Statistical Analysis Plan

Study ID: 213960

Official Title of Study: A Randomised, Double-Blind, Placebo Controlled, Single Dose Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of GSK3888130B in Healthy Participants aged 18-55 inclusive

Date of Document : 17-Aug-2023

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A Randomised, Double-Blind, Placebo Controlled, Single Dose Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of GSK3888130B in Healthy Participants aged 18-55 inclusive.

Study Number: 213960

Compound Number: GSK3888130B

Abbreviated Title: A FTIH study to evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of GSK3888130B in Healthy Participants aged 18-55 inclusive.

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
EudraCT	2021-002063-22

TABLE OF CONTENTS

PAGE

1. INTRODUCTION 5
1.1. Objectives and Endpoints 5
1.2. Study Design 8

2. STATISTICAL HYPOTHESES 9
2.1. Multiplicity Adjustment 9

3. ANALYSIS SETS 10

4. STATISTICAL ANALYSES 11
4.1. General Considerations 11
4.1.1. General Methodology 11
4.1.2. Model Checking and Diagnostics 12
4.1.3. Baseline Definition 12
4.2. Safety Analyses 13
4.2.1. Adverse Events 13
4.2.2. Laboratory Data 14
4.2.3. Vital Signs 15
4.2.4. ECG 15
4.3. Secondary Endpoint(s) Analyses 16
4.3.1. Pharmacokinetic Analyses 16
4.3.2. Immunogenicity Analyses 17
4.3.3. Pharmacodynamic Biomarker Analyses 17
4.3.4. Target Engagement Biomarker Analyses 20
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
4.5. Other Analyses 26
4.5.1. Subgroup analyses 26
4.5.2. Other variables and/or parameters 26
4.6. Dose Escalation 26
4.7. Interim Analyses 26
4.8. Changes to Protocol Defined Analyses 28

5. SAMPLE SIZE DETERMINATION 29

6. SUPPORTING DOCUMENTATION 31
6.1. Appendix 1 Study Population Analyses 31
6.1.1. Participant Disposition 31
6.1.2. Demographic and Baseline Characteristics 31
6.1.3. Protocol Deviations 31

6.1.4. Prior and Concomitant Medications 32
6.1.5. Additional Analyses Due to the COVID-19 Pandemic 32
6.2. Appendix 2 Data Derivations Rule 33
6.2.1. Reporting Standards 33
6.2.2. Criteria for Potential Clinical Importance 33
6.2.3. Study Day and Reference Dates 34
6.2.4. Assessment Window 34
6.2.5. Multiple measurements at One Analysis Time Point 35
6.2.6. Handling of Partial Dates 35

7. REFERENCES 39

Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	14 Dec 2021	Protocol Amendment 1 (27-SEP-2021)	Not Applicable	Original version
SAP Amendment 1		Protocol Amendment 2 (10-FEB-2022)	Revised Section 4.6 Dose Escalation to exclude S&P providing $CD4^+$ T cell counts outputs for each DEC meetings.	Revised due to delay in data transfer for each DEC.
			Revised Section 4.7 Interim Analyses to include Immunogenicity, PD Bcl-2 and TE Total IL-7 plots to be reviewed during first Interim Analyses. Also added clarity on the outputs provided for each DEC and IA.	Revision based on Protocol Amendment 2
		Protocol Amendment 6 (21-MAR-2023)	Updated Sections 1.1. Objectives and Endpoints, 1.2. Study Design, CCI [redacted], 4.7. Interim Analyses and 5. Sample Size Determination	Revised based on Protocol Amendment 6
			Added CCI [redacted]	

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 213960. Details of the planned interim analysis, as well as the final analyses, are provided.

1.1. Objectives and Endpoints

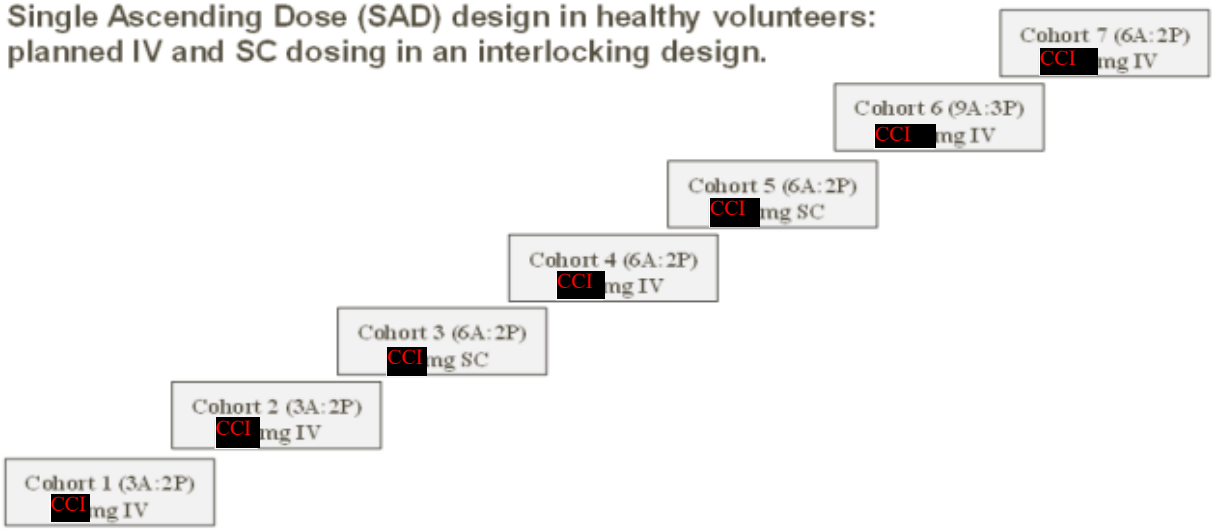
Objectives	Endpoints
Primary	
To investigate the safety and tolerability of single IV and SC doses of GSK3888130B in healthy participants.	• Occurrence of Adverse Events (AEs) and Serious Adverse Events (SAEs). • Occurrence of clinically significant changes in laboratory values ($CD4^+$ T cell counts, haematology, chemistry, urinalysis and virology), vital signs and 12lead electrocardiogram (ECG) readings.
Secondary	
To characterise the serum PK profile of single IV or single SC doses of GSK3888130B in healthy participants.	Serum concentrations of GSK3888130B and derived PK parameters as data permit, including area under the concentration-time curve [AUC], maximum concentration [Cmax], time to Cmax [Tmax], half-life [$t_{½}$], clearance [CL].
To evaluate the immunogenicity of single doses of GSK3888130B in healthy participants.	Incidence of Anti-Drug Antibodies (ADAs) against GSK3888130B.
To characterise the effects of GSK3888130B on target engagement (TE).	Change from baseline in derived free IL-7 levels (calculated from total IL-7 assay measurements) over time.
To characterise the effect of single doses of GSK3888130B on PD biomarker Bcl-2.	Change from baseline in T cell Bcl-2, measured in blood over time.
Tertiary/Exploratory/Other	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

