Information Type: Statistical Analysis Plan (SAP)

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TITLE PAGE

Protocol Title:	B-Fine: An open label, single arm study to mechanistically interrogate the therapeutic effect of GSK3228836 in patients with Chronic Hepatitis B via intrahepatic immunophenotyping
Study Number:	212602
Compound Number:	GSK3228836
Abbreviated Title:	A mechanistic study of GSK3228836 with fine needle aspiration (FNA) in Participants with Chronic Hepatitis B
Acronym:	B-Fine

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
CT.gov	NCT04544956

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP amendment 1	28 Jun 2023	Protocol Amendment 01, 15Mar2021; Protocol Amendment 1/CAN-1, 22-Jul2021	Section 1: Details of administrative interim analysis added.	Requirement to add details to SAP.
			Section 4.1.1: Removed mention of HBeAg imputation.	Only collecting HBeAg at Baseline, so imputation rules not required for this variable.
			Section 3: Removed Pharmacodynamic (PD) population.	PD population is not used for any output.
			Section 4.3.1.3, for Time-to-Event: Added clarification on censoring	Detail missed previously.
			Section 4.1.1: Updating imputing rules around values <LLOQ, TND values and significant digits.	Implementing learning from other studies.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Section 2: Added reference to OPS for terms for Peg-interferon and other immunomodulator therapies.	For clarity.
			Section 4.6.1 (Table 7): Added additional HBsAg subgroup.	Addition/clarification
			Section 4.6.1: Removed text describing statistical analysis of subgroups. Only descriptive stats will be presented for subgroup analyses.	Correction
			Section 4.1.1 and Section 4.4.1.3: 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.
			Section 4.2.2.1 Updated visit windowing for the end of	To ensure that on-treatment values are not used when there is a more

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			treatment analysis timepoint	appropriate end of treatment value available.
			Section 4.3.1.1: Added HBs antibody variable, which was omitted from the previous version.	Omission
			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.	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: Addition of table showing mutation by response for	Addition at request of virology expert.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			binding site mutations with >=1% allelic frequency	
			Section 6.1.2: Removed baseline characteristics from demographic characteristics table and added clarification on which summary stats to use for continuous characteristics. Added listing of nucleos(t)ide treatment at baseline	Correction & omission
			Section 6.2.2: Updated text to describe visit windowing for early termination visits	Clarification
			Section 6.2.3: Added text "Off Treatment Day 1 occurs 7 days after the last study treatment dose received,	Clarification

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			regardless of whether the participant completes treatment as planned or the participant is withdrawn from study treatment."	
SAP V1.0	03 Dec 2021	Protocol Amendment 01, 15Mar2021; Protocol Amendment 1/CAN-1, 22-Jul2021	Not Applicable	Original version

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 212602. Details of the planned interim analysis are detailed in a separate Interim Analysis Reporting Analysis Plan.

An administrative interim analysis will be conducted when the first 10 subjects have fully complete and clean data. A reduced set of outputs will be produced as detailed in the OPS.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
Efficacy: To assess the effect of 12 weeks of GSK3228836 on serum HBsAg levels in participants with CHB	The Primary Estimand supporting the primary objective of the study is defined as: • Population: Participants with CHB who receive at least one dose of IP • Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy) • Variable: Achieving serum HBsAg level <LLOQ at any time point up to and including Week 12 without the use of PEG-interferon or other immunomodulator therapies. • Population-level summary: Percent of participants that achieve serum HBsAg level < LLOQ at any time point up to and including Week 12 • Intercurrent events: Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). The primary estimand is the percentage of participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) who achieve serum HBsAg level <LLOQ at any time point up to and including Week 12, without the use of PEG-interferon or other immunomodulator therapies, regardless of completing IP, interruptions in IP or adherence to IP.
Secondary	

Objectives	Endpoints
Efficacy: To assess sustainability of serum HBsAg loss by GSK3228836 for up to 24 weeks off-treatment.	The Estimand supporting the objective is defined as: • Population: Participants with CHB who receive at least one dose of IP • Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy) • Variables: o Sustained HBsAg Response (HBsAg <LLOQ) for 24 weeks after the planned end of GSK3228836 treatment ▪ HBsAg from Week 13 to Week 36 will be used to assess sustained HBsAg response after the planned end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies. o Sustained HBsAg Response (HBsAg <LLOQ) for 24 weeks after the actual end of GSK3228836 treatment ▪ HBsAg for 24 weeks after end of actual treatment will also be used to assess sustained HBsAg response after the actual end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies. • Intercurrent events: Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). The group of estimands supporting this objective in participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) is the percentage of participants for each variable regardless of completing IP, interruptions in IP or adherence to

Objectives	Endpoints
	IP, without the use of PEG-interferon or other immunomodulator therapies.
Efficacy: To assess sustainability of serum HBsAg and HBV DNA loss by GSK3228836 for up to 24 weeks off treatment.	The Estimand supporting the objective is defined as: • Population: Participants with CHB who receive at least one dose of IP • Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy) • Variables: • Sustained Virologic Response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of GSK3228836. • HBsAg and HBV DNA from Week 13 to Week 36 will be used to assess sustained virologic response after the planned end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies. • Sustained Virologic Response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the actual end of GSK3228836 treatment • HBsAg and HBV DNA for 24 weeks after end of actual treatment will be used to assess sustained virologic response after the actual end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies • Intercurrent events: Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). The group of estimands supporting this objective in participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) is the percentage of participants for each

