Statistical Analysis Plan Amendment 3

Study ID: 214760

Official Title of Study: Four -part, Randomized, Double-blind (Part 1, 2A, 3 and 4), Multi-center, Placebo-controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GSK3965193 Monotherapy in Healthy Participants and in Participants Living with Chronic Hepatitis B Infection; and GSK3965193 in Combination with Bepirovirsen in Participants Living with Chronic Hepatitis B Infection

NCT number: NCT05330455

Date of Document: 07-April-2026

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title:	Four -part, Randomized, Double-blind (Part 1, 2A, 3 and 4), Multi-center, Placebo-controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GSK3965193 Monotherapy in Healthy Participants and in Participants Living with Chronic Hepatitis B Infection; and GSK3965193 in Combination with Bepirovirsen in Participants Living with Chronic Hepatitis B Infection
Study Number:	214760
Compound Number:	GSK3965193, Bepirovirsen (GSK3228836)
Abbreviated Title:	PH 1/2, Study of GSK3965193 in Healthy Participants and alone and in combination with Bepirovirsen in Participants Living with Chronic Hepatitis B Infection

Sponsor Name: GSK Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
Registry name	Registry ID
Clintrials.gov	2021-005117-13

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	30 May 2024	Protocol Amendment Version 8.0 (26 March 2024)	Original Version	Statistical Analysis Plan for Part 3
SAP Amendment 1	26 May 2025	Protocol Amendment Version 10.0 (10 March 2025)	Section 1.: Details on Intercurrent event have been updated	Clarification
			Section 3: Additional text has been added for Randomized, PK and PD analysis set in defining the population and how the data will be reported	Clarification
			Section 4. Added the imputation value to be used for the biomarkers value if they turn out to be LLOQ or TND. Methodology has been added for the derivation of log10 Change from Baseline for HBsAg and Maximum reduction of log10 HBsAg	Clarification

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Removed CCI [redacted] CCI [redacted] CCI [redacted] from Parameters list in the Table 4 as they are in the collect and hold strategy list Methodology to summarize laboratory, vital signs and ECG Data has been updated Additional summaries related to TEAEs are added	
			Section 6. Updated the information on PCI criteria and Assessment window	Clarification
SAP Amendment 2	01 August 2025	Protocol Amendment Version 10.0 (10 March 2025)	4.4.2.4 Additional details on the analysis to understand target engagement added	Detailed specification
SAP Amendment 3	07 Apr 2026	Protocol Amendment Version 10.0 (10 March 2025)	Section 4.3.1.2.3: Updated the derivation of TEAEs for Bepi period	Clarification and Detailed specification

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Section 4.4.3: Reduced Number of PK parameters which will be assessed for Bepi period	

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses for study Part 3 to be included in the Clinical Study Report for Protocol 214760. All details of the interim analyses will be outlined in a separate Interim Analysis Charter.

Statistical Analysis Plan for parts 1 and 2 are documented in a separate plan document and stored in Veeva Vault (TMF-14543291).

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Part 3 and Part 4 (participants living with chronic hepatitis B infection [PLWCHB])	
Primary	
• To assess the safety and tolerability of oral administration of GSK3965193 monotherapy (Part 3) and in combination with bepirovirsen (Part 4)	• Incidence of AEs, SAEs, withdrawals due to AEs • Incidence of clinically significant laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs, cardiac parameters (electrocardiogram), and sensory nerve conduction
• To evaluate pharmacodynamic (PD) effect of GSK3965193 monotherapy in PLWCHB (Part 3)	• Maximum reduction of serum HBsAg levels from baseline CCI [redacted] CCI [redacted] CCI [redacted]
Secondary	
• To evaluate the PK characteristics of repeat doses of GSK3965193 in PLWCHB (Part 3)	• AUC(0-tau), Cmax, Tmax, and apparent terminal half-life (T1/2) will be calculated as data permits
• To evaluate pharmacodynamic (PD) effect of GSK3965193 monotherapy in PLWCHB (Part 3)	• ≥0.5x log IU/mL reduction of serum HBsAg levels from baseline anytime during the study (on-treatment and post-treatment)
• To assess the safety and tolerability of bepirovirsen monotherapy in PLWCHB who have completed GSK3965193/placebo monotherapy (Part 3)	• Incidence of AEs, SAEs, withdrawals due to AEs • Incidence of clinically significant laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

1.1.1. Primary Estimand

The primary clinical question of interest is*: What is the difference in maximum reduction of HBsAg from baseline* CCI [redacted] CCI [redacted] *) in GSK3965193 vs. placebo in participants living with chronic hepatitis B infection, prior to prohibited medication use or temporary/permanent discontinuation of treatment?*

Attributes of Estimand:

Variable/Endpoint	Treatment	Population	Population Summary
Maximum reduction of serum HBsAg levels from baseline CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]	GSK3965193 and Placebo	PLWCHB treated on stable nucleos(t)ide analog (NA) therapy therapy	Mean of maximum reduction in change from baseline over all patients in GSK3965193 and Placebo. Treatment difference (GSK3965193 – Placebo).

Intercurrent Event			Strategy	
Intercurrent Event	**Details on the Intercurrent Event**	**Decision on the usage of data**	**Strategy**	**Rationale**
Temporary or permanent discontinuation of dosing	Temporary or permanent discontinuation of IP dose include any of the following occurrences: • Missing 2 or more consecutive doses • Permanent discontinuation from treatment • Permanent discontinuation from study	Data from Day 1 (post randomization) until start of temporary discontinuation or permanent discontinuation.	While on-treatment	Data will only be used until the start of temporary discontinuation or date of permanent discontinuation. This is to capture that the participant could not tolerate the study treatment as planned.

CCI [redacted]

CCI [redacted]

1.1.2. Secondary Estimand

The primary clinical question of interest is*: What is the difference in the proportion of responders (reduction of serum HBsAg levels ³0.5x log IU/mL) from baseline* CCI [redacted] *) of GSK3965193 vs. placebo in participants living with chronic hepatitis B prior to prohibited medication use or temporary/permanent discontinuation of treatment?*

Attributes of Estimand:

Variable/Endpoint	Treatment	Population	Population Summary
≥0.5 log IU/mL reduction in serum HBsAg levels from baseline CCI [redacted]	GSK3965193 and Placebo	PLWCHB treated on stable NA therapy	Proportion of responders

Intercurrent events will be handled in the same way as the primary endpoint (see Section 1.1.1).

1.1.3. Supplementary Estimand

The supplementary estimand will only be explored if >20% (4 or more) participants experience any intercurrent event.

The primary clinical question of interest is*: What is the difference in maximum reduction of HBsAg from baseline* CCI [redacted] *) of GSK3965193 treatment vs. placebo on participants living with chronic hepatitis B infection regardless of usage of prohibited medication or temporary/permanent discontinuation?*

Attributes of Estimand:

Variable/Endpoint	Treatment	Population	Population Summary
Maximum reduction of serum HBsAg levels from baseline CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]	GSK3965193 and Placebo	PLWCHB treated on stable NA therapy	Mean of maximum reduction in change from baseline over all patients in GSK3965193 and Placebo. Treatment difference (GSK3965193 – Placebo).

Intercurrent Event			Strategy	
Intercurrent Event	**Details on the Intercurrent event**	**Decision on the usage of data**	**Strategy**	**Rationale**
Temporary or permanent discontinuation of dosing	Temporary or permanent discontinuation of dose may include any of the following occurrences: • Missing 2 or more consecutive doses • Permanent discontinuation from treatment • Permanent discontinuation from study	Any data available will be used	Treatment policy strategy	Observed data will be used as is to estimate the treatment effect in the scenario where the temporary or permanent discontinuation of dosing had not occurred.

1.2. Study Design

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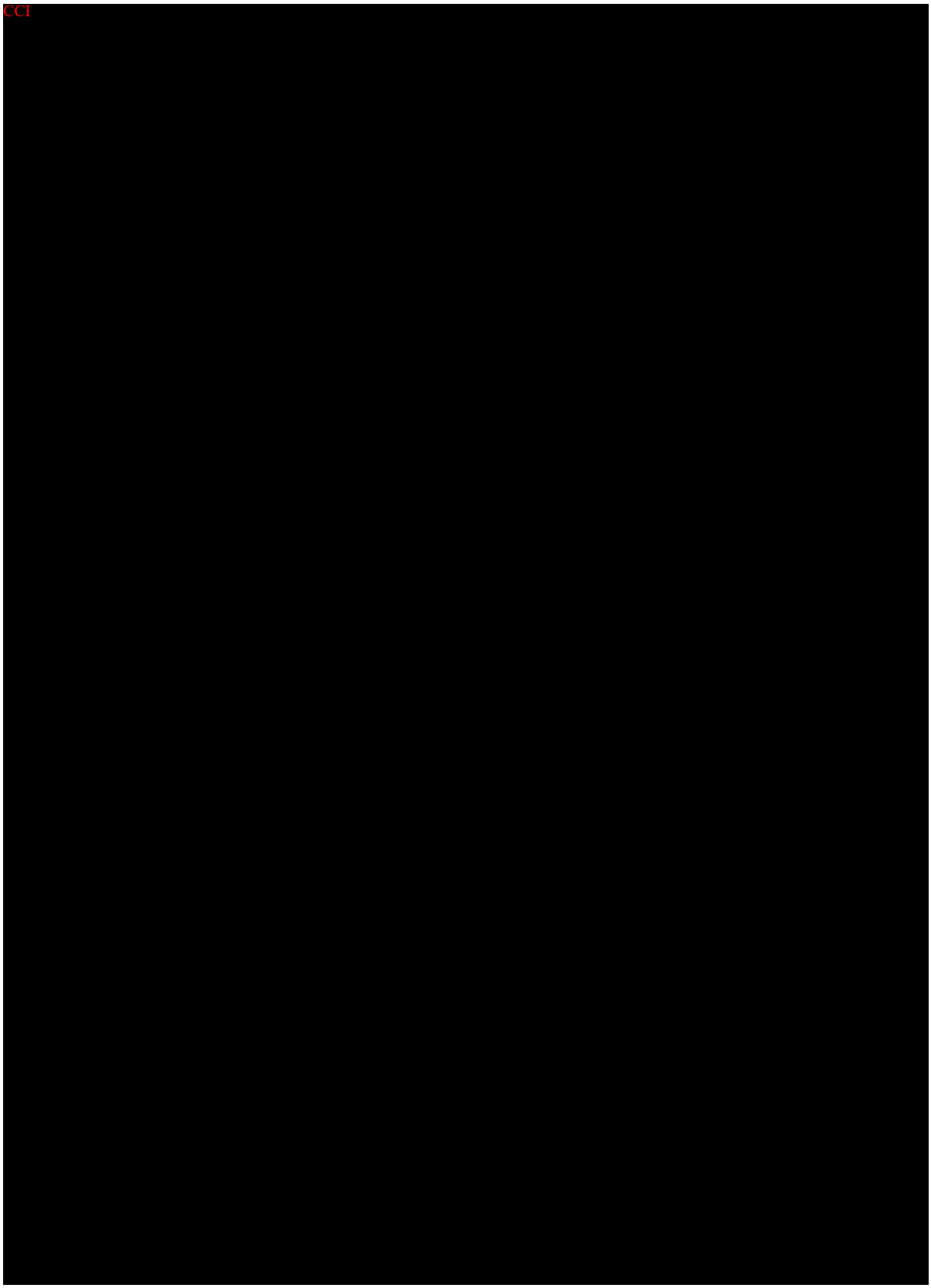

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2. STATISTICAL HYPOTHESES

There are no formal hypothesis that will be statistically tested in this study.

2.1. Multiplicity Adjustment

Not applicable as no formal statistical hypothesis will be tested.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	Study Population
Enrolled	All participants who passed the screening and entered the study (who were randomized and/or received or not received study intervention or underwent a post-screening procedure). NOTE: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled Analysis set as they did not enter the study.	Study Population

Analysis Set	Definition / Criteria	Analyses Evaluated
Randomized	All participants who were randomly assigned to study intervention. NOTE: The screened, enrolled and randomized sets must be nested, i.e. the enrolled set must be a subset of the screened set, the randomized set must be a subset of the enrolled set. Data will be reported according to randomized treatment.	Study Population
Safety	All participants in randomized set who received at least one dose of study intervention. Participants will be assigned to the actual study intervention group if they received that intervention for more than 50% of the cumulative dose.	Safety
Pharmacokinetic (PK)	All participants in the Safety analysis set who had at least one non-missing PK assessment, with non-quantifiable (NQ) values considered as non-missing. Furthermore, participants must not have a history of taking prohibited therapies (as per the exclusion criteria), nor have participated in previous clinical studies that are prohibited in the protocol exclusion criteria that might affect the PK exposure assessment. Data will be reported according to the actual study intervention.	PK
Pharmacodynamic (PD)	All participants in the Safety analysis set who had at least one non-missing PD assessment and have neither taken any prohibited medication nor participated in previous clinical studies that are prohibited, as defined in the protocol exclusion criteria, which might affect the efficacy assessment. NOTE: Data will be summarized based on randomized treatment.	PD
Bepirovirsen Extension (OBE)	All participants who are eligible and opted for Bepirovirsen extension and had received at least one dose of Bepirovirsen will be considered.	Safety, PK and PD Bepirovirsen

4. STATISTICAL ANALYSES

4.1. General Considerations

Participant-level data will be available interactively via Reporting and Analysis Plan Improving Design and Delivery of Output Data Viewer (RAPIDO DV) at Study Analysis Complete (SAC). Only selected listings specified in the Output Programming Specification (OPS) will be created in a static fashion.