1.2. Study Design

Overview of Study Design and Key Features



Design Features

- Phase 1, single centre, randomised, double-blind, placebo controlled, dose escalation study comprising of seven planned SAD cohorts of GSK3888130B over a range of dose levels (from CCI mg to CCI mg) in healthy participants.
- CCI
  CCI
  .
- CCI
  - Participants will attend a screening visit within 28 days of study intervention. In participants who require an influenza vaccination and/or SARS-CoV-2 vaccination or booster, the screening window may be increased to 60 days.
  - Participants will receive study intervention on Day 1. For the IV cohorts, participants will remain in the unit for CCI days and for the SC cohorts for CCI days.
  - All participants will then attend the clinic for up to CCI outpatient visits after dosing, over the course of CCI days, for safety assessments and sample collection and will receive two follow-up telephone calls; the first will be CCI days post last study visit and the second will be CCI days post last study visit. If required, additional follow-up visits may be scheduled.

Study intervention

Cohorts	Study Intervention
Cohort 1 – IV Dose	GSK3888130B CCI mg vs Placebo

Overview of Study Design and Key Features		
	Cohort 2 – IV Dose	GSK3888130B[CCI] mg vs Placebo
	Cohort 3 – SC Dose	GSK3888130B[CCI] mg vs Placebo
	Cohort 4 – IV Dose	GSK3888130B[CCI] mg vs Placebo
	Cohort 5 – SC Dose	GSK3888130B[CCI] mg vs Placebo
	Cohort 6 – IV Dose	GSK3888130B[CCI] mg vs Placebo
	Cohort 7 – IV Dose	GSK3888130B[CCI] mg vs Placebo
Study intervention Assignment	• The study will aim to recruit 54 participants into seven SAD cohorts. • **Cohort 1 and 2:** Eligible participants will be randomised to receive either GSK3888130B or placebo in a 3:2 ratio comprising of five participants. • **Cohort 3 to 7:** Eligible participants will be randomised in a 3:1 ratio comprising of eight participants, except for cohort 6 which [CCI]	
Interim Analysis	First Interim analyses will be performed once a minimum of four participants dosed with GSK3888130B in cohort 4 have completed up to and including the Day [CCI] visit. Second Interim analyses will be performed once all participants in cohort 6 have completed up to and including the Day [CCI] visit for PK, TE (total IL7 levels), PD (T cell Bcl2) and [CCI] and up to and including Day[CCI]. Refer Section 4.7 for details.	

2. STATISTICAL HYPOTHESES

The primary objective of this study is to assess the safety and tolerability of single IV and SC doses of GSK3888130B in healthy participants.

No formal hypotheses are being tested in this study.

2.1. Multiplicity Adjustment

There will be no adjustments for multiplicity in this study.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who signed the ICF and are screened for eligibility.	Study Population
Enrolled	• All participants in the Screened analysis set who are entered into the study. • Note screening failures (who never passed screening even if rescreened) and 'reserved' or 'not used' participants are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Randomised	• All participants who are randomly assigned to study intervention in the study.	Study Population
Safety	• All participants who received study intervention. • Participants will be analysed according to the study intervention administered.	• Study Population • Safety
Pharmacokinetic (PK)	• All participants in the Safety analysis set who had received an active study intervention and had at least 1 non-missing post dose PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • 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 post baseline PD result. • Data will be reported according to the actual study intervention.	• PD/Biomarker

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Participants who prematurely withdraw from study may be replaced.

Unless otherwise specified, the Screened, Enrolled, Randomised or Safety Analysis Sets will be used for all Study Population analyses, the Safety Analysis Set will be used for all Safety analyses, the PK Analysis Set will be used for all Pharmacokinetic analyses and the PD Analysis Set will be used for all Pharmacodynamic/ Biomarker analyses.

For all summaries, statistical analyses and plots, Placebo participants will be pooled across all cohorts in which the endpoint was collected, except for the following endpoints:

- Cellular Biomarkers, CCI and CCI (Section 4.4.3): Placebo data will be pooled across Cohorts 1,2,3,4 and 7 CCI .
- CCI Placebo data will be summarised by cohort since there are limited timepoints relative to the CCI which are common to these cohorts.

CCI

CCI

Absolute baseline values will be included in all change from baseline or ratio to baseline summaries. Line plots will be produced on absolute values unless otherwise specified.

95% equal tailed Credible Intervals (CrI) will be used for statistical analyses unless otherwise specified.

Summary tables will provide the following descriptive statistics as a minimum, unless otherwise specified:

- For continuous untransformed data (or where many zeros exist in the data): n, mean, 95% Confidence Intervals (CI), standard deviation (SD), median, minimum and maximum. Number of Zeros may also be added as an additional statistic, if deemed appropriate.
- For continuous log-normally distributed data: n, geometric mean, 95% CI of the geometric mean, standard deviation on the log scale (SD (log)), %CVb (only for PK Parameters), median, minimum and maximum.
- For categorical data: number and percentage of participants in each category.

4.1.2. Model Checking and Diagnostics

The analyses will be conducted in the Bayesian framework. Models will be fitted by MCMC simulations using non-informative priors.