Objectives	Endpoints
	variable regardless of completing IP, interruptions in IP or adherence to IP, without the use of PEG-interferon or other immunomodulator therapies.
Efficacy: To assess the effect of 12 weeks GSK3228836 on biomarkers and virus-specific antibody response.	Estimands supporting the secondary objective of assessing the effect of 12 weeks GSK3228836 on biomarkers and virus-specific antibody responses are defined as follows: • Population: Participants with CHB who receive at least one dose of IP • Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy) • Intercurrent events: Discontinuation of, interruption of, adherence to IP will be ignored (treatment policy). PEGinterferon or other immunomodulator therapies will be handled with hypothetical strategy. 1. Categorical Variables: • Achieving: • HBsAg <LLOQ over time • HBV DNA <LLOQ over time • HBsAg and HBV DNA <LLOQ over time • Categorical changes from baseline in HBsAg (e.g. <0.5, ≥0.5, ≥1, ≥1.5, ≥3 log10 IU/mL) over time. • ALT>3X ULN at over time • HBe antibody (anti-HBeAg) levels over time Population summary: percentage of participants in each category. 2. Continuous Variables: • Actual values and change from baseline over time for HBsAg and HBV DNA

Objectives	Endpoints
	• HBs antibody (anti-HBsAg) and HBe antibody (anti-HBeAg) levels over time • Area under the curve (AUC) for ALT on treatment (12 weeks), during follow up (24 weeks), and on treatment + follow up (36 weeks) Population summary: mean values and/or mean changes from baseline for each variable 1. Time to Event Variable • Time to Maximum ALT (ALT must be greater than 3xULN) during 36 weeks of treatment + follow up Population summary: Turnbull estimate for median Time to Maximum ALT (>3xULN) The group of estimands supporting this objective in participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) are the population summary for each variable in the absence of PEGinterferon or other immunomodulator therapies, regardless of completing IP, interruptions in IP, or adherence to IP.
Safety	
Safety: To assess the safety and tolerability of GSK3228836 when dosed for 12 weeks in participants with CHB	Clinical assessments including, but not limited to vital signs, laboratory measurements and adverse events
Exploratory	
CCI [redacted]	

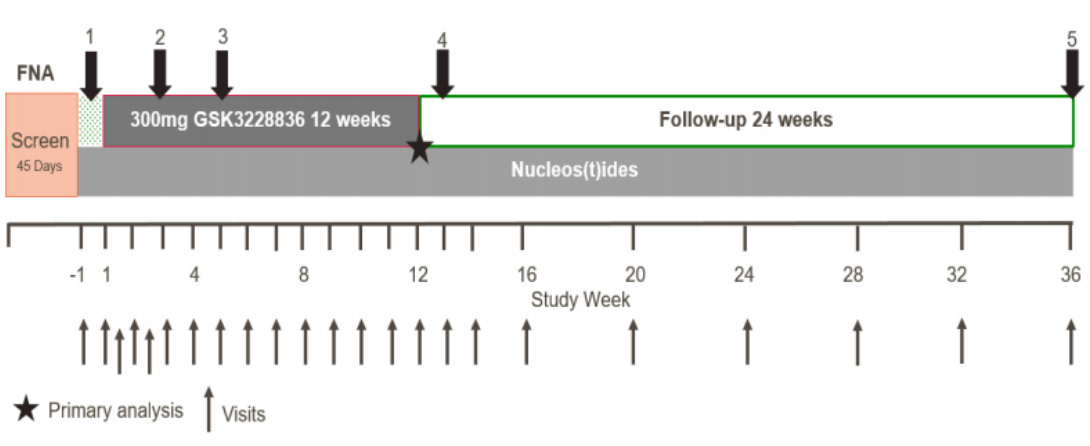
Objectives	Endpoints
CCI	

Objectives	Endpoints
CCI	[redacted]

1.2. Study Design

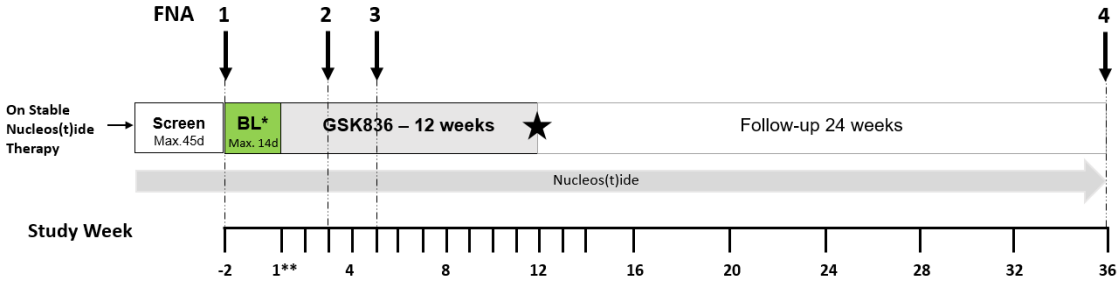
Overview of Study Design and Key Features

The schema for all countries except Canada is as follows:



An optional 6th FNA may be included between Weeks 6 and 36 following discussion between investigator and medical monitor.

The schema for Canada is as follows:



*Baseline (BL) up to 45 days after screening
**Visit Day 1, Week 1, up to 14 days after Baseline (BL) 'Week -2' FNA
★Primary analysis

Note: The key difference between the two schema, is the following: Canada site has one less scheduled FNA than the other sites.

Design Features	• Phase IIa, single arm, multi-centre open label exploratory study of the therapeutic mechanism of GSK3228836 in participants with HBeAg-negative CHB on stable nucleos(t)ide therapy using repeat fine needle aspirations of the liver for intrahepatic immunophenotyping • The total duration of the study, including screening, treatment and post-treatment follow-up, is not expected to exceed 45 weeks.