The term "Analysis Set" in the SAP will be referred to as "Population" in displays. The term "Participant" in the SAP will be referred to as "Subject" and/or "Patient" in the displays of the OPS document.

The term "Study intervention" and "Study Treatment" are used interchangeably unless specified.

A list of all planned displays will be provided in the OPS document.

Adverse event analysis will be based on GSK Core Data Standards. All AE and SAE summaries will be by SOC and PT only unless otherwise specified.

If there are more than CCI [redacted] who choose to take part in the optional Bepirovirsen extension arm, then summary tables will be produced. If less than CCI [redacted] choose to participate, then only listings will be produced.

4.1.1. General Methodology

Summary tables unless otherwise specified will include the following descriptive statistics at a minimum -

- For continuous data (untransformed): n, mean, standard deviation (SD), 95% CI, median, minimum, and maximum.
- For continuous data (log transformed): n, Geometric Mean (GM), 95% CI, between subject coefficient of variation (%CV_b)
- For categorical data: number and percentage of participants in each category

Where appropriate, statistical modelling will be performed, and point estimates with 95% Confidence Interval (CIs).

HBV DNA, HBsAg, and anti-HBs levels that are below the Lower Limit of Quantification (LLOQ) or target not detected (TND) will be imputed for summaries of actual values and change from baseline.

Table 1 Imputation details for LLOQ values of Biomarker

Biomarker	LLOQ	Imputing Value
HBV DNA	10 IU/mL	9.9 IU/mL
HBV DNA	20 IU/mL	19.9 IU/mL
HBsAg	0.05 IU/mL	0.04 IU/mL
anti-HBs	4 IU/mL	3.99 IU/mL

Table 2 Imputation details for TND values of Biomarker

Biomarker	Limit of Detection	Imputing Value
HBV DNA	2.4 IU/mL	2.3 IU/mL
HBcrAg	2.0 log10 U/mL	1.99 log10 U/mL
HBV RNA	309 copies/mL (Assay LOD)	308 copies/mL
anti-HBs	2.0 IU/mL	1.99 IU/mL

For all other laboratory values, if a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of decimal places in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. Similarly, if a character value starting with '<=x' or '>=x' is present, x will be used as the corresponding numeric value.

- Example 1: 2 Decimal places: = '< x' becomes x – 0.01
- Example 2: 1 Decimal places: = '> x' becomes x + 0.1
- Example 3: 0 Decimal places = '< x' becomes x – 1
- Example 4: 2 Decimal places: = '<= x' becomes x
- Example 5: 1 Decimal places: = '<= x' becomes x
- Example 6: 0 Decimal places: = '<= x' becomes x

Derivation of log10 Change from Baseline for HBsAg and Maximum reduction of log10 HBsAg:

- Compute log10 HBsAg at baseline by converting the baseline HBsAg value to its logarithm base 10 form
- For all post-baseline visits, compute corresponding log10 HBsAg by converting the actual HBsAg values to their logarithm base 10 form

- Compute the change in log10 HBsAg values from baseline for each post-baseline visit as: Log10 HBsAg at post baseline - Log10 HBsAg at baseline
- Maximum reduction in log10 HBsAg value is the minimum value of the calculated change from baseline at any post-baseline visit within the specified timeframe (CCI CCI)

4.1.2. Bayesian Methodology

The main statistical analyses will be carried out using a Bayesian framework.

Prior distributions are specified for each analysis. Posterior mean and 95% credible intervals (CrIs) along with the posterior probabilities of crossing pre-specified values of interest will be displayed, unless otherwise stated.

4.1.3. Baseline Definition

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

Table 3 Baseline definition of different parameters for GSK3965193 Monotherapy

Parameters	Study Assessment Visit considered as Baseline for GSK3965193 monotherapy	Derivation of Baseline
12-Lead ECG	Pre-dose Day 1	Average of triplicate ECG measurements
Vital Sign	Pre-dose Day 1	Average of triplicate Vital Sign parameters measurement
Sensory nerve conduction test (SNCV)	Screening, Day -1	The best measurement out of Screening and Day -1 will be considered as baseline, where best being the higher measurement.
Nerve Function	Screening, Day -1	The worst measurement out of Screening and Day -1 will be considered as baseline, where worst being the higher total score.
Cognitive assessment	Day -1 or Prior to dosing Day 1 (whichever is latest)	Single measurement
Clinical laboratory (Chemistry and hematology)	Day -1 or Prior to dosing Day 1 (whichever is latest)	Single measurement
Liver Function	Day -1 or Prior to dosing Day 1 (whichever is latest)	Single measurement
Prothrombin time (PT), international normalized ratio	Day -1 or Prior to dosing Day 1 (whichever is latest)	Single measurement
Urinalysis	Day -1 or Prior to dosing Day 1 (whichever is latest)	Single measurement

Parameters	Study Assessment Visit considered as Baseline for GSK3965193 monotherapy	Derivation of Baseline
Urine albumin-creatinine ratio (ACR)	Day -1 or Prior to dosing Day 1 (whichever is latest)	Single measurement
HBsAg, HBV DNA	Prior to dosing Day 1	Single measurement
CCI	CCI CCI	CCI

Table 4 Baseline definition of different parameters in optional Bepirovirsen monotherapy

Parameters	Study Assessment Visit considered as Baseline for Optional Bepirovirsen arm	Derivation of Baseline
Vital Sign	CCI	Single measurement
Clinical laboratory (Chemistry and hematology)		
Urinalysis	CCI	Single measurement
Urine albumin-creatinine ratio (ACR)		
HBsAg, HBV DNA		

Note: Unscheduled visits prior to dosing will also be considered while deriving baseline.

4.2. Primary Endpoint(s) Analyses

The primary objectives of Part 3 are:

- To assess the safety and tolerability of oral administration of GSK3965193 monotherapy
- To evaluate PD effect of GSK3965193 monotherapy in PLWCHB

4.2.1. Definition of endpoints

The following endpoints will be assessed:

- Occurrence of AEs and SAEs
- Occurrence of clinically significant changes in laboratory values (hematology, clinical chemistry, and urinalysis), vital sign parameters, 12-lead ECG parameters, and sensory nerve conduction parameters
- Maximum reduction of HBsAg levels from baseline CCI CCI)

4.2.2. Main analytical approach

The safety analyses will be based on the safety set, unless otherwise specified.

All the PD analyses will be based on PD set, unless otherwise specified.

4.2.2.1. Adverse events, Serious Adverse events, and Adverse Event of Special Interest (AESI)

An adverse event (AE) is considered study treatment emergent if the AE onset or worsen date is on or after Study treatment start date.

For this part, TEAE will be derived as following:

- TEAE for GSK/Placebo = Date of First GSK/Placebo Dose ≤ Date of AE Onset/Worsening ≤ Date of GSK/Placebo Last Dose + 7 Days

Any AE which occurs outside the above-mentioned time window will not be considered as TEAE due to GSK3965193 or placebo.

All AE summaries will be based on treatment emergent events and summarised by treatment. Serious AE (SAE) summaries will be also based on all treatment emergent SAEs. All non-treatment emergent AEs and SAEs will be listed. The following displays for Adverse events will be generated:

Table 5 Details of Adverse Event Summaries

	GSK3965193 Monotherapy
AEs	Overview of all Adverse Events
	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term
	Summary of Treatment Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term
	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Maximum Grade
	Summary of Drug-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Maximum Grade
	Summary of Treatment Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrence)
	Summary of Common (>=10%) Treatment Emergent Non-Serious Adverse Events by Overall Frequency
SAEs	Summary of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Maximum Grade
	Summary of Serious Treatment Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term

	GSK3965193 Monotherapy
	Summary of Serious Fatal and Non-Fatal Drug-Related Treatment Emergent Adverse Events by Overall Frequency
	Summary of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)
AESI	Summary of Adverse Events of Special Interest by System Organ Class and Preferred Term

AEs will be coded using the latest version of Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary, to give a Preferred Term (PT) and a System Organ Class (SOC). These PTs and SOCs will be used when summarising the data. The severity of AEs and SAEs will be determined by the investigator according to the [Division of AIDS DAIDS, 2017] grading system Version 2.1, unless specified otherwise in the protocol.

4.2.2.2. Laboratory Data, Vital Signs and ECG Data

For laboratory (haematology, clinical chemistry, urinalysis), vital signs, and ECG data, the following will be summarized:

1. For selected parameters, values outside the Potential Clinical Importance (PCI) range at each visit will be summarized as clinically significant. All other parameters will be summarized based on normal range values.
2. Change from baseline values at each visit.

Additional ECG summaries:

- Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category
- Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category

Laboratory parameters will be graded using [DAIDS, 2017] grading system Version 2.1, Table for Grading the Severity of Adult and Paediatric Adverse Events.

RAPIDO listings will be generated for the laboratory parameters.

4.2.2.3. Sensory Nerve Conduction (SNCV), Nerve Function Examination, Cognitive assessment

Sensory nerve conduction test and nerve function examination will be performed at Baseline, CCI [redacted]. Nerve function will be conducted using Toronto Clinical Neuropathy Scoring System (TCNS).

Following summaries will be provided for SNCV and nerve function examination –

- Summary of Change from Baseline in Sensory Nerve Conduction by Visit and Treatment

- Summary of Nerve Conduction Shifts from Baseline
  - Incidents of participants having 25% decrease in nerve conduction velocity.
  - Incidents of participants having 50% decrease in nerve conduction amplitude.
- Summary of Change from Baseline in Nerve Function Examination by Visit and Treatment using TCNS
- Summary of Nerve Function Exam Shifts from Baseline
  - Incidents of participants having change from baseline ≥ 2-point increase with respect to the total score will be reported.
  - Incidents of participants having a ≥ 4-point increase.

Cognitive assessment will be conducted in case of neurocognitive symptoms observed using Modified Mini-Mental Status Exam (MMSE) and RAPIDO listings will be provided.

4.2.2.4. Pharmacodynamic (HBsAg)

Unless otherwise specified, all PD analysis will be reported using PD analysis set.

CCI [redacted]
CCI [redacted]
CCI [redacted]

CCI [redacted]
CCI [redacted].Following summaries will be provided -

- Summary of Change from Baseline in HBsAg by Visit and Treatment
- Summary of Time to Maximum Reduction in HBsAg

To estimate the mean of maximum reduction of serum HBsAg levels from baseline CCI [redacted], a Bayesian approach will be used. This approach will use Gumbel distribution F (x, α, β) as the likelihood function for the maximum log10 HBsAg reduction.

For each participant, a non-informative prior will be used with α and β is assumed to be known. The posterior distribution for α will be derived and the posterior probabilities P (mean of maximum log10 HBsAg reduction ≥ cutoff | data) will be obtained from the posterior distribution.

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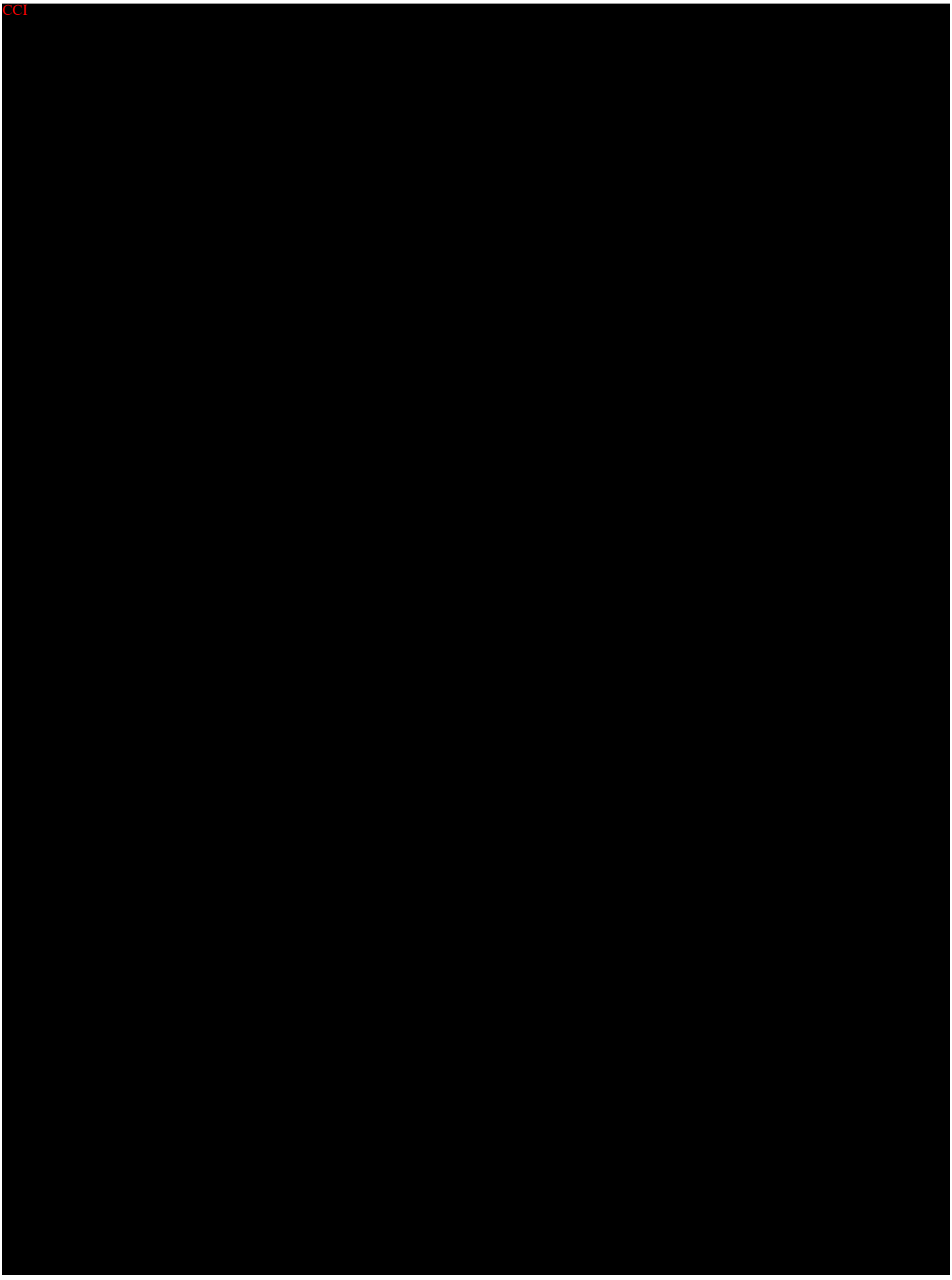