A thinning sample may be used to aid convergence; where k is the thinning ratio and the number of samples are a minimum of 10,000*k. For example, 100,000 MCMC samples may be generated with a thin of 10, providing 10,000 samples to be used for the estimate of the posterior distribution. A burn-in of 5,000 samples will be used by first intent.

The following list of convergence diagnostics will be applied for each parameter (diagnostic checking outputs will be stored in the refdata folder in HARP in the relevant reporting effort):

- The Monte Carlo Standard Errors (MCSE) should be compared with the standard deviation of the posterior distribution (SD) to ensure that only a fraction of the posterior variability is due to the simulation. The number of samples generated, and/or the thinning may be increased to reduce the ratio of the MCSE/SD as deemed necessary.
- Trace plots of samples versus the simulation index will be visually inspected to assess some aspects of convergence. The centre of the chain should appear stable with very small fluctuations, i.e., the distribution of points should not change as the chain progresses and the posterior mean and variance are relatively constant.
- Autocorrelation plots will be visually inspected to assess degree of autocorrelation (should decline rapidly and show no oscillation patterns).
- Density plots of the posterior for the model parameters will be plotted (should be smooth and with a single hump).

If the model is not deemed to have converged then increasing the number of MCMC samples and/or the thinning will be explored. The blocking of the parameters will also be considered.

4.1.3. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment (unless otherwise specified) with a non-missing value, including those from unscheduled visits. If time is not collected at Day 1:

- If a pre-dose sample collection is the only scheduled visit (as per the schedule of activities table in the protocol), then Day 1 will be used as baseline.
- Otherwise, if an assessment prior to Day 1 is available, this will be used as baseline.
- Otherwise, baseline will be set to missing.

4.1.3.1. Derivations and Handling of Missing Baseline Data

For untransformed data, change from baseline at each time point is expressed as a difference. For $\log_e$ transformed data, change from baseline will be expressed as a ratio. For individual gene data, change from baseline will be expressed as a fold change.

Definition	Reporting Details
Change from Baseline	= Post-Baseline Visit Value – Baseline Value
Ratio to Baseline	= Post-Baseline Visit Value / Baseline Value **OR** = **Exponential** of (**Log** (Post-Baseline Visit Value) – **Log** (Baseline Value))
Fold Change Relative to Baseline	= **2 to the power** of (Post-Baseline Visit Value* – Baseline Value*) [*note that individual gene data is received on the log_2 scale]

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

4.2. Safety Analyses

The primary objective of this study is to assess the safety and tolerability of single IV and SC doses of GSK3888130B.

4.2.1. Adverse Events

An adverse event (AE) is considered study intervention emergent if the AE onset date is on or after study intervention start date. 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. All AE and SAE summaries will be by System Organ Class (SOC) and Preferred Terms (PT) or only by PT, unless otherwise specified.

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary) and graded by the investigator according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 5).

An overview summary of AEs, including counts and percentages of participants, will be summarized for the following categories and subcategories.

- AE
    - Any AEs
    - AEs related to study intervention
    - AEs leading to study withdrawal
- SAE
    - Any SAEs
    - SAEs related to study intervention

A study intervention-related AE/SAE is defined as an AE for which the investigator classifies the possible relationship to study intervention as “Yes”. If relationship to study intervention is missing then worst-case approach will be applied (i.e. missing will be handled in the same way as ‘Yes’).

4.2.1.1. Adverse Events of Special Interest

There are no adverse events of special interest identified for this study.

4.2.1.2. COVID-19 Assessment and COVID-19 AEs

The case report form will collect all COVID-19 AEs.

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

4.2.2. Laboratory Data

Summary tables for change from baseline of $CD4^+$ T cell counts, haematology and clinical chemistry laboratory tests will be produced. Worst-case post-baseline relative to baseline CCI results will be presented.

Additionally, worst-case (i.e., the highest grade) change in the categories at post-baseline relative to baseline summary table will be provided for $CD4^+$ T cell counts and CCI based on the cut-off provided in the Table 1 below.

Individual participant plots of the raw values of $CD4^+$ T cell counts over time will be presented by study intervention. Line plots of the unadjusted geometric means and corresponding 95% CIs of $CD4^+$ T cell counts will be presented over time.

Listings of all Potential Clinical Important abnormalities will be presented for clinical chemistry and haematology (see Section 6.2.1).

Listings of Potential Clinical Important Urinalysis data will be presented. Potential Clinical Important is referred as an increase in Protein or an increase in Occult Blood results, or if microscopy is performed during the study.

Table 1 Clinically Significant Grades Cut-Offs

Parameter	Grade	Grade Cut-Off
$CD4^+$ T Cell Counts	Grade 0	Above 0.5×10^9/L
	Grade 1	<0.5 to 0.2×10^9/L
	Grade 2	<0.2 to 0.05×10^9/L
	Grade 3	Below 0.05×10^9/L
CCI		

[1]: Include both absolute and change from baseline values.
[2]: Only absolute values

4.2.2.1. Virology Data

Virology data includes both quantitative and qualitative data as shown in Table 2. Appropriate summary tables (for quantitative data, these will be based on continuous untransformed data) will be provided (see Section 4.1.1).

Table 2 Virology Data

Biomarker	Result	Classification
Serology (Immunology as per SDTM data standards)		
CMV IgG (AU/mL)	Quantitative Result	<6.0 is Non-reactive >= 6.0 is Reactive
CMV IgM	Qualitative Result	Positive/Negative
EBNA IgG (U/mL)	Quantitative Result	< 5 U/mL is Negative
VCA IgG (U/mL)	Quantitative Result	< 20 U/mL is Negative
EBV VCA ab (IgM) (U/mL)	Quantitative Result	< 20 U/mL is Negative
Varicella Zoster IgG (mIU/mL)	Quantitative Result	<150 mIU/mL is Negative
Varicella Zoster IgM	Qualitative Result	Positive/Negative
Viral quantification		
EBV (Copies/mL)	Quantitative Result	N/A
CMV (Copies/mL)	Quantitative Result	N/A
Varicella	Qualitative Result	Positive/Negative

4.2.3. Vital Signs

Summary table for change from baseline of Vital Signs will be produced. Listing of all Potential Clinical Important abnormalities will be presented (see Section 6.2.1).