Overview of Study Design and Key Features	
Study intervention	• 300 mg GSK3228836 for 12 weeks (loading schedule on Day 4 and Day 11). Participants will continue to receive their stable nucleos(t)ide therapy
Study intervention Assignment	• N/A. This is a single arm study.

Interim Analysis	• Data will be incorporated into regular safety reviews by an IDMC and may be used to supplement the safety data review for the Phase IIb B-Clear study (approximately every 3 months).
	• There are 2 interims planned for this study, which align with the following timepoints in the Phase IIb B-Clear study:
	  o Interim 1: approximately 30% participants complete Week 12 to assess safety and futility.
	  o Interim 2: approximately 50% participants complete Week 24 to assess safety and futility.
	• Further details found in a separate Interim Analysis Reporting Analysis Plan.

2. STATISTICAL HYPOTHESES

The primary objective of the study is to assess the efficacy of 12 weeks of GSK3228836 treatment in Hepatitis B e-antigen negative participants on nucleos(t)ide analogue therapy. The primary endpoint is achieving serum HBsAg level <LLOQ by Week 12 (at any time point up to and including Week 12) without the use of PEG-interferon or other immunomodulator therapies in CHB participants who receive at least one dose of IP. For list of terms for PEG-interferon or other therapies, refer to Output and Programming Specification.

An estimation approach with no hypothesis testing will be used to address the primary objective. The primary assessment of interest is the point estimate of percent of participants achieving serum HBsAg level <LLOQ (without the use of PEG-interferon or other immunomodulator therapies) by Week 12 with the 95% credible interval. Other intercurrent events such as discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy). In addition, posterior probabilities that the true percent is greater than the desired threshold of 50% will be provided using a Bayesian probability approach.

2.1. Multiplicity Adjustment

Analyses of efficacy endpoints will not be subject to any multiplicity adjustment.

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 • Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study are excluded from the Enrolled population as they did not enter the study	• Study Population
Safety	• All participants who received at least one dose of study treatment	• Safety • Virology
ITT	• All participants who received at least one dose of study treatment • Note: As no randomization took place on this study, Safety and ITT analysis set will contain the same set of participants.	• Efficacy • Virology
Pharmacokinetic (PK)	• All participants in the Safety population who received an active study treatment and had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values) • Note: PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded	• PK

Defined Analysis Data Sets	Description
Analysis set for primary estimand	All Intent to Treat Participants including all observations on and off treatment.
Analysis set for secondary estimands	All Intent to Treat Participants including all observations on and off treatment.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Participants who prematurely withdrew from study will not be replaced.

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 and HBsAg levels that are below the LLOQ will be imputed for summaries of actual values and change from baseline.

The numeric values for HBV DNA <LLOQ (LLOQ=20 IU/mL) will be imputed as 19.9. The numeric values for HBsAg <LLOQ (LLOQ=0.05 IU/mL) will be imputed as 0.04. For HBV RNA and HBcrAg, values <LLOQ are imputed based on the number of significant digits, similar to other lab parameters. For further handling of significant digits, please see OPS.

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

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

Baseline of 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 will be conducted once the last participant has completed the Week 36 visit (completed 24-weeks of follow-up period) and database lock has been achieved. The primary efficacy endpoint is achieving serum HBsAg level <LLOQ at any time point during 12-weeks (including Week 12) of GSK3228836 treatment. HBsAg at any time point up to and including Week 12 will be used to assess the primary endpoint.

4.2.1. Definition of estimands

The Primary Estimand supporting the primary objective of the study is defined as:

- **Population**: Participants with CHB who receive at least 1 dose of IP
- **Treatment**: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy)

- **Variable**: Achieving serum HBsAg level <LLOQ at any time point up to and including Week 12 without the use of PEG-interferon or other immunomodulator therapies
- **Population-level summary**: Percent of participants that achieve serum HBsAg level <LLOQ at any time point up to and including Week 12
- **Intercurrent events:** Discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy).

The primary estimand is the percentage of participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) who achieve serum HBsAg level <LLOQ at any time point up to and including Week 12, without the use of PEG-interferon or other immunomodulator therapies, regardless of completing IP, interruptions in IP or adherence to IP. If PEG-interferon or other immunomodulator therapies are used, then the participant's primary outcome will be treated as a non-responder.

4.2.2. Main analytical approach

The primary assessments of interest are the point estimate and the 95% credible interval of achieving serum HBsAg level <LLOQ up to and including Week 12.

In addition, posterior probability that the true virologic response rate is greater than 50% will be provided. A Bayesian approach will be used to estimate the posterior probability. A weakly informative prior beta (0.5, 0.5) will be used.

Let Y be the number of responders from N participants,

Y~ Binomial (N, p)

Where p is virologic response rate.

The posterior distribution for p is $P(p|y, N) \sim \text{Beta}(y + 0.5, N - y + 0.5)$

The posterior probability that the true rate of participants achieving LLOQ by Week 12 being greater than 50% will be calculated from the posterior distribution.

The following will be presented:

Model Results Presentation
• Number and percent of participants achieving serum HBsAg level <LLOQ by Week 12. • Posterior 95% credible interval (Highest Density Interval, HDI) of participants achieving serum HBsAg level <LLOQ by Week 12. • Posterior probability that the true rate of participants achieving LLOQ by Week 12 being greater than 50%

4.2.2.1. Intercurrent Events and Missing Data

The intercurrent event of discontinuation of, interruption of, and adherence to IP will be ignored (treatment policy).

A participant's response (Responder or Non-responder) is determined as follows:

- If participant took rescue medication of PEG-interferon or other immunomodulator therapies during 12 week treatment period or during 24 week follow-up period then participant is Non-Responder
- Else if participant reached HBsAg < LLOQ at any point during the 12 week treatment period then participant is a Responder.
- Otherwise participant is Non-Responder.