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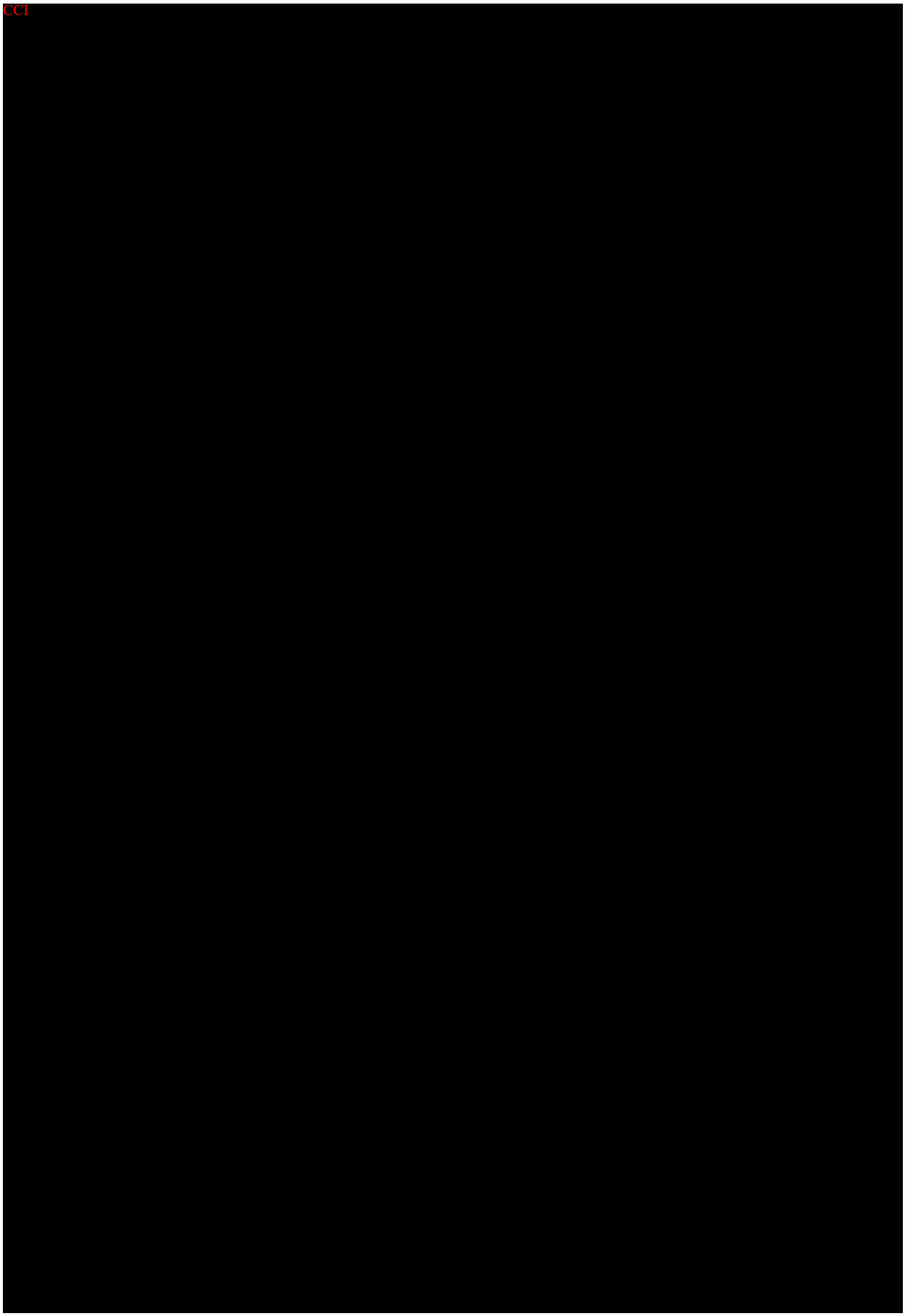

CCI [redacted]

4.2.3. Sensitivity analyses

Not Applicable

4.3. Secondary Endpoint(s) Analyses

The secondary objectives of Part 3 are following –

- To evaluate the PK characteristics of repeat doses of GSK3965193 in PLWCHB
- To evaluate PD effect of GSK3965193 monotherapy in PLWCHB
- To assess the safety and tolerability of bepirovirsen monotherapy in PLWCHB who have completed GSK3965193/placebo monotherapy.

4.3.1. Key secondary endpoint(s)

4.3.1.1. Definition of endpoints

The following endpoints will be assessed.

- AUC(0-tau), Cmax, Tmax, and apparent terminal half-life (T1/2) will be calculated as data permits.
- ≥0.5x log IU/mL reduction of serum HBsAg levels from baseline anytime during the study (on-treatment and post-treatment)
- Optional Bepirovirsen Extension Only: Incidence of AEs, SAEs, withdrawals due to AEs. Incidence of clinically significant laboratory parameters (haematology, clinical chemistry, urinalysis) and vital signs.

4.3.1.2. Main analytical approach

All secondary PK analyses will be based on the PK Analysis Set. PK analysis will be the responsibility of Clinical Pharmacology Modelling and Simulation (CPMS), GSK. Statistical analysis of the derived PK parameter data will be the responsibility of Clinical Statistics, GSK.

Plasma GSK3965193 concentration-time data will be analyzed by non-compartmental methods. Calculations for the final analysis will be based on the actual sampling time points recorded during the study. The various analyses will be conducted as permitted by data available.

For the calculation of the area under the concentration-time curve (AUC), the linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations (i.e., Linear Up/Log Down calculation method). A

minimum number of three data points (not including Cmax) should be used in calculating λz.

Unless otherwise specified, all PK analysis for GSK3965193 will be reported using PK set. PD analysis for GSK3965193 will be reported using PD set.

Safety, PK and PD of Bepirovirsen will be reported using the OBE set. These outputs will only be produced if more than 5 participants choose to take part in the optional Bepirovirsen extension arm.

4.3.1.2.1. Pharmacokinetic Analysis

PK parameters to be analyzed are listed below in Table 7.

Table 7 List of Pharmacokinetic parameters

PK Parameter	Parameter Description
Cmax	Maximum observed concentration, determined directly from the concentration-time data
Tmax	Time to reach Cmax, determined directly from the concentration-time
$AUC_{(0\text{-}tau)}$	Area under the concentration-time curve CCI [redacted] CCI [redacted] CCI [redacted]) using, the linear trapezoidal rule for each incremental trapezoid and the loge trapezoidal rule for each decremental trapezoid (linear up/log down calculation method in Phoenix WinNonlin).
Ctrough	Trough Concentration (CCI [redacted]
Terminal Half-life $T_{1/2}$	Apparent terminal half-life will be calculated after first dosing CCI [redacted] CCI [redacted]) and last dose CCI [redacted]: $t1/2 = ln2/\lambda z$ Note: λ_z is terminal phase rate constant

PK concentrations sampled outside the PK sampling windows will be included in listings and in subject level figures but will not be included in summaries.

$AUC_{(0\text{-}tau)}$, Cmax, and Ctrough will be summarized by timepoint based on the log-transformed data. Tmax and t1/2 will be summarized by treatment and timepoint as applicable based on untransformed data.

The following figures will be produced:

- A by-participant graph of the concentration data over time, on linear and semilogarithmic scales
- Mean and median concentration +/- CI will be plotted on linear and semilogarithmic scales.

A by-participant listing of pharmacokinetic concentration values at each time point will be produced. All PK parameters will also be listed.

Model analysis for PK endpoints –

Table 8 Model Analysis Specification for Steady State

Endpoint(s)	
• Ctrough	
Analysis Method	
• Frequentist approach, Analysis of Variance	
Model Specification and Analysis for different parameters	
Steady State Analysis	Steady state will be assessed by analysing $\log_e$ transformed trough plasma concentration using Mixed Model with the following effects: • Fixed effect: Day • Random effect: Subject An unstructured covariance matrix will be considered for the G matrix describing the between subject variability. If this model fails to converge, alternative covariance structures may be considered such as Variance Component, Compound Symmetry, etc. Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure. The Kenwood and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. The coefficients of the slopes for the day CCI [redacted]) effect on log scale for each dose, along with 90% CI, will be used to determine whether steady state was achieved.

4.3.1.2.2. Pharmacodynamic Analysis

HBsAg will be collected CCI [redacted] GSK3965193 treatment period. Again, HBsAg will be collected from CCI [redacted] CCI [redacted]

Individual line plot will be provided for change from baseline for HBsAg levels GSK3965193 and Placebo CCI [redacted]

Following summaries will be provided -

- Proportion of PLWCHB who achieved HBsAg ≥ 0.5 log10 IU/mL decline and/or <LLOQ in HBsAg at any Visit during the Treatment

CCI

4.3.1.2.3. Adverse events, Serious Adverse events, and Adverse Event of Special Interest (AESI)

An AE is considered study treatment emergent if the AE onset date or worsen date is on or after study treatment start date.

For this part and for optional Bepirovirsen arm TEAE will be derived as following -

- TEAE for Bepirovirsen = Date of First Bepirovirsen Dose ≤ Date of AE Onset/Worsening

All AE summaries will be based on treatment emergent events and summarised by treatment. SAE summaries will also be based on treatment emergent SAEs. All non-treatment emergent AEs and SAEs will be listed. The following displays for Adverse events will be generated:

Table 10 Adverse event summary table for optional Bepirovirsen

	Optional Bepirovirsen Arm
AEs	Overview of all Adverse Events
	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term
	Summary of Treatment Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term
	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Maximum Grade
	Summary of Treatment Emergent Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade

	Optional Bepirovirsen Arm
	Summary of Treatment Emergent Common (>=10%) Non-Serious Drug-Related Treatment Emergent Adverse Events by Overall Frequency
	Summary of Treatment Emergent Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)
SAEs	Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term and Maximum Grade
	Summary of Treatment Emergent Serious Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term
	Summary of Treatment Emergent Serious Fatal and Non-Fatal Drug-Related Adverse Events by Overall Frequency
	Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)
	Summary of Deaths
AESI	Summary of Adverse Events related to ALT increase by System Organ Class and Preferred Term
	Summary of Adverse Events related to vascular inflammation and complement activation by System Organ Class and Preferred Term
	Summary of Adverse Events related to thrombocytopenia by System Organ Class and Preferred Term
	Summary of Adverse Events related to renal injury by System Organ Class and Preferred Term
	Summary of Adverse Events related to injection site reaction by System Organ Class and Preferred Term
	Summary of Adverse Events related to Neuropathy Events by System Organ Class and Preferred Term
	Summary of Adverse Events related to Neurocognitive Events by System Organ Class and Preferred Term

4.3.1.2.4. Laboratory Data, and Vital Sign

For laboratory data (haematology, clinical chemistry, urinalysis) and vital signs data, the following will be summarized:

1. For selected parameters, values outside the PCI range at each visit will be summarized as clinically significant. All other parameters will be summarized based on normal range values.
2. Change from baseline values at each visit.

Laboratory parameters will be graded using [DAIDS, 2017] Table for Grading the Severity of Adult and Paediatric Adverse Events Version 2.1.