4.2.4. ECG

Summary tables for ECG findings and change from baseline of 12-Lead ECG will be produced. Maximum QTcF (Friderica's QT Interval Corrected for Heart Rate) values post-baseline relative to baseline will be produced and will be used to detect any clinical important changes. The categories are defined as:

- Maximum QTcF values at post baseline relative to baseline:
  - To <=450 msec or No Change
  - Any Increase, To >450 to <=480 msec
  - Increase To >480 to <=500 msec
  - Increase To >500 msec
- Maximum increase in QTcF values post baseline relative to baseline:
  - Increase <=30 msec
  - Increase of 31-60 msec
  - Increase of >60 msec

Listing of all Potential Clinical Important abnormalities will be presented (see Section 6.2.1).

Full details of the planned safety displays are provided in the Output and Programming Specification (OPS).

4.3. Secondary Endpoint(s) Analyses

The secondary objectives of this study are to evaluate the Pharmacokinetics, Immunogenicity, Target Engagement (TE) and Pharmacodynamic biomarkers.

4.3.1. Pharmacokinetic Analyses

The PK analyses will be performed by, or under the direct auspices of GSK Biostatistics, as well as Clinical Pharmacology Modelling and Simulation (CPMS).

4.3.1.1. Definition of endpoint(s)

- Serum PK concentrations
- PK Parameters as data permits:
  - Area under the Concentration-time curve CCI
  - CCI
  - Maximum Concentration [Cmax]
  - Time to Cmax [Tmax]
  - Half-life [t½]
  - CCI
  - Clearance [CL or CL/F (SC cohorts)]
  - CCI

4.3.1.2. Main analytical approach

Serum PK concentrations are assumed to be log-normally distributed and appropriate summary statistics will be displayed (see Section 4.1.1) by study intervention over time. Plots of individual concentration and median concentration data with range over time will be produced by GSK Biostatistics.

PK parameters will be calculated by standard non-compartmental analysis using the current supported version of WinNonlin by CPMS and transferred back to GSK Biostatistics to provide descriptive statistics. All calculations of non-compartmental parameters will be based on actual sampling times.

The untransformed and $\log_e$ transformed PK Parameters will be summarized separately. Appropriate summary statistics will be displayed (see Section 4.1.1) as follows:

- Untransformed PK parameter variables: Tmax, CCI

- Log_e transformed PK parameter variables: AUC [redacted], Cmax, Clearance [CL or CL/F (SC cohorts)], [redacted] and Half-life ($t_{½}$)

4.3.2. Immunogenicity Analyses

The immunogenicity analyses will be based on the Safety Analysis Set.

Immunogenicity testing involves a screening assay and a confirmation assay that together produce 3 results:

- Screening assay result (positive / negative)
- Confirmatory assay result (positive / negative) if positive result in the screening assay
- Titre result (numeric) if positive result in the confirmation assay

The immunogenicity analyses will be summarised by incidence, i.e., the number of participants with anti-drug antibodies by study intervention over time and the titre of immunogenicity results will be listed.

4.3.3. Pharmacodynamic Biomarker Analyses

4.3.3.1. Definition of endpoint(s)

- Peripheral blood T Cell Bcl-2 expression (Data captured as Bcl-2 expression in T cells):
  - Bcl-2 expression in T cells (%)
  - Bcl-2 expression in T cells (MdFI)
  - [redacted]

4.3.3.2. Main analytical approach

It is assumed that endpoints defined in Section 4.3.3.1 are log_e normally distributed, unless distributional properties suggest otherwise.

The absolute values for the endpoints mentioned in Section 4.3.3.1 will be summarized descriptively. Line plots of the unadjusted geometric means and corresponding 95% CIs will be presented over time. Individual participant plots of the raw values over time will be presented by study intervention.

A Bayesian Mixed Model Repeated Measures (MMRM) analysis for the pooled placebo data across all cohorts and all doses of GSK3888130B will be fitted for Bcl-2 expression in T cells (MdFI) endpoint.

Non-informative priors will be used in this analysis. The prior for the regression coefficients will be normally distributed with mean 0 and a variance of 10^6. Should there be convergence issues due to relatively small data values, the latter may be reduced to 10^4. The variance-covariance matrix will use an inverse-Wishart prior distribution, consisting of the identity matrix and the degrees of freedom set to the number of visits included in the model. Sensitivity to changes in the degrees of freedom will be considered.

Terms in the model are specified below:

- Response: Absolute value on $\log_e$ scale.
- Category: Study intervention, Visit.
- Interaction: Study intervention*Visit.
- Repeated: Visit.

Baseline values will be included in the response for this model, with visit = 'Baseline' and a distinct arbitrary code assigned for study intervention (the same for all baseline visits).

The following will be calculated from the model:

- For Baseline: The posterior mean for $\log_e$ transformed Bcl-2,
- For each study intervention: The posterior means for $\log_e$ transformed Bcl-2 for each post-baseline visit,
- For each study intervention: The posterior means for the difference from baseline for $\log_e$ transformed Bcl-2 for each post-baseline visit,
- For each active study intervention: The posterior means for the difference from placebo for $\log_e$ transformed Bcl-2 (GSK3888130B XX mg – Pooled placebo across cohorts) for each post-baseline visit.

These values will then be back transformed and the following presented:

- For Baseline: The posterior geometric mean,
- For each study intervention: The posterior geometric means for each post-baseline visit,
- For each study intervention: The posterior geometric means of the ratio to baseline for each post-baseline visit,
- For each active study intervention: The posterior geometric means of the ratio of each active dose to placebo for each post-baseline visit.

Equal tailed 95% credible intervals will be presented for each of the above back transformed values. In addition, the posterior probability that posterior ratios of each active dose to placebo are less than (<) CCI [redacted] will be calculated. A line plot of the adjusted posterior geometric means and credible intervals over time will be presented.