If a participant has missing data during the 12 week treatment period, but still falls under the responder then they will still be considered a responder.

HBsAg values at any timepoint up to and including Week 12 are considered, including Unscheduled visits. See Section 6.2.5 for details on upper bound of analysis date.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Key secondary endpoint(s)

4.3.1.1. Sustainability of Serum HBsAg loss

Definition of estimands

Estimands supporting the secondary objective of assessing sustainability of serum HBsAg loss by GSK3228836 for up to 24 weeks off-treatment are defined as follows:

- The group of estimands supporting this objective in participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) is the percentage of participants for each variable regardless of completing IP, interruptions in IP or adherence to IP, without the use of PEG-interferon or other immunomodulator therapies. If PEG-interferon or other immunomodulator therapies are used then the participant's outcome will be treated as a non-responder.

- **Variables**:
    - Sustained HBsAg Response (HBsAg <LLOQ) for 24 weeks after the planned end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies
        - HBsAg from Week 13 to Week 36 will be used to assess sustained HBsAg response after the planned end of GSK3228836 treatment.

  - Sustained HBsAg Response (HBsAg <LLOQ) for 24 weeks after the actual end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies
    - HBsAg for 24 weeks after end of actual treatment will also be used to assess sustained HBsAg response after the actual end of GSK3228836 treatment.

- **Population Summary:** percentage of participants for each variable.

Main analytical approach

Percentages will be summarised and presented for:

- Sustainability of Serum HBsAg loss

Analysis windows for the post GSK3228836 treatment assessments are defined in Section 6.2.5.

If all analysis windows have non-missing response information, a participant's response (Responder or Non-responder) for sustained HBsAg response after the planned end of GSK3228836 treatment is determined as follows:

- If participant took PEG-interferon or other immunomodulator therapies during 12 week treatment period or 24 week follow-up period then participant is Non-Responder
- Else if participant had sustained HBsAg response (HBsAg <LLOQ) for 24 weeks after planned end of GSK3228836 treatment then participant is a Responder.
- Otherwise participant is Non-Responder.

If all analysis windows have non-missing response information, a participant's response (Responder or Non-responder) for sustained HBsAg response after the actual end of GSK3228836 treatment is determined as follows:

- If participant took PEG-interferon or other immunomodulator therapies during 24 week follow-up period then participant is Non-Responder
- Else if participant had sustained HBsAg response (HBsAg <LLOQ) for 24 weeks after actual end of GSK3228836 treatment then participant is a Responder.
- Otherwise participant is Non-Responder.

For participants where sustained HBsAg response in the absence of PEG-interferon or other immunomodulator therapies cannot be ascertained due to missing data (withdrawal from the study or missing due to other reasons), the participant will be assumed not to have achieved SVR (non-responder imputation).

4.3.1.2. Sustainability of Serum HBsAg and HBV DNA loss (Sustained Virologic Response)

Definition of estimands

Estimands supporting the secondary objective of assessing sustainability of serum HBsAg and HBV DNA (Sustained Virologic Response) loss by GSK3228836 for up to 24 weeks off treatment are defined as follows:

- The group of estimands supporting this objective in participants with CHB receiving 300 mg GSK3228836 for 12 weeks (with at least one dose of IP) is the percentage of participants for each variable regardless of completing IP, interruptions in IP or adherence to IP, without the use of PEG-interferon or other immunomodulator therapies. If PEG-interferon or other immunomodulator therapies are used then the participant's outcome will be treated as a non-responder.

- **Variables**:
    - Sustained Virologic Response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the planned end of GSK3228836 treatment
        - HBsAg and HBV DNA from Week 13 to Week 36 will be used to assess sustained virologic response after the planned end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies.
    - Sustained Virologic Response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after the actual end of GSK3228836 treatment
        - HBsAg and HBV DNA for 24 weeks after end of actual treatment will be used to assess sustained virologic response after the actual end of GSK3228836 treatment without the use of PEG-interferon or other immunomodulator therapies.

- **Population Summary:** percentage of participants for each variable.

Main analytical approach

Percentages will be summarised and presented for:

- Sustainability of Serum HBsAg and HBV DNA loss (Sustained Virologic Response).

Analysis windows for the post GSK3228836 treatment assessments are defined in Section 6.2.5.

If all analysis windows have non-missing response information, a participant's response (Responder or Non-responder) for sustained virologic response after the planned end of GSK3228836 treatment is determined as follows:

- If participant took PEG-interferon or other immunomodulator therapies during 12 week treatment period or 24 week follow-up period then participant is Non-Responder
- Else if participant had sustained virologic response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after planned end of GSK3228836 treatment then participant is a Responder.
- Otherwise participant is Non-Responder.

If all analysis windows have non-missing response information, a participant's response (Responder or Non-responder) for sustained virologic response after the actual end of GSK3228836 treatment is determined as follows:

- If participant took PEG-interferon or other immunomodulator therapies during 12 week treatment period or 24 week follow-up period then participant is Non-Responder
- Else if participant had sustained virologic response (HBsAg <LLOQ and HBV DNA <LLOQ) for 24 weeks after actual end of GSK3228836 treatment then participant is a Responder.
- Otherwise participant is Non-Responder.

For participants where sustained virologic response in the absence of PEG-interferon or other immunomodulator therapies cannot be ascertained due to missing data (withdrawal from the study or missing due to other reasons), the participant will be assumed not to have achieved SVR (non-responder imputation).