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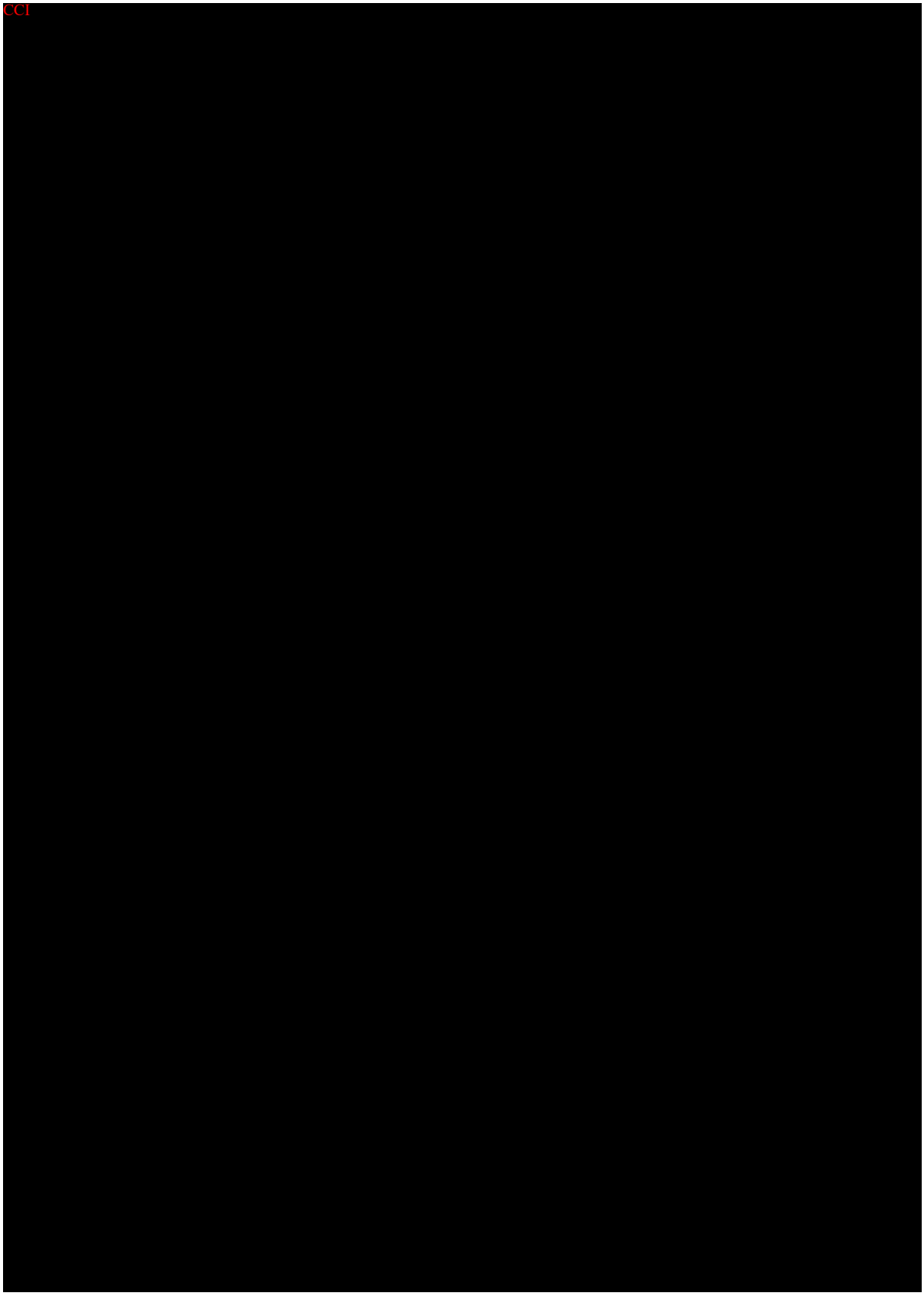

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4.5. Other Safety Analyses

The safety analyses will be based on the Safety Set for GSK3965193, and OBE set for Optional Bepirovirsen arm, unless otherwise specified.

4.5.1. Extent of Exposure

Extent of exposure to study intervention will be summarized. The number of days of exposure to study treatment (GSK3965193/Placebo) will be calculated based on the formula given below:

Duration of Exposure (in Days) = (Treatment Stop Date – Treatment Start Date) + 1

Participants who were randomized but did not report a treatment start date will be categorized as having zero days of exposure. The cumulative dose will be based on the formula:

Cumulative Dose = Sum of (Number of Exposure Days x Total Daily Dose)

Optional Bepirovirsen arm will be using 300mg Bepirovirsen Subcutaneous (SC) weekly dose until week 24 weekly, plus additional 300mg loading doses in weeks 1 and 2.

Number of participants with < 6 weeks, <=12 weeks, <=24 weeks exposure and > 24 weeks exposure will be presented, and overall duration will be summarized.

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

The cumulative dose will be based on the formula below:

Cumulative Dose = Number of Injections of 300mg x 300mg + Number of Loading doses x 300mg.

In case of temporary treatment hold for 1 or more than 1 day, for both GSK3965193 and for optional bepirovirsen arm, the following formula will be used for calculation of "Duration of Exposure".

Duration of Actual Exposure (in Days) = (Treatment Stop Date – Treatment Start Date + 1) – Number of days treatment on hold.

4.6. Other Analyses

4.6.1. Subgroup analyses

Not Applicable

4.6.2. Other variables and/or parameters

Not applicable.

4.7. Interim Analyses

In Part 3, CCI [redacted]

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Details of all interim analyses will be described in the Part 3 Interim Analysis Charter.

4.8. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 12.

Table 12 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
• Endpoints for Bepirovirsen optional arm	• Cardiac and ECG assessments have not been documented in SAP for Bepirovirsen Optional arm	• Cardiac assessment for Bepirovirsen arm has been removed as a secondary objective since cardiac assessment endpoint was incorrectly included in the protocol, and the data is not being collected on the database.
• Definition of Analysis Sets	• Definition of PD Analysis Set has been updated to remove any participant who takes a prohibited medication (as per the protocol) pre-treatment.	T CCI [redacted] • There was a need to define an additional analysis population to

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
	• An additional analysis set, Bepirovirsen Extension (OBE) set has been defined	evaluate participants who choose to take part in the optional Bepirovirsen arm
• Estimand	• Primary estimand and secondary estimand has been re-defined (clinical question, estimand policy strategy, and estimation of estimand) in Section 1.1.1 and Section 1.1.2 . Also, Supplementary estimand added in Section 1.1.3 as per the suggestion of Estimand SME group.	• Following clinical discussion, the estimand framework was updated to align with best practice.

5. SAMPLE SIZE DETERMINATION

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6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses for GSK3965193 vs Placebo part of the study will be based on the Safety Set and optional Bepirovirsen arm will be using Optional Bepirovirsen Extension set. A summary of the number of participants in each of the participant level analysis set will be provided.

This is a multicenter global study; enrolment will be presented by country and site.

6.1.1. Participant Disposition

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. For those who have neither completed nor withdrawn, they will be categorized as on study intervention or in follow up.

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

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, height/weight at screening and race will be summarized with descriptive statistics. In addition, the following age categories 18-33, 34-49, 50-65 and HBsAg categories at screening will be also presented for GSK3965193 monotherapy arm. Demographic data will be summarized using Safety Analysis Set.

For Optional Bepirovirsen Extension arm demographic characteristics including sex, age, ethnicity, race, height, and weight will be summarized with descriptive statistics using OBE set. Hepatitis B characteristics, as collected on the Hepatitis B Disease Characteristics eCRF, will be summarized using descriptive statistics and will be listed.

Past medical conditions and current medical conditions as of screening will be summarized respectively.

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 categorized 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 WHO Drug dictionaries. However, the summary will be based on WHO Drug dictionary only. 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.

6.1.5. Study Intervention Compliance

A summary of overall compliance based on the exposure data will be produced. Overall compliance will be summarized using descriptive statistics as well as

the categories <75%, 75%-100%, and >100%.

Compliance will be summarized both in terms of number of tablets/injections consumed 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

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

Laboratory test values will be considered of potential clinical importance if they fall outside the specified PCI ranges provided in the table compared to the baseline values.

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal or low abnormal.

Grading categories for laboratory tests are determined using the [DAIDS, 2017] grading system Version 2.1.

Table 14 List of PCI Ranges for selected Laboratory Parameters

Analyte	Unit	PCI Range
ALT	IU/L	>2XULN
Albumin	g/dL	≤3.5
Glomerular filtration rate (GFR)	mL/min /1.73m^2	≤60
INR		>1.25
Platelet count	x 10^9 /L	<140
Total bilirubin	umol/L	>1.25 x ULN

Table 15 List of PCI Ranges for ECG Parameters

ECG Parameters	Unit	PCI Range	
		Lower(<x)	Upper(>x)
Absolute QTc	msec	300	450
Absolute QTcF	msec	300	450
Uncorrected QT	msec	N/A	600
Heart rate	bpm	50	110
Absolute QRS interval	msec	70	120
Absolute PR Interval	msec	90	220
Change from Baseline:			
QTcF	msec	>60	

Table 16 List of PCI Ranges for Vital Sign Parameters

Vital Parameters	Unit	PCI Range	
		Lower(<x)	Upper(>x)
Pulse rate	bpm	50	110
Respiratory Rate	Breaths/min	8	20
Systolic blood pressure	mmHg	85	160
Diastolic Blood Pressure	mmHg	45	100

6.2.2. Study Period

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

Table 17 Study Period Definition

Study Intervention Period	Definition
Pre-GSK3965193/Placebo Period	Date < GSK3965193/Placebo Start Date
GSK3965193/Placebo Monotherapy Period	GSK3965193/Placebo Start Date ≤ Date < GSK3965193/Placebo Last Date
GSK3965193/Placebo Off treatment period	GSK3965193/Placebo last dose ≤Date < GSK3965193/Placebo Last date + 14 days
GSK3965193/Placebo Follow-up	GSK3965193/Placebo Last date + 14 days ≤ Date if the participant doesn't take part in the optional bepirovirsen extension or GSK3965193 Off treatment period ≤ Date < Bepirovirsen Treatment Period Start date
Bepirovirsen Treatment Period	Bepirovirsen Treatment Start date ≤ Date ≤ Bepirovirsen End date
Bepirovirsen Treatment Follow-up	Date > Bepirovirsen Treatment End date

6.2.3. Study Day and Reference Dates

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

The efficacy reference date is [the date of randomization OR the study intervention start date] and will be used to calculate study day for efficacy measures and baseline characteristics, as well as efficacy durations.

The study day is calculated as below:

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

6.2.4. Assessment Window

Data summaries will utilize the nominal visit descriptions as outlined in the Part 3 schedules of activities. In cases of early discontinuation or withdrawal visits, data will be assigned to a target visit whenever possible, using the visit window guidelines specified in the table below. For all parameters, including safety and efficacy (PD parameters), if multiple assessments occur within the same window, scheduled visits will be prioritized over unscheduled visits. In instances where all assessments are from unscheduled visits, the latest assessment will be taken for safety parameters, while the assessment closest to the scheduled visit will be prioritized for efficacy assessments.

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For data summaries by visit, baseline, scheduled visits with nominal visit description will be displayed. However, for determining the worst-case post baseline unscheduled visit assessments will be considered. In general, all un-scheduled visits will be displayed in the listing.

6.2.5. Multiple measurements at One Analysis Time Point

When triplicate ECG and/or Vital assessments are taken, mean of the measurement will be calculated first and summary statistics will be based on the calculated mean. This will be applied to both baseline and post baseline assessments.

For lab tests on a study day, if more than one assessment is taken on the same day, the test from a central lab will be taken over the test from a local lab. If multiple assessments are taken from the same type of lab, the worst case will be used.

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.
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:

• 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.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.

Else if study intervention start date is not missing:

• 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.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>No Imputation</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail	
	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: • 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

6.2.7. List of Abbreviations

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
API	Active Pharmaceutical Ingredient
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration time curve
BID	Twice Daily
CI	Confidence Interval
CL	Clearance
C_{max}	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling and Simulation
CS	Compound Symmetry
CSH	Heterogeneous Compound Symmetry
CV	Co-efficient of variation
$C\tau$	Trough Concentration
DAIDS	Division of AIDS
DEC	Dose Escalation Committee
ECG	Electrocardiogram
FTIH	First time in humans
GSK	GlaxoSmithKline
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
LLOQ	Lower Limit Of Quantification
LOD	Limit of Detection
MMSE	Modified Mini-Mental Status Exam
NCV	Nerve Conduction Velocity
NOAEL	No Observed Adverse Effect Level
NQ	Non- quantifiable
OBE	Optional Bepirovirsen Extension
OPS	Output and Programming Specification
PBMC	Peripheral blood mononuclear cells
PCI	Potential Clinical Importance
PD	Pharmacodynamics
PK	Pharmacokinetics
PLWCHB	Participants Living with Chronic Hepatitis B Infection
PT	Preferred Term
QTc	Electrocardiogram QT interval corrected for Heart Rate
RAPIDO DV	Reporting and Analysis Plan Improving Design and Delivery of Output Data Viewer
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

Abbreviation	Description
SNCV	Sensory Nerve Conduction Velocity
SOC	System Organ Class
SRM	Study Reference Manual
$t_{1/2}$	Apparent terminal half-life
TCNS	Toronto Clinical Nerve Conduction Scoring System
T_{max}	Time to maximum observed concentration
WHO	World Health Organization
α	Alpha
β	Beta
λ_z	Lambda-z – Terminal Phase Rate

6.2.8. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
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SAS
WinNonlin

7. REFERENCES

[Division of AIDS (DAIDS), 2017] for Grading the Severity of Adult and Paediatric Adverse Events Version 2.1. National Institutes of Health; Institute of Allergy and Infectious Diseases, Bethesda, MD; 2017. Available at: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2.1_2017.pdf

World Health Organization (WHO). Guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection. March 2015.