Dose Response Modelling

If deemed appropriate, the following dose-response models will be fitted for maximum change from baseline on a $\log_e$ scale (Max Δ) for Bcl-2 expression in T cells (MdFI) endpoint. In order to incorporate data from both SC and IV cohorts, the estimated bioavailability will be taken into account. This bioavailability estimate will be provided by CPMS following instream PK analysis, utilising data up to and including Cohort 6 data, prior to the end of study database lock (DBL).

- Four-parameters sigmoid Emax model is defined as,

$$Max\ \Delta(Bcl-2\ expression\ in\ T\ cells) = (E_o + X\beta_1) + (E_{max} + X\beta_2) * \left(\frac{dose^h}{{ED_{50}}^h + dose^h}\right) + \in$$

- Three-parameters E_{max} model is defined as,

$$Max\ \Delta(Bcl-2\ expression\ in\ T\ cells) = (E_o + X\beta_1) + (E_{max} + X\beta_2) * \left(\frac{dose}{ED_{50} + dose}\right) + \in$$

Where -
X is the continuous baseline value of Bcl-2 expression in T cells ($\log_e$ scale),
E_0 is the minimum dose effect (placebo) ($\log_e$ scale),
E_{max} is maximum achievable effect above E_0 ($\log_e$ scale),
ED_{50} is the dose which produces half of E_{max},
h is hill parameter determining the steepness of the dose response curve,
$\in$ is random error assumed to be normally distributed with mean zero and constant variance (σ^2)

The final model will be selected based on the best fit to the data.

Non-informative priors will be used in the analysis. The prior for E_0, E_{max}, β_1 and β_2 will be normally distributed with mean 0 and a variance 10^6. A functional uniform prior will be used for ED_{50} and h (Bornkamp, 2014), where the prior density for the functional uniform prior is based on all the parameters in the model. However, if a prior distribution appears not to be truly non-informative then alternative prior distributions may be used. An inverse gamma prior with shape of 0.001 and scale of 0.001 will be used for the residual variance (σ^2).

Once the dose response model has been fitted, the posterior distribution of model parameter ED50 will be summarized through mean, standard deviation and equal-tailed 95% credible intervals and the back transformed posterior distribution of model parameters E_0 and E_{max} will be summarised through geometric means, standard deviation on $\log_e$ scale and equal-tailed 95% credible intervals.

The following will be calculated from the model:

- For each study intervention: The posterior mean for Max Δ,
- For each active study intervention: The posterior difference in Max Δ for each dose vs placebo (GSK3888130B XX mg – Pooled placebo across cohorts),

These values will then be back transformed to give:

- For each study intervention: The posterior geometric mean for the ratio to baseline (for Max Δ),
- For each active study intervention: The posterior geometric means of the ratio of each active dose to placebo.

Equal-tailed 95% credible intervals will be presented for each of the above back transformed values. The dose response curve will be plotted for the geometric mean for the ratio to baseline (for Max Δ) with 95% credible intervals. The adjusted posterior geometric means and 95% credible intervals from the Bayesian MMRM analysis will also be included on this plot.