4.3.1.3. Effect of 12 weeks GSK3228836 on biomarkers and virus-specific antibody responses

Definition of estimands

Estimands supporting the secondary objective of assessing the effect of 12 weeks GSK3228836 on biomarkers and virus-specific antibody responses are defined as follows:

- Population: Participants with CHB who receive at least one dose of IP

- Treatment: 300 mg GSK3228836 for 12 weeks (also on stable nucleos(t)ide therapy)

- Intercurrent events: Discontinuation of, interruption of, adherence to IP will be ignored (treatment policy). For the categorical variable summaries, and continuous variable summaries, PEG-interferon or other immunomodulator therapies will be handled with hypothetical strategy.

- Variables:

1) Categorical Variables:

- Achieving HBsAg <LLOQ over time
- Achieving HBV DNA <LLOQ over time
- Achieving HBsAg <LLOQ and HBV DNA <LLOQ over time

- HBe antibody (anti-HBeAg) levels over time
- Categorical changes from baseline in HBsAg (e.g. <0.5, ≥0.5, ≥1, ≥1.5, ≥3 log_{10} IU/mL) over time
  Note: <0.5 category includes subjects with no change or an increase in HBsAg from baseline.
- ALT>3X ULN over time
- 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:** Percent of participants in each category.

2) Continuous Variables:

- Actual values and change from baseline over time for HBsAg and HBV DNA
- HBs antibody (anti-HBsAg) levels over time
- Area under the curve (AUC) for ALT on treatment (12 weeks), during follow up (24 weeks), and on treatment + follow up (36 weeks).

- **Population summary**: mean values and/or mean changes from baseline for each variable

3) Time to Event Variable

- Time to First Occurrence of Maximum ALT (ALT must be greater than 3xULN) during 36 weeks (treatment + follow up)

Time to first occurrence of maximum ALT (first peak in ALT) during 36 week (treatment + follow-up) is defined as time from baseline to the time of first peak in ALT.

Outcome will be assumed missing (Missing At Random) from the timepoint when subjects first receive PEG-interferon or other immunomodulator therapies.

- Time to First Occurrence of Maximum ALT (ALT must be greater than 3xULN) during 12 week on-treatment period

Time to first occurrence of maximum ALT (first peak in ALT) during 12 week treatment period is defined as time from baseline to the time of first peak in ALT (given the peak occurred during 12 weeks of study treatment. See Section 6.2.2 for definition of on-treatment period.

Outcome will be assumed missing (Missing At Random) from the timepoint when subjects first receive PEG-interferon or other immunomodulator therapies.

- Time to First Occurrence of Maximum ALT (ALT must be greater than 3xULN) during 24 week follow-up period

Time to first occurrence of maximum ALT (first peak in ALT) during 24 week off treatment period is defined as time from last dose of study treatment to the time of first peak in ALT occurring after study treatment had ended. See Section 6.2.2 for definition of post-treatment period.

Outcome will be assumed missing (Missing At Random) from the timepoint when subjects first receive PEG-interferon or other immunomodulator therapies.

- Time to Maximum ALT (ALT must be greater than 3xULN) during 36 weeks (treatment + follow up)

Time to maximum ALT (maximum peak in ALT) during 36 week (treatment + follow-up) is defined as time from baseline to the time of first peak in ALT.

For this analysis, taking PEG-interferon or other immunomodulator therapies will be ignored. Participants will be censored at the last record within the specified time period.
- Population summary: Turnbull estimate for median Time to Maximum ALT (>3xULN)

Missing data for variables in this group of estimands will be ignored, only available data will be summarized.

4.4. Exploratory Endpoint(s) Analyses

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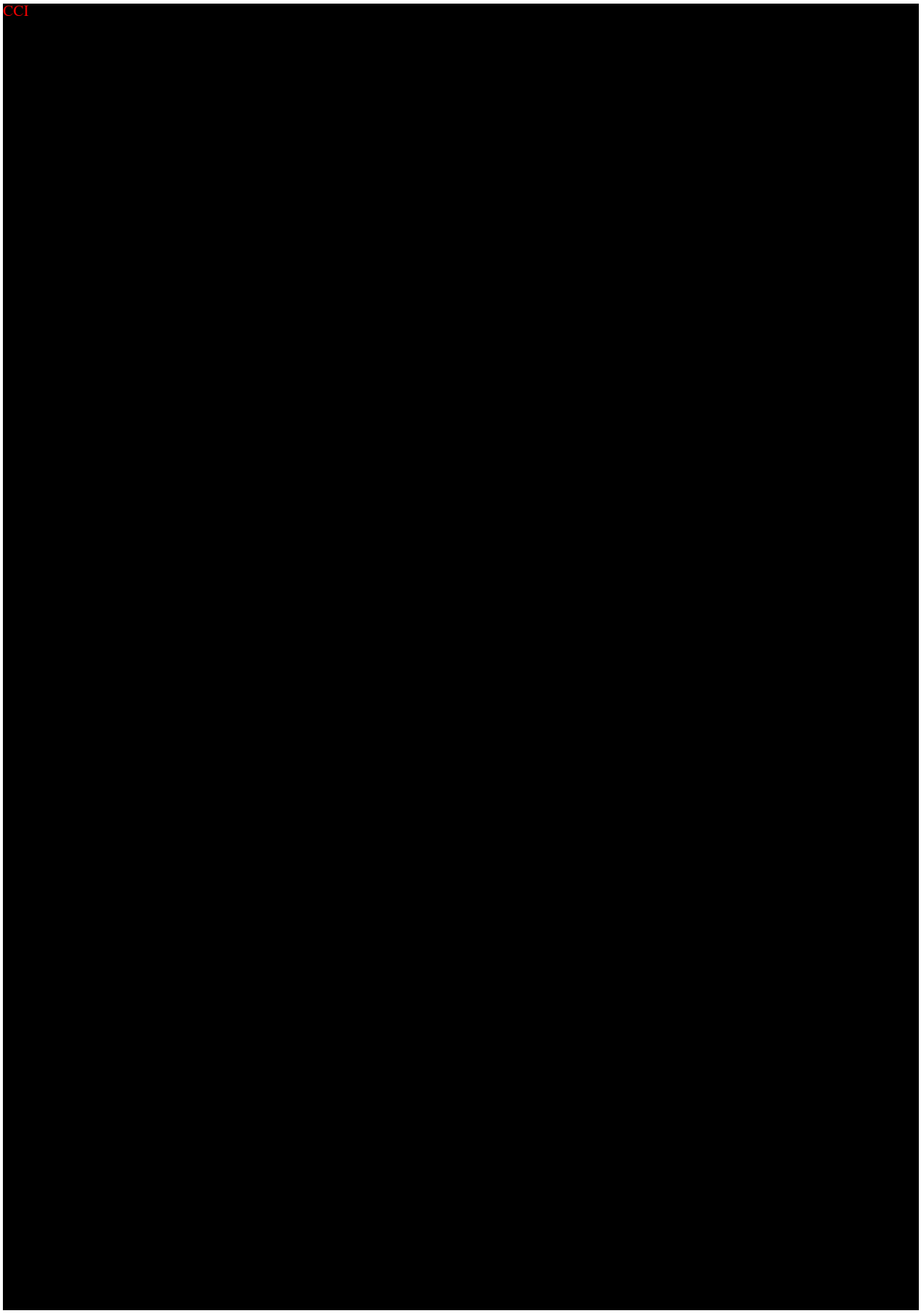