Yuen MF, Heo J, Jang JW, et al. Safety, tolerability, and antiviral activity of the antisense oligonucleotide bepirovirsen in patients with chronic hepatitis B: a phase 2 randomized controlled trial. *Nat Med*. 2021;10: 1725-1734. DOI: 10.1038/s41591-021-01513-4

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: Four-part, Randomized, Double-blind (Parts 1, 2A, 3 and 4), Multi-centre, Placebo controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GSK3965193 Monotherapy in Healthy Participants and in Participants Living with Chronic Hepatitis B Infection; and GSK3965193 in Combination with Bepirovirsen in Participants Living with Chronic Hepatitis B Infection

Study Number: 214760

Compound Number: GSK3965193, Bepirovirsen (GSK3228836)

Abbreviated Title: Phase 1/2 Study of GSK3965193 in Healthy Participants and Participants Living with Chronic Hepatitis B Infection

Sponsor Name: GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Regulatory Agency Identifier Number(s).

Registry	**ID**
EudraCT	*2021-005117-13*

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP1.0	05 Apr 2022		Not Applicable	Original version
SAP Amendment 1.0	18 Oct 2022	Protocol Amendment 3.0	Section 4.4.2	Definition of "Intervention Emergent Adverse Event" has been updated for Part 1 and Part 2B due to the short half-life of Study intervention
			Section 4.4.3.1	Mention of Grading System of Laboratory Parameters was missing, and it has been updated
			Section 6.1.4	Adopted to use only WHO drug Dictionary since the study is in Veeva CDMS
			Section 6.2.1	Updated a note on how to deal with missing laboratory parameter clinical concern ranges

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses for study Parts 1, 2A and 2B to be included in the Clinical Study Report for Protocol 214760. Analyses of Parts 3 and 4 will be covered in the separate SAP. All details of the dose escalation process and associated data review are outlined in the dose escalation plan. Metabolite evaluations will be conducted by DMPK and are not covered in this SAP.

Descriptive study population analyses such as summary of demography and baseline characteristics and additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Part 1 and 2 (Healthy Participants)	
Primary	
• To assess the safety and tolerability of oral administration of GSK3965193	• Incidence of adverse events (AEs), serious adverse events (SAEs), withdrawals due to AEs • Incidence of clinically significant laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs, cardiac parameters (electrocardiogram [ECG]), and sensory nerve conduction (Part 2A)
• To evaluate the PK characteristics of single and repeat doses of GSK3965193	• Area under the plasma-concentration time curve (AUC): AUC(0-∞) for single dose and AUC(0-tau) for repeat dose. • Maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (Tmax), and apparent terminal half-life (T1/2) will be calculated as data permits per part

Objectives	Endpoints
Secondary	
• To investigate the effect of food on the PK characteristics of single tablet doses of GSK3965193	• Area under the plasma-concentration time curve (AUC): AUC (0-∞), and maximum observed plasma drug concentration (Cmax) as data permits
Exploratory	
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1.1.2. Estimand

Treatment condition:

- Part 1 and 2: Ascending single and multiple doses of GSK3965193 and Placebo

Population:

- Part 1 and Part 2: Healthy participants

Estimand			
Estimand Category	**Variable/Endpoint**	**Intercurrent Strategy**	**Population Level Summary Measure**
To assess the safety and tolerability of oral administration of GSK3965193	1. Incidence of AEs, SAEs, and AEs leading to withdrawal 2. Incidence of clinically significant laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs, and cardiac parameters (electrocardiogram [ECG]), and sensory nerve conduction (Parts 2)	Part 1: Single dose. No intercurrent event identified Parts 2: Intercurrent event of discontinuation of, interruption in, and non-adherence to GSK3965193 will be handled by treatment policy strategy, i.e., regardless of the intercurrent event occurring	Categorical variables: proportions Continuous variables: mean, standard deviation, median, minimum, and maximum

1.2. Study Design

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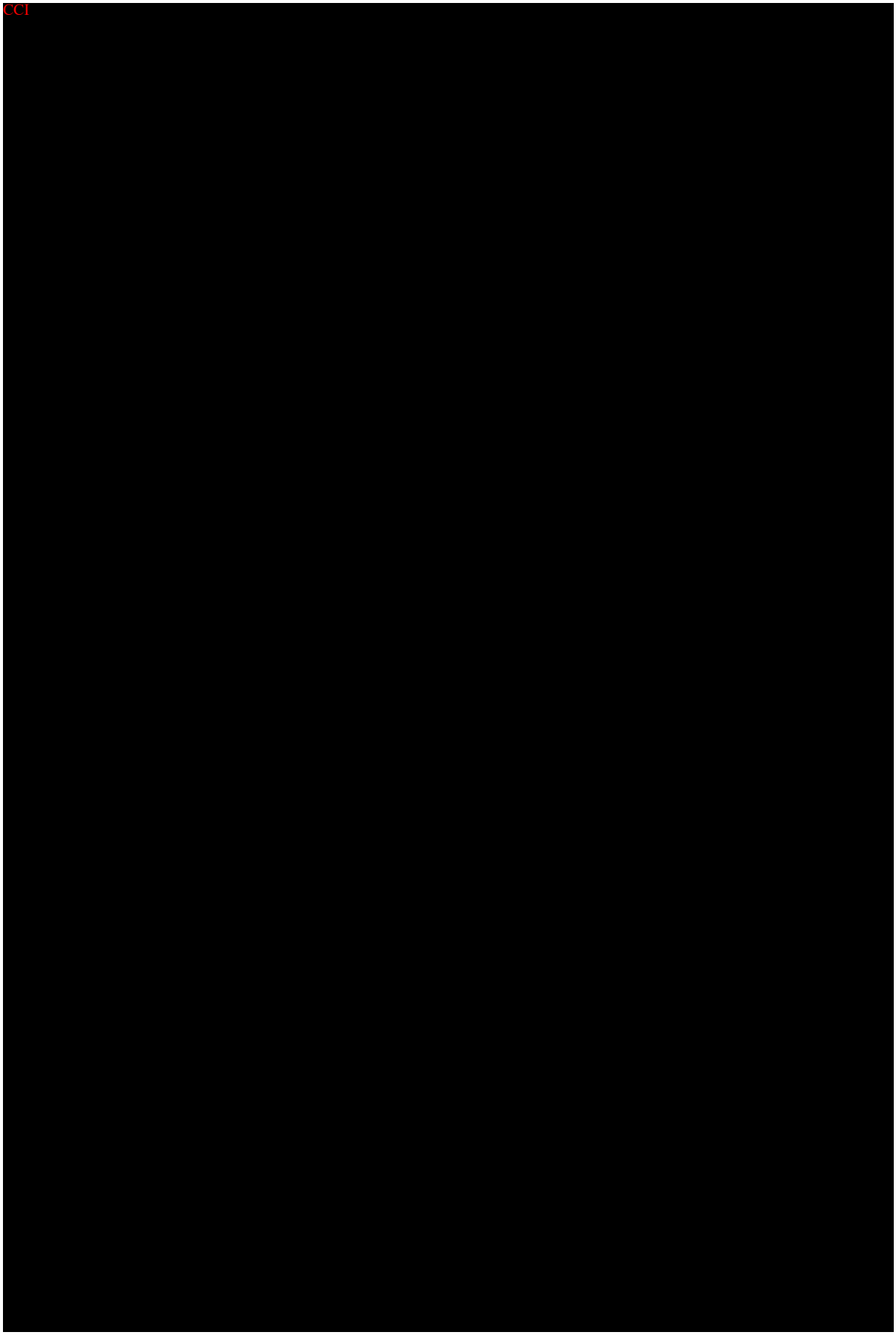

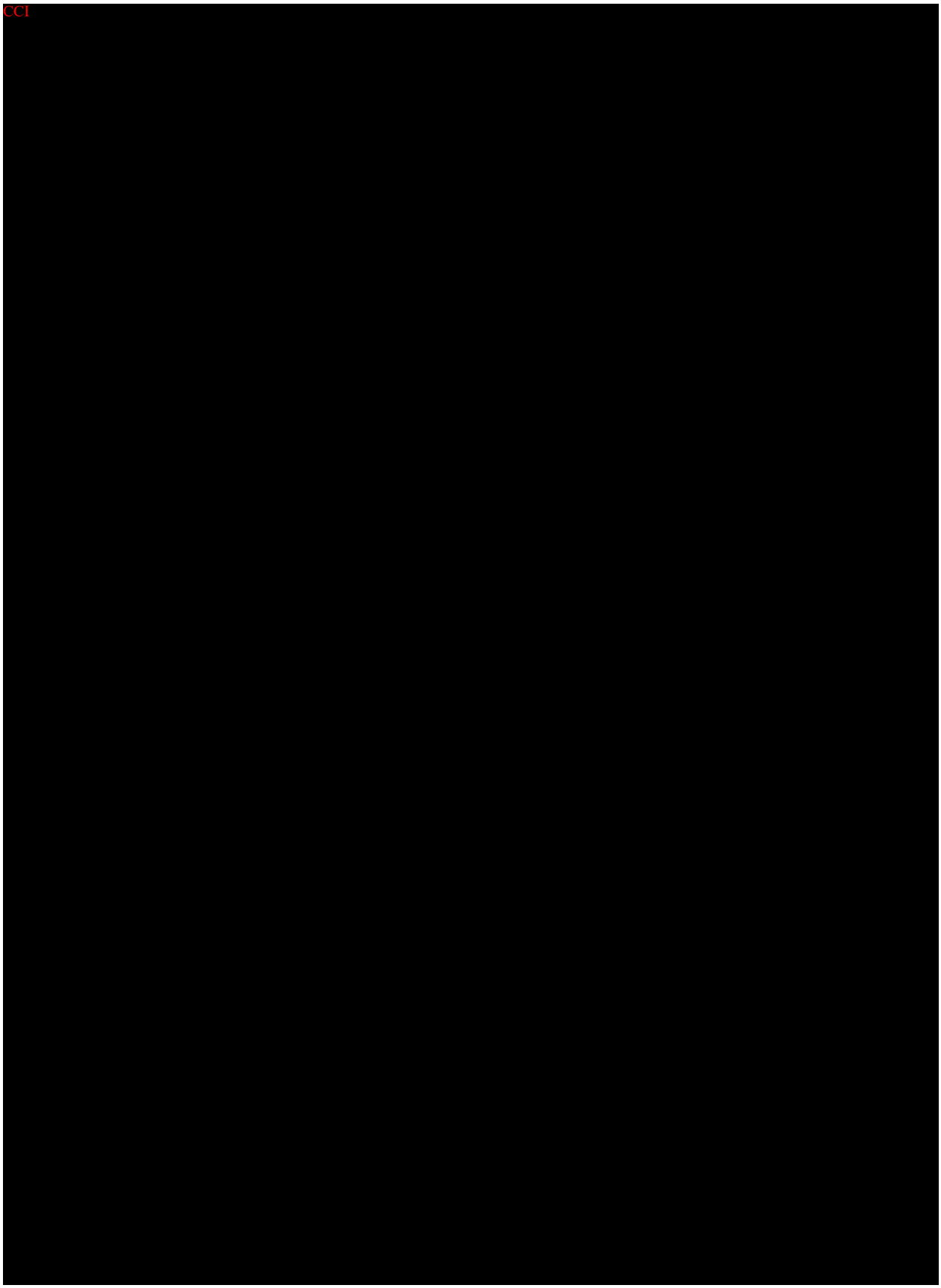
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2. STATISTICAL HYPOTHESES

The primary objectives of parts 1 and 2A of this study are to assess the safety and tolerability of single and repeat ascending doses of GSK3965193 in healthy participants and the primary objective of part 2B is to evaluate the food effect of GSK3965193 of single dose 1 with fed and fasted condition and comparison of GSK3965193 of single dose 1 and GSK3965193 of single dose 2 both in fasted conditions.

No formal hypotheses will be tested. However, wherever appropriate, an estimation approach will be used, and point estimates and confidence intervals (CIs) will be constructed.

2.1. Multiplicity Adjustment

Not Applicable

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
All Screened Subject	• All participants who were screened. Note: screening failures and participants screened but never enrolled into the study (Met eligibility but not needed) are included in this analysis set.	• 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 (Met eligibility but not needed) are excluded	• Study Population

Analysis Set	Definition / Criteria	Analyses Evaluated
	from the Enrolled analysis set as they did not enter the study.	
Randomized	• All participants who were randomized and may or may not have received study treatment.	• Study Population
Safety	• All participants who received at least 1 dose of study treatment. This population will be based on the treatment the participant received.	• Safety • Study Population
Pharmacokinetic (PK) Concentration	• All participants in the Safety population who received an active study treatment and had at least 1 non-missing PK assessment (Nonquantifiable [NQ] values will be considered as non-missing values). • This population will be used for PK concentration listing and plotting of concentration data.	• PK
Pharmacokinetic Parameter	• All participants in the PK Concentration population who received an active study treatment and had at least 1 non-missing PK assessment and have evaluable PK parameters estimated. • This population will be used for PK parameter listing and statistical analysis.	• PK

4. STATISTICAL ANALYSES

4.1. General Considerations

The study population analyses will be based on the Safety set, unless otherwise specified. Safety analyses will also be based on the safety set. PK concentration listings will be based on the PK concentration set. PK analyses will be based on PK and PK parameter set respectively.