4.3.4. Target Engagement Biomarker Analyses

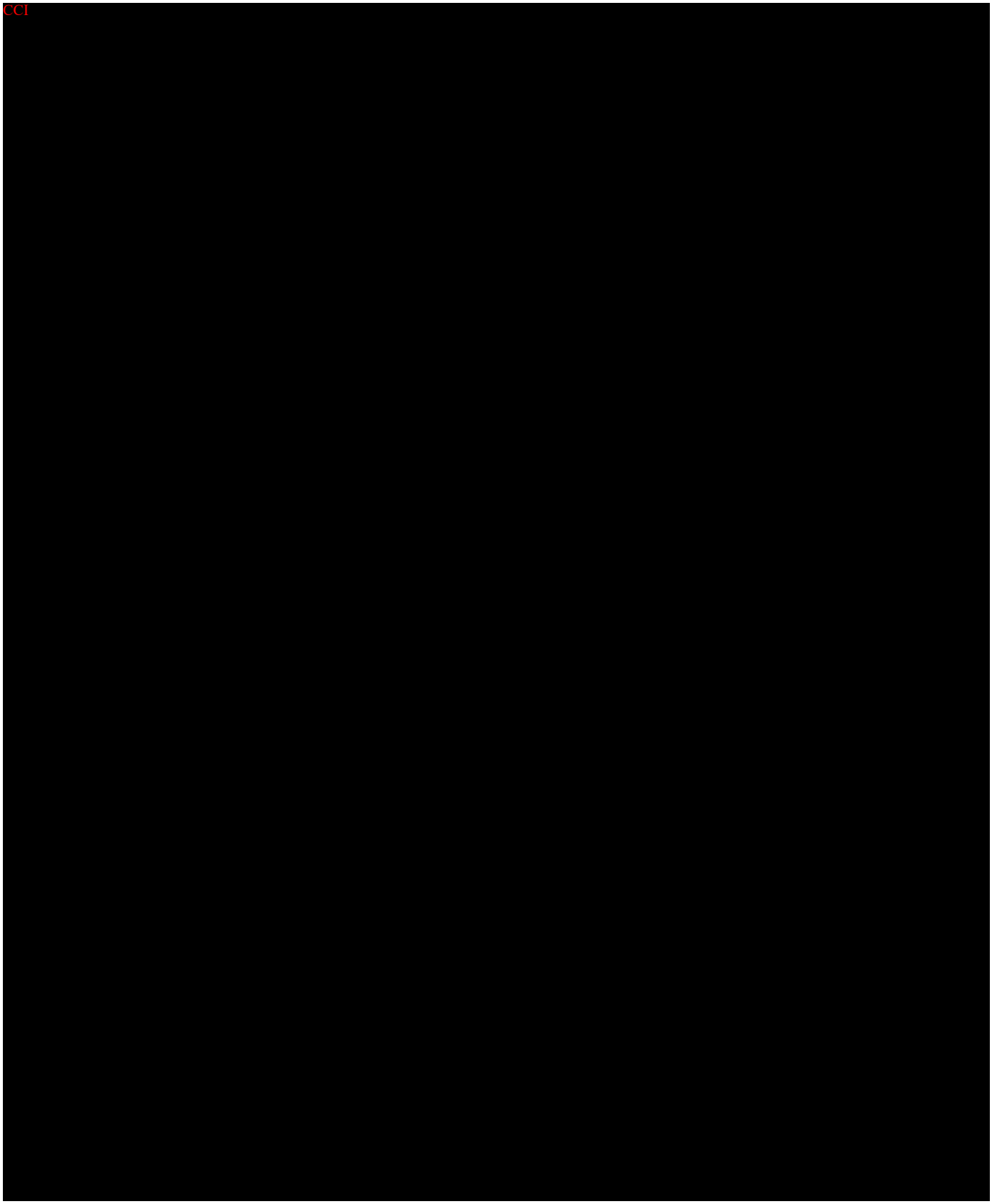
4.3.4.1. Main analytical approach

Free IL-7 levels will be derived from total IL-7 concentrations (named as Derived Free IL-7) over time using a nonlinear mixed effects modelling approach by the Clinical Pharmacology Modelling and Simulation (CPMS) department as described in Section 4.4.5. Summary outputs (geometric mean and 95% CIs) for derived free IL-7 inhibition will be reported by CPMS, separately to those outputs in the OPS but listed/cross-referenced in the CSR.

CCI [redacted]

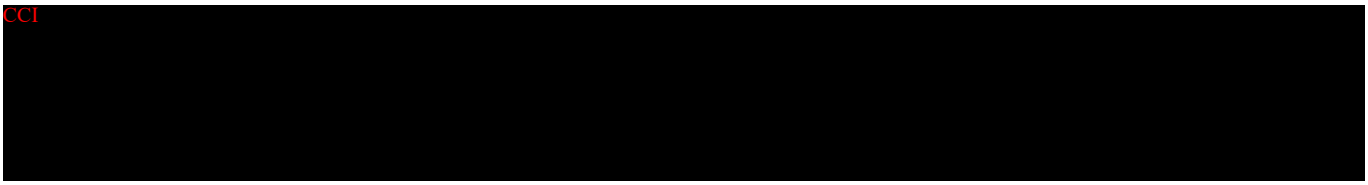
CCI [redacted]