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4.5. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

4.5.1. Extent of Exposure

Extent of exposure will be summarized using summary statistics. Number of subjects with < 6 weeks, ≥6 – 12 weeks exposure will be presented, and the overall duration of exposure will be summarized. Study intervention compliance will be summarized as described in Section 6.1.5.

Number of days of exposure to study drug for each participant 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 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 following 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. Non-serious AEs by SOC and PT
14. Non-serious drug-related AEs by overall frequency
15. Serious fatal and non-fatal 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 Section 6.2.7.

Deaths will be listed including primary cause of death.

4.5.2.1. Adverse Events of Special Interest

The following AEs of special interest will be reported:

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

An up to date list of specific MedDRA Queries (SMQs), high level terms (HLTs) or individual preferred terms (PTs) used to identify 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 and renal injury) to explore the data in more detail if data permits.

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

4.5.2.2. COVID-19 Assessment and COVID-19 AEs

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

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

COVID-19 assessments for participants with COVID-19 AEs will be summarized.

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

4.5.2.3. Impact of COVID-19 Pandemic on Safety Results

The impact of the COVID-19 pandemic on the safety results will be assessed. Pandemic measures began in different countries at different times. A dataset containing the date when pandemic measures began, as determined by the GSK country Issue Management Teams (IMT), will be used to determine the start date of each wave of pandemic measures within each country.

Summaries of the incidence rates of AEs, Common AEs, SAEs and Grade 3 and 4 AEs / severe AEs, before (AE onset date < pandemic measure start date) and after (AE onset date >= pandemic measure start date) the start of the COVID-19 pandemic will be produced, overall and by country/region, gender and age group (<18, 18-64, >=65).

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.

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, 2017].

Summary of post-baseline hepatobiliary laboratory abnormalities will be provided based on both planned and unplanned assessments (e.g. unscheduled visit, monitoring event).

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 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). The summaries will be produced for worst case post baseline only.

4.6. Other Analyses

4.6.1. Subgroup analyses

The list of subgroups below will be used in descriptive summaries of baseline characteristics and may be examined for study outcomes. Summary statistics (n(%)) for the number of responders of the HBsAg <LLOQ response rate will be reported by subgroups. No statistical comparison between subgroups will be performed.

If the percentage of participants is small within a particular subgroup, then the subgroup categories may be redefined. Given the small sample size of this study, if all subjects fall into one single subgroup category, then subgroup analyses for study outcomes will not be necessary and therefore will not be performed. Additional subgroups of clinical interest may also be considered.

Subgroup	Categories
Baseline HBsAg	Low (≤ 3 log10 IU/mL), High (>3log10 IU/mL) <=3, >3-3.5, >3.5-4 and >4 Low (<=3000 IU/mL), High (>3000 IU/mL)
Duration of Hep B Infection	<5 years, ≥ 5 years - <10 years, ≥ 10 years - <20 years, ≥ 20 years
Hep B Infection Route	Vertical transmission (e.g., from mother to child); From childhood; Injectable Drugs; Sexual Contact; Blood transfusion; Work exposure (e.g., needle stick); Unknown; Other/prefer not to say
Baseline viral genotype	B, C, Other, Unknown
Baseline BMI	<30, ≥30

4.7. Interim Analyses

Data will be incorporated into regular safety reviews by an IDMC and may be used to supplement the safety data review for the Phase IIb B-Clear study [GSK Document Number 2019N420582_00, Study 209668].

Details of study interim analyses are provided in a 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 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
Section 4.3.1.3, single table presented for: Time to Event Variable • Time to Maximum ALT (ALT must be greater than 3xULN) during 36 weeks of	Now presenting 4 tables instead of one: • Summary of Time to First Occurrence of Maximum ALT	• At the time of writing the protocol, it was expected that only one peak in ALT would be seen. We have since seen on other studies, that more than one peak can occur.