Analysis and reporting of Part 1 data for cohorts 1 and 2 will be completed at the end of Part 1.

Also, analysis and reporting of Part 2 (2A and 2B) data for cohorts 3,4, and 5 for Part 2A and cohort 6 for Part 2B will be performed at the end of Part 2B.

4.1.1. General Methodology

Safety evaluations are planned to be descriptive in nature.

Unless otherwise specified, summary tables will provide the following descriptive statistics as a minimum:

- Continuous data:
  n, mean, standard deviation (SD), median, minimum, and maximum.
- Log transformed data:
  n, geometric mean, 95% confidence interval for geometric mean, SD on the log scale (SD (log)), Between subject coefficient of variation (%CV_b).
- Categorical data:
  number and percentage of participants in each category.

4.1.2. Baseline Definition

Baseline is defined as the last non-missing assessment prior to first dose.

For Part 1 periods 1, 2, 3 and 4 and in Part 2B periods 1, 2, and 3 the day 1 pre-dosing assessment will be the baseline. However, if there are no pre-dose assessment collected at Day 1, the last available data from either Day -1 or screening (as schedule of assessment in each Cohort permits) will be defined as baseline. If there are no valid assessments from day 1, day -1 or screening, the baseline will be set to missing.

In Part 1 and 2B period baselines will be defined utilising the assessments taken in the specific period. Participant level baselines will also be computed and will be the means of the available period level baselines for each participant.

For Vital Signs parameters, the pre-dose data is captured as triplicate. In these cases, the baseline will be defined as the mean of the triplicate assessments.

For ECG parameters, except for QTcF, the pre-dose data is captured as triplicate. In these cases, the baseline will be defined as the mean of the triplicate assessments. In Part 1 for both cohorts 1 and cohort 2, baseline QTcF will be based on the mean of 3 pre-dose ECGs collected on Day 1 pre-dose of each treatment period.

In Part 2A, sensory nerve conduction studies at baseline will be collected twice, one at the time of screen and one prior to dosing. Mean (arithmetic mean) of two measurements will be considered as baseline.

4.2. Primary Pharmacokinetic Analyses

Then co-primary objective of Part 1 and 2A is to evaluate the Pharmacokinetic (PK) characteristics of single and repeat doses of GSK3965193, respectively.

4.2.1. Definition of endpoints

Derived Pharmacokinetic Parameters:

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current Clinical Pharmacology Modelling & Simulation (CPMS) working practices and using currently supported version of WinNonlin version 8.0 (or higher).

All calculations of non-compartmental parameters will be based on actual sampling times recorded during the study.

Pharmacokinetic parameters listed in the table below will be determined from the plasma concentration time data, provided there are enough evaluable data available for the calculations. If parameters cannot be determined, a 'Not done' or 'Not calculable' flag will be present in the data.

Additional plasma will also be collected in Part 1 and Part 2A (Days 1 and 14) for analysis of circulating metabolites of GSK3965193. The results will be reported separately.

Residual PK samples collected for analyses of GSK3965193 plasma concentration may also be used to evaluate GSK3965193-derived metabolites.

Table 1 Derivations for Plasma PK Parameters

Parameter	Parameter Description
Plasma PK Parameters for Part 1:	
C_{max}	Maximum observed concentration, determined directly from the concentration-time data
C_{max}/D	Maximum observed concentration normalized by dose: $\frac{Cmax}{D} = Cmax/Dose$
T_{max}	Time to reach Cmax, determined directly from the concentration-time

Parameter	Parameter Description
	data
T_{last}	Time of last quantifiable concentration
$t_{1/2}$	Apparent terminal half-life will be calculated as: $t1/2 = ln2/\lambda z$ Note: λ_z is terminal phase rate constant
$AUC_{(0\text{-}t)}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using linear trapezoidal rule for each incremental trapezoid and the loge trapezoidal rule for each decremental trapezoid (linear up/log down calculation method in Phoenix WinNonlin).
$AUC_{(0\text{-}inf)}$	Area under the concentration-time curve extrapolated to infinity will be calculated as: $\mathrm{AUC}(0-\mathrm{inf}) = \mathrm{AUC}(0-\mathrm{t}) + \frac{C(t)}{\lambda z}$ Note: λ_z is terminal phase rate constant and C(t) last quantifiable concentration
$AUC_{(0\text{-}inf)}/D$	Area under the concentration-time curve extrapolated to infinity normalized by dose will be calculated as: $\frac{AUC(0-\mathrm{inf})}{D} = AUC(0-inf)/Dose$
λ_z	λz is the terminal phase rate constant. A minimum number of three data points in the terminal phase will be used starting at any post-Cmax data point, only those data points that are judged to describe the terminal log-linear decline will be used in regression. Note: • The adjusted correlation coefficient (R2 adjusted) in general should be greater than 0.85. Any value < 0.85 will be flagged but may be used at the PK Scientist's discretion. • The interval used to determine λz should be equal or greater than 2-fold the estimated t1/2 or otherwise flagged and used at the PK Scientist's discretion.

Parameter	Parameter Description
CL/F	The apparent clearance will be calculated as Dose/ $AUC_{(0\text{-inf})}$
Plasma PK Parameters for Part 2A:	
C_τ	Trough concentration, determined directly from concentration-time data at CCI for cohorts 3, 4, and 5. Additionally, it will be captured after first dose on Day 1 CCI
C_τ/D	Trough concentration, prior to CCI normalized by dose: $\frac{C\tau}{D} = C\tau\ (Day\ N)/Dose$ Where, N is CCI for Part 2A for Cohort 3, 4 and 5
C_{max}	Maximum observed concentration, determined directly from the concentration-time data after first dose of Day 1 CCI for Part 2A cohort 3, 4 and 5
C_{max}/D	Maximum observed concentration after CCI normalized by dose: $\frac{Cmax}{D} = Cmax\ (Day\ N)/Dose$ Where, N is CCI for Part 2A for Cohorts 3, 4 and 5
T_{max}	Time to reach Cmax, determined directly from the concentration-time data after first dose of Day 1 and CCI of Part 2A of cohorts 3, 4 and 5
AUC_τ	Area under the concentration-time curve over the dosing interval (CCI will be calculated after first dose of Day 1 and CCI for Part 2A cohorts 3, 4 and 5 using, the linear trapezoidal rule for each incremental trapezoid and the loge trapezoidal rule for each decremental trapezoid (linear up/log down calculation method in Phoenix WinNonlin).
AUC_τ/D	Area under the concentration-time curve over the dosing interval normalized by dose for the CCI:

Parameter	Parameter Description
	$\frac{AUC\tau}{D} = AUC\tau\ (Day\ N)/Dose$ Where, N is CCI for Part 2A for Cohorts 3, 4 and 5
$AUC_{(0\text{-}t)}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) on after first dose on Day 1 and CCI will be calculated using linear trapezoidal rule for each incremental trapezoid and the loge trapezoidal rule for each decremental trapezoid (linear up/log down calculation method in Phoenix WinNonlin).
$AUC_{(0\text{-}inf)}$	Area under the concentration-time curve extrapolated to infinity will be calculated as: $AUC(0-inf) = AUC(0-t) + \frac{C(t)}{\lambda z}$ Note: λ_z is terminal phase rate constant and C(t) last quantifiable concentration of first dose on Day 1 and CCI
$t_{1/2}$	Apparent terminal half-life will be calculated after first dosing on Day 1 CCI for Part 2A cohorts 3, 4, and 5: $t1/2 = ln2/\lambda z$ Note: λ_z is terminal phase rate constant
λ_z	λz is the terminal phase rate constant (after dosing of Part 2A, after first dose of Day 1(CCI for cohorts 3, 4 and 5). A minimum number of three data points in the terminal phase will be used starting at any post- C_{max} data point, only those data points that are judged to describe the terminal log-linear decline will be used in regression. Note: • The adjusted correlation coefficient (R2 adjusted) in general should be greater than 0.85. Any value < 0.85 will be flagged but may be used at the PK Scientist's discretion. The interval used to determine λz should be equal or greater than 2-fold the estimated t1/2 or otherwise flagged and used at the PK

Parameter	Parameter Description
	Scientist's discretion.
$R_{C\tau}$	Accumulation ratio based on C_τ will be calculated as the ratio of C_τ for last dose (pre-dose on Day N) and C_τ after first dose (concentration at [redacted] post Day 1 dose in the BID regimen): $RC\tau = \frac{C\tau(Day\ N)}{C\tau(Day\ 1)}$ Where, N is [redacted] for Part 2A for Cohorts 3, 4 and 5
R_{Cmax}	Accumulation ratio based on C_{max} will be calculated as $RCmax = \frac{Cmax(Day\ N)}{Cmax(Day\ 1)}$ Where, N is [redacted] for Part 2A for Cohorts 3, 4 and 5
$R_{AUC\tau}$	Accumulation ratio based on AUC_τ will be calculated as: $RAUC\tau = \frac{AUC\tau(Day\ N)}{AUC(0-12)}$
Plasma PK Parameters for Part 2B:	
C_{max}	Maximum observed concentration, determined directly from the concentration-time data
$AUC_{(0\text{-inf})}$	Area under the concentration-time curve extrapolated to infinity will be calculated as: $AUC(0-inf) = AUC(0-t) + \frac{C(t)}{\lambda z}$ Note: λ_z is terminal phase rate constant and C(t) last quantifiable concentration
T_{max}	Time to reach C_{max}, determined directly from the concentration-time data

4.2.2. Main analytical approach

The following descriptive summaries for log-transformed data will be provided for concentration data. Summaries for log transformed as well as un-transformed data will be provided for the PK parameters mentioned in Table 1. Concentrations will be listed for all participants by actual time and summarised by nominal time. All data will be summarized by dose regimen:

- **Untransformed data:** N (number of subjects in the populations), n (number of subjects used for the analysis), arithmetic mean, 95% confidence interval (CI) of arithmetic mean, standard deviation (SD), median, minimum, maximum for untransformed data.

- **Log transformed data:** N (number of subjects in the populations), n (number of subjects used for the analysis), geometric mean, 90% confidence interval (CI) of geometric mean, standard deviation (SD) of log transformed data and % Coefficient of variation between subjects (%CV_b), (except for T_{max} and $t_{1/2}$) for log transformed data.

4.2.3. Dose Proportionality (For Part 1 and Part 2A)

Dose proportionality for single dose will be assessed by visual inspection of dose normalised parameters for $AUC_{(0\text{-}inf)}/D$, and/or C_{max}/D values for Part 1 (single dose), and AUC_{τ}/D, and/or C_{max}/D and/or C_{τ}/D values for Part 2A (repeat dose) values versus dose.

Power model will also be fitted to assess dose proportionality as follows: $y = \alpha * dose^{\beta}$. In the log transformed manner this power model can be written as following

$$\log_e(Y) = \beta \times \log_e(dose) + \log_e(\alpha);$$

Where, y denotes the PK parameter being analysed, dose denotes the dose administered to a subject. α depends upon random subject effect and period effect and β is the coefficient of covariate log(dose). Log_e transformed data will be analysed using a mixed effect model as:

- Fixed effect: $\log_e(dose)$
- Random effect: Subject

Data from all available doses will be considered, but if there is limited data > NQ (less than 5 participants approximately) for doses at the lower end of the dose range, these doses will be excluded from the analysis. An unstructured covariance matrix will be considered for the G matrix describing the between subject variability. If this model fails to converge, alternative covariance structures may be considered such as Variance Component, Compound Symmetry, etc. Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.

For Part 2A cohorts 3, 4 and 5, dose proportionality will be assessed and reported only on [redacted] Hence, random effect needs not be included in the model.

Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. If the assumptions are not satisfied, then alternative transformations or models can be considered.

The estimated mean slopes and 90% CIs of $\log_e$(dose) will be presented.

Note that a slope ≈ 1 implies dose proportionality.

Additionally, analysis will be performed using Analysis of Variance (ANOVA) model to assess dose proportionality. The PK parameters (AUC_τ , C_{max}) will be dose normalised first and following a $\log_e$ transformation, dose normalized PK parameters (AUC_τ, C_{max} and C_τ)will be analysed separately using mixed effects model.

- Fixed effect: $\log_e$(dose)
- Random effect: Subject

Data from all available doses will be considered, but if there is limited data > NQ (less than 5 participants approximately) for doses at the lower end of the dose range, these doses will be excluded from the analysis. An unstructured covariance structure will be considered for the G matrix describing the between subject variability.

Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

Adjusted geometric means for each dose will be presented along with the standard errors (SE) and 90% CIs. Estimated treatment ratios to reference dose (First or lowest dose of each part) and corresponding 90% CI will also be presented.

4.2.4. Accumulation Ratio (Part 2A Repeat Dose)

The extent of accumulation after repeat dosing will be determined via computation of accumulation ratios based on AUC_τ (R_{AUC}), on C_{max} (R_{Cmax}) and on C_τ($R_{C\tau}$).