CCI



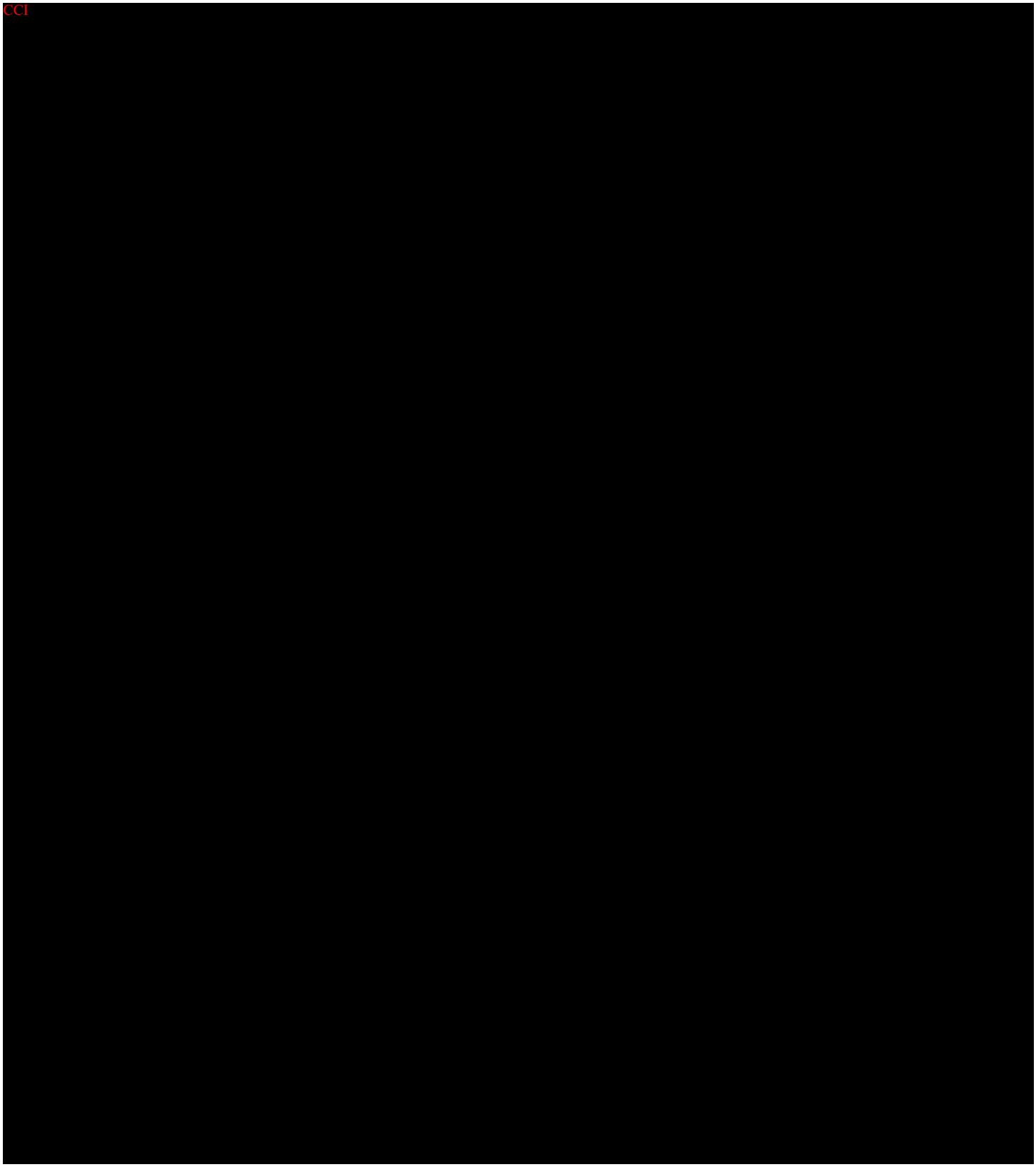
CCI

CCI



CCI

CCI



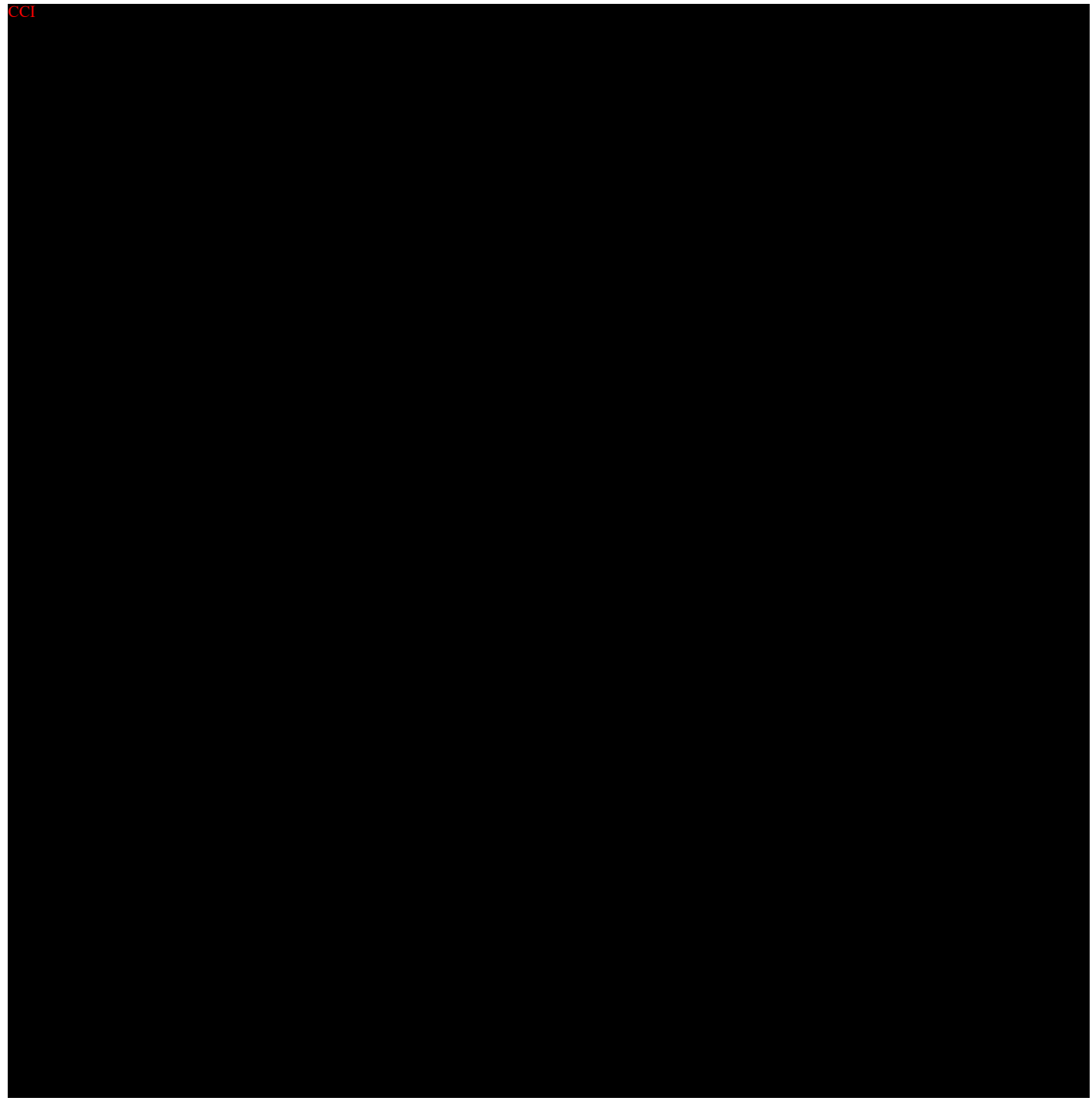
CCI

[redacted]

CCI

[redacted]

CCI



CCI

CCI [redacted]

4.5. Other Analyses

4.5.1. Subgroup analyses

No formal subgroup analyses are planned.

4.5.2. Other variables and/or parameters

CCI [redacted]

4.6. Dose Escalation

The Dose Escalation Plan describes the responsibilities, conduct of the DEC and how the integrity of the study, including blinding, will be maintained.

The site will provide safety reports (including $CD4^+$ T cell counts) for each dose escalation. CPMS will provide PK outputs including PK profiles and derived PK parameters from non-compartmental PK data analysis as permitted by data.

Additionally, study Statistics and Programming team members will provide outputs for each DEC meeting. describes the details of the analyses and outputs reviewed in the Dose Escalation meetings.

4.7. Interim Analyses

- **Interim Analysis – 1**

The first Interim Analysis will be performed once a minimum of four participants dosed with GSK3888130B in cohort 4 have completed up to and including the Day CCI visit.

During this interim analysis, safety data (including $CD4^+$ T cells counts), immunogenicity, PD biomarker T cell Bcl-2, TE total IL-7 levels and PK data will be reviewed.

Most of the outputs will be provided during the Cohort 4 DEC meeting. Additionally, study Statistics and Programming team members will provide Immunogenicity, Total IL-7 and PD biomarker T Cell Bcl-2 outputs for review. describes the details of the analyses and outputs that will be provided for this interim analysis.

CCI [redacted]

CCI [redacted]

- **Interim Analysis – 2**

The second Interim Analysis will be performed once all participants in cohort 6 have completed up to and including the Day CCI visit for PK, TE total IL-7 levels, PD secondary endpoint T cell Bcl-2, CCI [redacted], CCI [redacted] and up to and including Day CCI for safety endpoints.

