = [Actual Total Dose / Planned Total Dose] * 100

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

### 6.2.2. Assessment Windows

Refer to Section 4.2.2.1 for details of visit windowing for the main efficacy estimands.

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 4.2.2.1 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.

#### 6.2.2.1. Definitions of Assessment Windows for Early Termination Visits

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

| Analysis Set / Domain | Parameter (if applicable) | Target | Analysis Window | | Analysis Timepoint |
|---|---|---|---|---|---|
| | | | Beginning Timepoint | Ending Timepoint | |
| Lab, Vital Signs | Numeric parameters | 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 |
| | | 22 | 19 | 25 | Week 4 |
| | | 1+7(x-1) | 1+7(x-1)-3 | 1+7(x-1)+3 | Week x |
| | | 169 | 166 | 172 | OT-Week 1 |
| | | 176 | 173 | 179 | OT-Week 2 |
| | | 190 | 180 | 203 | OT-Week 4 |
| | | 218 | 204 | 231 | OT-Week 8 |
| | | 246 | 232 | 259 | OT-Week 12 |
| | | 274 | 260 | 287 | OT-Week 16 |

| | | | | | |
|---|---|---|---|---|---|
| | | 302 | 288 | 315 | OT-Week 20 |
| | | 330 | 316 | 340 | OT-Week 24 |

Notes:

1. Week x includes on-treatment weeks 5 – 24

2. Visit windows are to be used for windowing of Early Termination visits only

#### 6.2.2.2. Definitions of Assessment Windows for Adverse Events

To allow comparison between safety in active treatment vs placebo, and loading dose vs no loading dose, selected safety displays will be presented by study Weeks 1 – 12, Weeks 13 – 24, and Weeks 25 – 48. Adverse events are not associated with a specific visit therefore the study week they are assigned to will be based on the AE start date.

| Analysis Set / Domain | Parameter (if applicable) | Analysis Window | | Analysis Timepoint |
|---|---|---|---|---|
| | | Beginning Timepoint | Ending Timepoint | |
| Adverse Events | All | 1 | 81 | Weeks 1 – 12 |
| | | 82 | 165 | Weeks 13 – 24 |
| | | 166 | - | Weeks 25 – 48 |

### 6.2.3. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study intervention period. Off Treatment Day 1 occurs 7 days after the last study treatment dose received, regardless of whether the participant completes treatment as planned or the participant is withdrawn from study treatment.

| Study Intervention Period | Definition |
|---|---|
| Pre-Treatment | Date ≤ Study Treatment Start Date |
| On-Treatment | Study Treatment Start Date < Date ≤ Off Treatment Day 1 – 1 day |
| Post-Treatment | Date ≥ Off Treatment Day 1 |

### 6.2.4. 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 – Ref Date
- Assessment Date ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

### 6.2.5. Multiple measurements at One Analysis Time Point

| **Multiple Measurements at One Analysis Time Point** |
|---|
| • Handling of multiple measurements within an analysis window for primary endpoint is described in Section 4.2.2<br>• 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.<br>• 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.<br>• 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. |

### 6.2.6. Handling of 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.<br>• 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.<br>• 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).<br>• Duration of Hep B infection (years) will be calculated based on year only</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.<br>• Else if study intervention start date is not missing:<br>o If month and year of start date = month and year of study intervention start date, then<br>▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.<br>▪ Else set start date = study intervention start date.<br>o Else set start date = 1st of month.</td></tr>
</table></td></tr>
</table>

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

| Element | Reporting Detail | |
|---|---|---|
| | | ○ If year of start date = year of study intervention start date, then<br>▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.<br>▪ Else set start date = study. intervention start date.<br>○ 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 |

# TRADEMARKS

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|---|---|
| None | WinNonlin |

# 7. REFERENCES

Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. Journal of Computational and Graphical Statistics. 1998;7:434–455.

Dolan P. Modeling valuations for EuroQol health states. Med Care 1997; 35(11): 1095-108

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

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°

Spiegel BM, Bolus R, Han S, Tong M, Esrailian E, Talley J, Tran T, Smith J, Karsan HA, Durazo F, Bacon B, Martin P, Younossi Z, Hwa-Ong S, Kanwal F. Development and validation of a disease-targeted quality of life instrument in chronic hepatitis B: the hepatitis B quality of life instrument, version 1.0. Hepatology. 2007 Jul;46(1):113-21