Also, accumulation ratios would be estimated and reported by analysing the $\log_e$ transformed AUC_τ, C_{max} and C_τ using Mixed Model with the following effects:

- Fixed effect: Day, dose, day*dose
- Random effect: Subject

An unstructured covariance matrix will be considered for the G matrix describing the between subject variability. If this model fails to converge, alternative covariance structures may be considered such as Variance Component, Compound Symmetry, etc. Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.

The Kenwood and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.

CCI in cohorts 3, 4 and 5 will be compared with Day 1 to estimate the accumulation ratio. Point estimates and 90% CIs for the geometric mean ratio for "CCI /Day 1" will be constructed.

4.2.5. Steady State Analysis (Part 2A Repeat Dose)

An assessment of time to achieve steady state will be made based on visual inspection, by plotting trough concentration levels, Cτ, collected pre-dose (on CCI versus collection day by dose.

Only if required steady state will be assessed separately for each dose by analysing $\log_e$ transformed trough plasma concentration (C_τ) using Mixed Model with the following effects:

- Fixed effect: Day
- Random effect: Subject

An unstructured covariance matrix will be considered for the G matrix describing the between subject variability. If this model fails to converge, alternative covariance structures may be considered such as Variance Component, Compound Symmetry, etc. Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.

The Kenwood and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.

Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

The coefficients of the slopes for the day (on CCI effect on log scale for each dose, along with 90% CI, will be used to determine whether steady state was achieved.

4.3. Secondary Endpoint Analyses

To investigate the effect of food on PK characteristics of single dose GSK3965193 tablets (Part 2B).

4.3.1. Endpoints

$AUC_{(0\text{-inf})}$, C_{max} and T_{max} at fed and fasted condition

4.3.1.1. Main Analytical approach

An assessment of food effect will be based on $\log_e$ transformed $AUC_{(0\text{-}inf)}$, C_{max} with fasted Dose 1 of the tablet formulation of GSK3965193 versus $\log_e$ transformed $AUC_{(0\text{-}inf)}$, C_{max} with fed Dose 1 of the tablet formulation of GSK3965193. Statistical analysis will be based on Mixed Model with following effects:

- Fixed effect: treatment (Fed GSK3965193 dose 1 of Tablet and Fasted GSK3965193 dose 1 of Tablet), period
- Random effect: Subject

An unstructured covariance matrix will be considered for the G matrix describing the between subject variability. If this model fails to converge, alternative covariance structures may be considered such as Variance Component, Compound Symmetry, etc. Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.

The Kenwood and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.

Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

The estimated geometric mean ratios and 90% CI for (Fed GSK3965193 dose 1 of Tablet formulation: Fasted GSK3965193 dose 1 of Tablet formulation) will be derived.

T_{max} will be analysed non parametrically applying a Wilcoxon signed rank test and a point estimate and distribution free 90% CI for the median difference in T_{max} for (Fed vs Fasted) will be derived. This analysis will be used to derive point estimate and distribution free 90% CI for the median difference of (Fed vs Fasted).

If data permits, Fasted GSK3965193 Tablet formulation will be compared with Fasted GSK3965193 Solution formulation of same strengths.

4.4. Safety Analyses

The co-primary objective of this study is to assess the safety and tolerability of single and repeat ascending doses in healthy participants.

The safety analyses will be based on the safety population, unless otherwise specified.

Estimand for Safety Analyses:

Refer to Section 1.1.2.

4.4.1. Extent of Exposure

The extent of exposure will be summarised using GSK Core Data Standards. Further details of the planned displays will be given in the OPS.

Number of days of exposure to study drug will be calculated based on the formula:

- Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1

Subjects who were randomized but did not report a treatment start date (i.e., were randomized in error) will be categorised as having zero days of exposure.

The cumulative dose will be based on the formula:

- Cumulative Dose = Sum of (Number of Dosing Days x Total Daily Dose)

Duration of exposure and cumulative dose will be calculated only for Part 2A for cohorts 3, 4 and 5.

4.4.2. Adverse Events

An adverse event (AE) is considered study intervention emergent if the AE onset date is on or after study intervention start date. This definition of study intervention emergent AE is applicable only for Part 2A.

For Part 1 and Part 2B, an AE is considered study intervention emergent if the AE onset date is on or after study intervention start date (i.e., Day 1) till [redacted] after study intervention administration. Any AE which starts post Day 5 of study intervention administration will not be considered as study intervention emergent AE.

All AE summaries will be based on study intervention emergent events unless otherwise specified. SAE summaries will be based on all SAEs reported regardless of whether they meet the definition of study intervention emergent or not.

Adverse event (AE) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary. Adverse evet analysis will be based on GSK Core Data Standards.

The following displays for Adverse events will be generated: All Adverse Events by System Organ Class and Preferred Term, AEs leading to withdrawal, Adverse Event by maximum severity grade, Treatment related Adverse Events, Treatment related AEs leading to withdrawal, Treatment relates AEs leading to death, Serious and non-serious Adverse Events and Serious Adverse Events. Further details of the planned displays will be given in OPS.

4.4.2.1. Adverse Events of Special Interest

No AEs of special interest will be collected in Part 1 and Part 2.

4.4.2.2. COVID-19 Assessment and COVID-19 AEs

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

Recommended COVID-19 displays as per GSK Core Standards will be reported. If required some additional (optional) COVID displays would be reported if there is any impact observed on the study.

4.4.3. Additional Safety Assessments

4.4.3.1. Laboratory Data

Laboratory evaluations including the analyses of Chemistry laboratory tests, haematology laboratory tests and Urinalysis, will be based on GSK Core Data Standards for Parts 1 and 2.

Laboratory parameters will be graded using DAIDs grading. Division of AIDS (DAIDS) for Grading Division of AIDS for Grading the Severity of Adult and Paediatric Adverse Events Version 2.0.

Summary statistics for change from baseline will be tabulated. Worst-case chemistry parameters will be summarised by toxicity grades (DAIDS). Laboratory evaluations will be based on GSK Core Data Standards. The details of the planned displays will be given in the OPS.

Incidence of clinically significant laboratory parameters will be reported. Refer the normal ranges of laboratory parameters in the Section 6.2.1.

4.4.3.2. Vital Signs

The analyses of vital signs will be based on GSK Core Data Standards, unless otherwise specified.

In vital sign assessment, pulse rate, respiratory rate and blood pressure will be assessed. Blood pressure and pulse measurement will be taken in the semi supine position.

Post dose vital sign measurements will be captured at Day 1 (0.5 hour, 1, 4, 12) and Day 2 (24 hour of Day 1) for Part 1 and Part 2B.

Vital sign will be captured pre-dose daily for Part 2A.

Incidence of clinically significant vital sign parameters will be reported. Refer the normal ranges of laboratory parameters in the Section 6.2.1.

Further details of the planned displays will be given in OPS.

4.4.3.3. ECG

The analysis of 12-lead ECG along with any ECG findings will be reported according to GSK Core Data Standards.

Safety ECGs will be performed in semi-supine position after at least 5 minutes rest. The parameters collected are PR, QRS, QT and QTc intervals.

Incidence of clinically significant ECG parameters will be reported. Refer the normal ranges of laboratory parameters in the Section 6.2.1.

Further details of the planned displays will be given in OPS.

4.4.3.4. Sensory Nerve Conduction Testing

The analyses of sensory nerve conduction testing will be based on GSK Core Data Standards, unless otherwise specified.

Sensory Nerve conduction testing will be performed to ascertain Nerve conduction velocity (NCV) and Nerve conduction amplitude in Part 2A. Summary statistics of actual and change from baseline by day CCI [redacted] in NCV and NCA will be provided.

Frequency and percentages of participants having 25% decrease in NCV and 50% decrease in nerve conduction amplitude from baseline will be reported.

Section 6.2.1 for Toronto Clinical Neuropathy Scoring System.

Further details of the planned displays will be given in OPS.

4.4.3.5. Nerve Function Test using Toronto Clinical Neuropathy Scoring System (TCNS)

Clinical nerve function testing will be conducted using TCNS. Summary statistics of actual and change from baseline by days CCI [redacted] in nerve function test will be reported.

Incidents of participants having a total score > 4 or an increase from baseline ≥ 2-point will be reported.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

4.6. Dose Escalation (For Part 1 and Part 2A)

Dose escalation for Part 1 and 2A will be based on predictive probability of any participant exceeding PK threshold at the next dose.

At each dose (Dose 2 onwards for Part 1 cohort 1), the Bayesian predictive probability of an individual exceeding the No Adverse Effect Limit (NOAEL) C_{max} and $AUC_{(0\text{-}inf)}$ threshold in Part 1 and No effect Nerve Conduction Velocity (NCV) $AUC_{(0\text{-}24)}$ in Part 2A will be calculated and compared with 50% probability threshold. This will be used to help selection of next dose together with safety and tolerability data. The Bayesian predictive probability will be based on Whitehead's model shown below [Whitehead,2001] using non-informative prior for model parameters.

$$y_{ij} = \theta_1 + \theta_2 d_{ij} + s_i + \varepsilon_{ij} \qquad [1]$$

Where y_i is log-PK parameter of i-th participant, di is the log-dose administered to i-th participant, s_i is the random effect of the ith participant. θ_1 and θ_2 are population intercept and slope, respectively and ε_i is random error of i-th participant in j-th dose.

If intra-subject variability cannot be estimated during PK predictions in Part 1(i.e., early in the study when there is not sufficient information to estimate intra-participant variability) and for conducting prediction for all doses in Part 2A, the same Whitehead's model, will be used for Bayesian predictive probability calculations as below.

$$y_i = \theta_1 + \theta_2 d_i + \varepsilon_i \qquad [2]$$

Where y_i is log-PK parameter of i-th participant, di is the log-dose administered to i-th participant. θ_1 and θ_2 are population intercept and slope, respectively and ε_i is random error of i-th participant in j-th dose.

MCMC procedure will be used to obtain the estimated parameters θ_1, θ_2, s_i (i=1,2,3,4,5,6) and σ^2.

To obtain predicted PK exposure at next dose from the posterior predictive distribution $N(\theta_1 + \theta_2 *\text{next dose} + si, \sigma^2)$ for each participant, i=1,2,3,4,5,6; 20000 iterations need to run.

N, i.e., number of iterations need to be counted to obtain at least one participant among 6 participants having exposure exceeding the C_{max} threshold at next dose. N/20000 is the probability p1= Prob (any participant's C_{max} at next dose level > C_{max} threshold).

In similar way, p2 = Prob (any participant's $AUC_{(0\text{-inf})}$ at next dose level > $AUC_{(0\text{-inf})}$ threshold) will be calculated.

If both probabilities p1 and p2 are less than the 50% threshold, then escalate to the next dose level.

4.7. Interim Analyses

Part 1 cohorts 1 and 2 data will be analysed and reported at the end of Part 1 cohort 2 completion.

Part 2 cohorts 3, 4 and 5 (Part 2A) and 6 (Part 2B) data will be analysed and reported at the end of Part 2B cohort 6 completion.

Also, preliminary safety data and PK data will be reviewed in-stream by the dose escalation committee prior to each dose escalation between cohorts in both Parts, 1 and 2A.

4.8. Changes to Protocol Defined Analyses

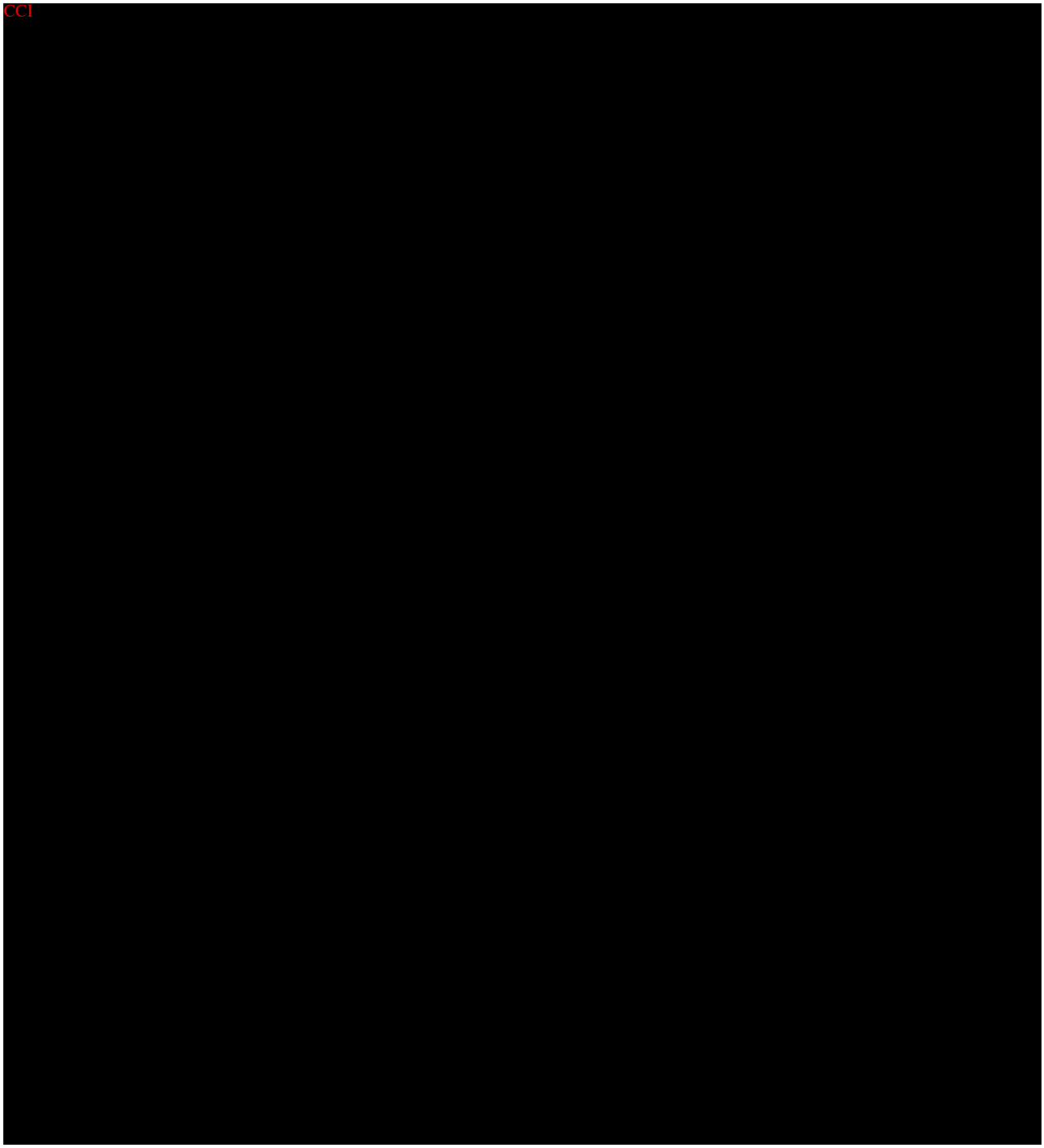
Details of changes or deviations to the originally planned statistical analysis specified in the Protocol Version 1.0 (Dated: 26-Jan-2022) are documented in Table 2