During this interim analysis, selected study population, safety data (including $CD4^+$ T cells counts), immunogenicity, PK, TE total IL-7 levels, PD secondary endpoint T cell Bcl-2, cellular biomarkers, CCI [redacted], CCI [redacted] will be reviewed. describes the details of the analyses and outputs that will be provided for this interim analysis.

- **Early Data Extraction to CPMS**

CPMS will access unblinded data earlier than Interim Analysis – 2 reporting for the derivation of free IL-7 named as 'Derived Free IL-7 and for PK/PD modelling to support dose selection in future studies as detailed in the Section 4.4.5. GSK Biostatistics will share PK concentrations and total IL-7 data with CPMS via the HARP system and the Randomization Office team will share randomization schedules upon request from GSK Biostatistics. Participants' body weight data will be provided by Data management. Bcl-2 data will be accessed from External Alliance Portal (EAP) by CPMS.

Table 3 Summary of Dose Escalation and Interim Analysis

Deliverables	Domain	Outputs
Each DEC	TE	Summary plot of Total IL-7 Levels by dose (if data is available)
Interim Analysis – 1	1. Immunogenicity 2. PD 3. TE	1. Summary of Immunogenicity Results 2. Listing of Immunogenicity Results (only if positive immunogenicity results) 3. Summary plot of T Cell Bcl-2 data 4. Summary plot of Total IL-7 data
Interim Analysis - 2	1. Study Population 2. Safety (including CD4+ cell counts) 3. Immunogenicity	Detailed list of outputs mentioned in OPS

Deliverables	Domain	Outputs
	4. PK 5. PD Secondary endpoint (Bcl-2 T Cell) 6. TE (Total IL-7) 7. CCI [redacted] CCI [redacted] 8. CCI [redacted] 9. CCI [redacted] 10. CCI [redacted] 11. CCI [redacted] 12. CCI [redacted]	

Note: The subset of CCI [redacted] endpoints will be descriptively summarized and plotted by GSK Biostatistics based on internal review and will be included in the second Interim analysis.

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 2 (Dated: 10-FEB-2022).

5. SAMPLE SIZE DETERMINATION

Approximately 54 participants will be recruited to seven single ascending dose cohorts. Five participants will be randomized to either GSK3888130B or placebo in 3:2 ratio in cohorts 1 and 2. Eight participants will be randomized to either GSK3888130B or placebo in 3:1 ratio in all other cohorts, CCI [redacted] CCI [redacted]

No formal statistical techniques were used to calculate the sample size for this study; it has been determined to allow preliminary assessment of safety, tolerability, PK and PD. However, as a key secondary endpoint, considerations has been given to the ratio to baseline of the PD biomarker Bcl-2. It is assumed that this endpoint is $\log_e$ normally distributed. Based on 6 participants from the highest GSK3888130B dosed cohort and 14 placebo participants pooled across all cohorts, the probability of different true inhibition (GSK3888130B vs. placebo) thresholds of interest is given in the table below. A non-informative prior distribution and a maximum between participant SD ($\log_e$ scale) of 0.3 is assumed for both GSK3888130B and placebo arms.

CCI [redacted]

CCI [redacted]

CCI [redacted]

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 set will be provided.

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.

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 will be summarized: 18-64, 65-84 and >=85 based on the Enrolled Analysis Set.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

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

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- The Statistics and Programming team will review any treatment deviations after unblinding and will notify the study team. This is also captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

In addition to the overall summary of important protocol deviations, separate summaries will be produced for important protocol deviations related to COVID-19, and important protocol deviations not related to COVID-19 respectively.

Visits and assessments missed due to the COVID-19 pandemic, together with visits conducted remotely, will be summarized.

6.1.4. Prior and Concomitant Medications

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

6.1.5. Additional Analyses Due to the COVID-19 Pandemic

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

6.2. Appendix 2 Data Derivations Rule

CCI

[redacted]

6.2.2. Criteria for Potential Clinical Importance

The following criteria will be used to flag potential clinical importance:

Laboratory Values:

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1			0.54
Hemoglobin	g/L			180
		Δ from BL	>25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry			
Laboratory Parameter	**Units**	**Clinical Concern Range**	
		Low Flag (< x)	**High Flag (>x)**
Albumin	g/L	30	
Calcium	mmol/L	2	2.75
Creatinine	umol/L		>1.5xbaseline or increase from baseline ≥26 umol/L
Glucose	mmol/L	3	9
Potassium	mmol/L	3	5.5
Sodium	mmol/L	130	150

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 1.5x ULN
T. Bilirubin + ALT	µmol/L U/L	High	1.5x ULN T. Bilirubin + ≥ 2x ULN ALT

12 Lead ECG Values:

ECG Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	**Upper**
PR Interval	msec	< 110	> 220
QRS Interval	msec	< 70	> 120
Absolute QTcF interval	msec		>450
Increase from baseline QTcF	msec		>30

Vital Signs Values:

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	**Upper**
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

6.2.3. Study Day and Reference Dates

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

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

For data summaries by visit, scheduled visits with nominal visit description as well as the worst-case post baseline will be displayed. Unscheduled visits will not be displayed or slotted into a visit window but will be included in the derivation of worst-case post baseline assessment. All unscheduled visits will be displayed in the listing.

6.2.5. Multiple measurements at One Analysis Time Point

When multiple assessments are taken, the 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 multiple assessments are taken, 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.
• 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)</td></tr>
<tr><td>Adverse Events</td><td>• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
o If month and year of start date = month and year of study intervention start date, then
▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
▪ Else set start date = study intervention start date.
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>
</table></td></tr>
</table>

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

Element	Reporting Detail		
	Completely missing start/end date	No imputation	

TRADEMARKS

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM
SAS
WinNonlin

7. REFERENCES

Bornkamp, B. (2014). Practical considerations for using functional uniform prior distributions for dose-response estimation in clinical trials. Biometrical Journal, 56(6), 947–962.

CCI [redacted]

CCI [redacted]

CCI [redacted]

GSK Document Number TMF-15650507. Study ID 213960: A Randomised, Double-Blind, Placebo Controlled, Single Dose Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of GSK3888130B in Healthy Participants aged 18-55 inclusive. 21-MAR-2023.