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
treatment + follow up Population summary: Turnbull estimate for median Time to Maximum ALT (>3xULN)	• Summary of Time to First Occurrence of Maximum ALT during 12 week treatment period • Summary of Time to First Occurrence of Maximum ALT after GSK3228836 treatment • Summary of Time to Maximum ALT	• The first analysis, is the analysis which was originally intended for the study looking at the first peak. • The other analyses reflect our newly updated learning for ALT, since the time of writing the protocol.

5. SAMPLE SIZE DETERMINATION

Approximately 20 participants will be targeted to assign to treatment.

Primary Endpoint

It is assumed that the number of participants achieving serum HBsAg level <LLOQ by Week 12 without the use of PEG-interferon or other immunomodulator therapies follows a Binomial distribution, with a weakly informative prior beta(0.5, 0.5) for the true response. The precision for a range of true response rates with 95% credible intervals are shown in Table 2.

Table 2 95% Credible Interval for Percent of Participants achieving HBsAg <LLOQ by Week 12

Sample size per arm	Number of Participants with HBsAg <LLOQ	Percent of Participants with HBsAg <LLOQ	95% Credible Interval*
20	8	40%	20% – 61%
	10	50%	29% - 71%
	12	60%	39% - 80%
	14	70%	50% - 87%
	16	80%	61% - 94%

*95% highest posterior density interval

With 20 participants, if the observed response rate is 60%, 70% and 80%, then the lower bound of the 95% credible interval excludes values below 39%, 50% and 61%, respectively. The posterior probability that the percent of participants achieving HBsAg<LLOQ by Week 12 is greater than 50% 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 percentage of participants achieving serum HBsAg level <LLOQ exceeds 50% (desired for further mechanistic exploration of the therapeutic effects of GSK3228836 via intrahepatic immunophenotyping) are shown in Table 3, for various assumed sample sizes and true response rates. A weakly informative prior beta (0.5, 0.5) is used. With a sample size of 20 participants, if there are at least 12 participants achieving HBsAg <LLOQ (observed percent of 60%) then the posterior probability that the true percent is greater than 50% will be greater than 75%.

Table 3 Study Operating Characteristics by Sample Size

Criteria	Sample Size	Min N (%) of Participants with HBsAg <LLOQ required for meeting Criteria	Probability of Meeting Criteria if True Response Rate =						
			30%	40%	50%	60%	65%	70%	75%
Probability (true response rate >50%)>75%	10	7 (70%)	1%	5%	17%	38%	51%	65%	78%
	15	9 (60%)	2%	10%	30%	61%	75%	87%	94%
	18	11 (61%)	1%	6%	24%	56%	73%	86%	94%
	20	**12 (60%)**	**1%**	**6%**	**25%**	**60%**	**76%**	**89%**	**96%**
	24	14 (58%)	0%	5%	27%	65%	82%	93%	98%
	30	17 (57%)	0%	5%	29%	71%	87%	96%	99%

* response rate defined as percent of participants achieving HBsAg<LLOQ by Week 12

Based on these operating characteristics, for a true response rate of 60%, the proposed sample-size of 20 has 60% probability of confirming a true rate of at least 50%, and if the true rate is 70%, there is an 89% chance of confirming a true rate greater than 50%.

Biomarker Endpoints

Given a sample size of 20, the confidence intervals for the ratio in change from baseline in RNAseq (signature) scores between those achieving versus not achieving HBsAg<LLOQ are shown below, assuming a range of effect sizes and between-participant coefficients of variation (CVb).

Example of one scenario with 60% of the participants achieving HBsAg < LLOQ is given below. With relatively smaller between participant variability and larger effect size, a sample size of 20 is appropriate to achieve an acceptable level of precision in detecting the differential responses in biomarker outcomes corresponding to HBsAg responses. For example, in the scenario where 60% of participants achieve HBsAg <LLOQ, if CVb = 0.4, the 95% CI excludes 1 for geometric mean ratios of 0.6 and below, and for 1.7 and above.

12 Participants (60%) Achieving HBsAg<LLOQ)							
CVb	95% CI for Ratio of Geometric Mean of Fold Change from Baseline for Participants achieving vs. not achieving HBsAg<LLOQ						
	0.6	0.8	1	1.2	1.4	1.7	2.0
0.2	**[0.50, 0.73]**	**[0.66, 0.97]**	[0.83, 1.21]	[0.99, 1.45]	**[1.16, 1.69]**	**[1.41, 2.06]**	**[1.65, 2.42]**
0.4	**[0.41, 0.87]**	[0.55, 1.16]	[0.69, 1.45]	[0.83, 1.74]	[0.97, 2.03]	**[1.17, 2.46]**	**[1.38, 2.89]**
0.6	[0.35, 1.02]	[0.47, 1.36]	[0.59, 1.70]	[0.71, 2.04]	[0.82, 2.38]	[1.00, 2.89]	**[1.18, 3.40]**
0.8	[0.31, 1.18]	[0.41, 1.57]	[0.51, 1.96]	[0.61, 2.36]	[0.71, 2.75]	[0.87, 3.34]	**[1.02, 3.93]**
1	[0.27, 1.33]	[0.36, 1.78]	[0.45, 2.22]	[0.54, 2.67]	[0.63, 3.11]	[0.77, 3.78]	[0.90, 4.44]
1.5	[0.21, 1.70]	[0.28, 2.27]	[0.35, 2.83]	[0.42, 3.40]	[0.49, 3.97]	[0.60, 4.81]	[0.71, 5.66]

There are no plans for sample size re-estimation. In certain cases, including but not limited to higher than anticipated drop-out rate, higher than anticipated rates of efficacy, or large variability in ALT flare patterns, the sample size may be increased to no more than 24.