Table 2 Changes from the Planned Analysis

Protocol Defined Analysis	SAP defined Analysis	Rationale for Changes
Analysis Sets: "All Screened Subjects" and "Randomized Set" were not defined in the protocol.	Analysis Sets: Two additional analysis sets defined for Part 1 and 2. These are "All Screened Subjects" and "Randomized Set"	OPS requirement to display number of screen failures and screen failure reasons.
Interim Analysis: Interim reporting for Part 1 at the end of Part 1 cohort 2 was not planned.	Interim Analysis: Interim reporting for Part 1 at the end of Part 1 cohort 2 is planned now.	To plan for Part 3, study team decided to analyse and report the data for Part 1 separately at the end of Part 1.

5. SAMPLE SIZE DETERMINATION

CCI



CCI

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

A summary of the number of participants in each of the participant level analysis sets will be provided for the Screened analysis set.

The Safety Analysis Set will be used for all other study population analyses unless otherwise specified. Please refer Section 3 for more information on the analysis sets.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, medical history, prior or concomitant medications and exposure will be based on GSK Core Data Standards. Detailed of the planned displays will be given in the OPS.

6.1.1. Participant Disposition

A summary of the number and percentages of subjects who completed the study as well as those who prematurely withdrew from the study will be provided. Reason for study withdrawal will be summarised. A subject is considered to have completed the study if they have completed study assessment till the end of the study as per the schedule of assessments, including the follow-up visit.

A summary of study intervention status will be provided. This display will show the number and percentage of subjects who have completed the scheduled study intervention, are ongoing with study intervention, or have discontinued study intervention prematurely, as well as primary reasons for discontinuation of study intervention. A summary of the number of subjects in each of the analysis sets described in the Section 3 will be provided.

All the data will be summarized based on GSK Core Data Standards.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, race, height/weight at screening and Body Mass Index (BMI) will be summarized using descriptive statistics.

Past medical conditions and current medical conditions as of screening will be summarized respectively. Medical history, vaccination, substance use, including smoking history, , alcohol and drug history will be summarized.

All the data will be summarized based on GSK Core Data Standards.

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 (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 WHO Drug Dictionary. Summary will also be based on WHO 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.

Concomitant medications include any medication that was taken at some point during the on-intervention period as defined in Section 6.2.2

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern.

Any additional laboratory parameters reported in the raw dataset for which no PCI ranges are provided in the following table will be listed.

Criteria specified below will be used to flag for potential clinical importance:

Analyte	Gender	Age range	Reference range	Units
Haematology				
HAEMOGLOBIN	Female	18-55yrs	115 - 155	g/L
	Male		130 - 170	g/L
HCT	Female		33 - 45	%
	Male		37 - 50	%
RED CELL COUNT	Female		3.95 - 5.15	x10^12/L
	Male		4.40 - 5.80	x10^12/L
MCV	Male/Female		80 - 99	fL
MCH	Male/Female		26.0 - 33.5	pg
PLATELET COUNT	Male/Female	18-55yrs	150 - 400	x10^9/L
WHITE CELL COUNT	Male/Female		3.0 - 10.0	x10^9/L
NEUTROPHILS	Male/Female		2.0 - 7.5	x10^9/L
LYMPHOCYTES	Male/Female		1.2 - 3.65	x10^9/L
MONOCYTES	Male/Female		0.2 - 1.0	x10^9/L

Analyte	Gender	Age range	Reference range	Units
EOSINOPHILS	Male/Female		0.0 - 0.4	x10^9/L
BASOPHILS	Male/Female		0.0 - 0.1	x10^9/L
PROTHROMBIN TIME	Male/Female		10 - 12	secs
INR	Male/Female		0.9 - 1.2	
APTT	Male/Female		25 - 37	Secs
ANTINUCLEAR ANTIBODIES	Male/Female		NEGATIVE	
SMOOTH MUSCLE ANTIBODIES	Male/Female		NEGATIVE	
CYTOMEGALOVIRUS AB (IGM)	Male/Female		NEGATIVE	
EPSTEIN-BARR VIRUS SCREEN	Male/Female		NEGATIVE	
EBNA IGG ANTIBODY	Male/Female		(< 5 U/ml Negative)	U/mL
EBV EARLY AG AB. (IGG)	Male/Female	18-55yrs	(<10 U/ml Negative)	U/mL
EBV VCA AB. (IGM)	Male/Female		(<20 U/ml Negative)	U/mL
DOUBLE STRANDED DNA ANTIBODY	Male/Female		<10 is Negative	IU/mL
SARS-COV-2 PCR	Male/Female		Not detected	
HEPATITIS B DNA	Male/Female		Not detected	
WBCS	Male/Female		0 - 52	cells/uL
RBCS	Male/Female		0 - 52	cells/uL

Analyte	Gender	Age range	Reference range	Units
HYALINE CASTS	Male/Female		Not seen	HPF
GRANULAR CASTS	Male/Female		Not seen	HPF
CELLULAR CASTS	Male/Female		Not seen	HPF
HEPATITIS B SURFACE ANTIGENS (HBSAG)	Male/Female		NEGATIVE	
HEPATITIS E AB - IGM	Male/Female		NEGATIVE	
CRYOGLOBULINS	Male/Female		Negative	
ALKALINE PHOSPHATASE ISOENZYMES	Male/Female		Negative	
Chemical Chemistry				
SODIUM	Male/Female	18-55yrs	135 - 145	mmol/L
POTASSIUM	Male/Female		3.5 - 5.1	mmol/L
CHLORIDE	Male/Female		98 - 107	mmol/L
UREA	Male/Female		1.7 - 8.3	mmol/L
BLOOD UREA NITROGEN	Male/Female		4.76 - 23.24	mg/dL
CREATININE	Female		49 - 92	umol/L
	Male		66 - 112	umol/L
BILIRUBIN	Male/Female		0 - 20	umol/L
DIRECT (CONJ) BILIRUBIN	Male/Female		0 - 5	umol/L
INDIRECT BILIRUBIN	Male/Female		<15	umol/l
ASPARTATE TRANSFERASE	Female		0 - 31	IU/L
	Male		0 - 37	IU/L
LDH	Female		135 - 214	IU/L
	Male		135 - 225	IU/L
TOTAL PROTEIN	Male/Female		63 - 83	g/L
ALBUMIN	Male/Female		34 - 50	g/L
CALCIUM	Male/Female		2.20 - 2.60	mmol/L

Analyte	Gender	Age range	Reference range	Units
RANDOM BLOOD GLUCOSE (SST)	Male/Female		3.5 - 7.9	mmol/L
C3	Male/Female		0.90-1.80	g/L
C4	Male/Female		0.10-0.40	g/L
COMPLEMENT C5A	Male/Female		13-179	ng/ml
COMPLEMENT BB	Male/Female		0.80-6.26	ug/ml
HEPATITIS D ANTIBODY	Male/Female		Negative	
HEPATITIS B 'E' ANTIGEN	Male/Female	18-55yrs	Negative	
SERUM ACETAMINOPHEN	Male/Female		10-30	

ECG Parameter Ranges:

ECG Parameters	Unit	Clinical Concern Range	
		Lower(<x)	Upper(>x)
Absolute QTc	msec	300	600
Absolute QTcF	msec	300	450
Uncorrected QT	msec	N/A	600
Heart rate	bpm	40	110
Absolute QRS interval	msec	70	120
Absolute PR Interval	msec	90	220
Change from Baseline:			
QTcF	msec	>60	

Vital Sign:

Vital Parameters	Unit	Clinical Concern Range	
		Lower(<x)	Upper(>x)
Pulse rate	bpm	40	110
Respiratory Rate	Breaths/min	8	20
Systolic blood pressure	mmHg	85	160
Diastolic Blood Pressure	mmHg	45	100

6.2.2. Study Period

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

Part	Study Intervention	Definition
1	Pre-intervention	Ref Date[1] < Study treatment start date
2A		
2B		
1	On-intervention	Study Intervention Start Date and Time ≤ Ref Date[1] < Next Study Intervention Start Date and Time, in each Period within a Cohort
2A		Study Intervention Start Date and Time ≤ Ref Date[1] < Study Intervention Stop Date and Time for each cohort
2B		Study Intervention Start Date and Time ≤ Ref Date[1] < Next Study Intervention Start Date and Time, in each Period within a Cohort
1	Post-intervention	Ref Date[1] > Last Study Intervention Stop Date + Last contact date
2A		
2B		

Part	Study Intervention	Definition
[1] Ref Date is the start date of the assessment/event.		

6.2.3. Study Day and Reference Dates

The safety reference date is the study intervention start date and will be used to calculate study day for safety 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 Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.4. Assessment Window

Refer to Section 5.2‘Timing of Assessments, Window Allowances and Order of Procedures’in the Study Reference Manual (SRM).

6.2.5. Multiple measurements at One Analysis Time Point

When triplicate ECG assessments are taken, mean of the measurement will be calculated first and summary statistics will be based on the calculated mean. This will apply to both baseline and post baseline assessments.

For lab tests on a study day, if more than one assessment is taken on the same day, the test from a central lab will be taken over the test from a local lab. If multiple assessments are taken from the same type of lab, the worst case will be used.

6.2.6. Handling of Partial Dates

Element	Reporting Detail
General	• 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 .

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>Adverse Events</td><td>
Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:

o If month and year of start date = month and year of study intervention start date, then

▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.

▪ Else set start date = study intervention start date.

Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.

Else if study intervention start date is not missing:

o If year of start date = year of study intervention start date, then

▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
▪ Else set start date = study intervention start date.
Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td></td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>
Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:

o If month and year of start date = month and year of study intervention start date, then

▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.

▪ Else set start date = study intervention start date.

Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.

Else if study intervention start date is not missing:

o If year of start date = year of study intervention start date, then

▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.

▪ Else set start date = study. intervention start date.

Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail	
	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
Age	Age will not be imputed	

6.2.7. List of Abbreviations

Abbreviation	Description
AE	Adverse Event
API	Active Pharmaceutical Ingredient
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration time curve
BID	Twice Daily
$C\tau$	Trough Concentration
CI	Confidence Interval
CL	Clearance
C_{max}	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling and Simulation
CSH	Heterogeneous Compound Symmetry
CS	Compound Symmetry
CV	Co-efficient of variation
DEC	Dose Escalation Committee
ECG	Electrocardiogram
FTIH	First time in humans
GSK	GlaxoSmithKline
LLOQ	Lower Limit Of Quantification
NCV	Nerve Conduction Velocity
NOAEL	No Observed Adverse Effect Level
NQ	Non- quantifiable
OPS	Output and Programming Specification
PK	Pharmacokinetics
PT	Preferred Term
QTc	Electrocardiogram QT interval corrected for Heart Rate
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SNCV	Sensory Nerve Conduction Velocity
SOC	System Organ Class
SRM	Study Reference Manual
$t_{1/2}$	Apparent terminal half-life
T_{max}	Time to maximum observed concentration
TCNS	Toronto Clinical Nerve Conduction Scoring System
WHO	World Health Organization
α	Alpha

Abbreviation	Description
β	Beta

6.2.8. Early PK Access Key Activities

Items	Details	Roles with Authorized Access	Secured Area
Early PK Access Starting Milestone	PK Cutoff Milestone Or PK Last Subject Last Visit	CPMS Lead BIB Lead	NA
Creation of PopPK with Scrambled Subject ID	PopPK	CPMS Lead/Modeler including modelers from vendors Unblinded PK Programmer	NA
Development of PopPK Preliminary Model	PopPK Preliminary Model	CPMS Lead/Modeler including modelers from vendors	NA

6.2.9. Trademarks

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