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, and will be based on the Screened Analysis Set. 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.

A listing and summary of number of planned and completed FNA’s per patient will be presented.

6.1.2. Demographic and Baseline Characteristics

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 hypertension, NSAID, 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.

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.

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 freezing the database to ensure all important deviations 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% and ≥80% - 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.

Additionally, if greater than 5% 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 Derivations Rule

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. 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[1] ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date[1] ≤ Off Treatment Day 1 – 1 day
Post-Treatment	Date[1] ≥ Off Treatment Day 1

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

6.2.3. Study Day and Reference Dates

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

The study day is calculated as below:

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

6.2.4. Assessment Windows for Early Termination

Unless otherwise specified, unscheduled visits will not be mapped to a visit window, and will be listed only.

Assessment for Early Termination visits are as follows:

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint (Days)	Ending Timepoint (Days)	
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 Day 15
		22	19	25	Week 4
		1+7(x-1)	1+7(x-1)-3	1+7(x-1)+3	Week x
		85	82	88	OT-Week 1
		92	89	95	OT-Week 2
		106	96	119	OT-Week 4
		134	120	147	OT-Week 8
		162	148	175	OT-Week 12
		190	176	203	OT-Week 16
		218	204	231	OT-Week 20
		246	232	246	OT-Week 24

6.2.5. Assessment Windows for Analyses and Multiple Measurements at One Analysis Timepoint

The primary endpoint is defined as "Achieving serum HBsAg level <LLOQ at any time point up to and including Week 12 without the use of PEG-interferon or other immunomodulator therapies". No analysis window will be assigned and all values up to Week 12, including unscheduled visit results, will be considered. The upper bound of the analysis date is defined as:

Target day of the Week 12 visit (78) + 3 days

Note: 3 days as allowed for the Week 12 dosing.

For secondary endpoints:

- sustained Virologic Response (HBsAg <LLOQ and HBV DNA <LLOQ)
- sustained HBsAg Response (HBsAg <LLOQ) for 24 weeks

after the **planned** end of GSK3228836 treatment (all values including unscheduled visit results will be considered):

	Parameter (if applicable)	Target Study Day	Analysis Window		Analysis Timepoint	Protocol Visit
			Beginning Timepoint	Ending Timepoint		
Efficacy	HBsAg and HBV DNA; or HBsAg	78	64	98	End of '836 Treatment – Planned	Week 12
		134	99	154	Post '836 treatment Week 8 – Planned	Week 20
		190	155	210	Post '836 treatment Week 16 – Planned	Week 28
		246	211	266	Post '836 treatment Week 24 – Planned	Week 36

For secondary endpoints:

- sustained Virologic Response(HBsAg <LLOQ and HBV DNA<LLOQ)
- sustained HBsAg Response(HBsAg <LLOQ) 24 weeks

after the **actual** end of GSK3228836 treatment (all values including unscheduled visit results will be considered):

	Parameter (if applicable)	Target Study Day	Analysis Window		Analysis Timepoint	Protocol Visit
			Beginning Timepoint	Ending Timepoint		
Efficacy	HBsAg and HBV DNA; or HBsAg	X = Target study day of the last treatment dose	Max (X-14, 1)	X+20	End of '836 Treatment - Actual	-
		X + 56	X+21	X + 76	Post '836 treatment Week 8 - Actual	-
		X + 112	X+ 77	X + 132	Post '836 treatment	-

	Parameter (if applicable)	Target Study Day	Analysis Window		Analysis Timepoint	Protocol Visit
			Beginning Timepoint	Ending Timepoint		
					Week 16 - Actual	
		X + 168	X + 133	X + 188	Post '836 treatment Week 24 - Actual	-

1. For example, if the subject received the last treatment dosing at the W2/D8 visit, then the target day is 8; if the subject received the last treatment dosing at the W2/D11 visit (loading schedule), then the target day is 11; if the subject received the last treatment dosing at the W9/D57 visit, then the target day is 57.

For the End of '836 Treatment Analysis Timepoint, if there are multiple values within an analysis window the following rules will be applied:

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

For Post '836 Treatment Analysis Timepoints, if there are multiple values within an analysis window the following rules will be applied:

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 in 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.

6.2.6. 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 • Assessments on unscheduled visit will not be included in the tables of summary statistics by visit but will be included in the associated listings. Also, such assessments on unscheduled visit will be used for the "any time on-treatment" or "Any visit post-baseline" time point. • If there are multiple assessments on scheduled visit within visit window, will query the site to identify the valid assessment as the assessment for the scheduled visit. • If after window assignment of Early Termination visits there are multiple valid assessments of a parameter within the same window, then the following hierarchy will be used to determine the value to be used for summary statistics of observed values: o the assessment closest to the window target Study Day; o if there are multiple assessments equidistant from the target Study Day, then the mean of these values will be used. • 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.

6.2.7. 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.
• However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below.
• Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.</td></tr>
<tr><td>Adverse Events</td><td>• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table><tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:

o If month and year of start date = month and year of study intervention start date, then</td></tr></table></td></tr>
</table>

Element	Reporting Detail	
		▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month. ▪ Else set start date = study intervention start date. Else set start date = 1st of month.
	Missing start day and month	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing: o If year of start date = year of study intervention start date, then ▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. ▪ Else set start date = study intervention start date. 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. Else if study intervention start date is not missing:

Element	Reporting Detail	
		○ If month and year of start date = month and year of study intervention start date, then ▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month. ▪ Else set start date = study intervention start date. Else set start date = 1st of month.
	Missing start day and month	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing: ○ If year of start date = year of study intervention start date, then ▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. ▪ Else set start date = study. intervention start date. 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

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