Reporting and Analysis Plan

Study ID: 207804

Official Title of Study: Reporting and Analysis Plan for study 207804 A two-part phase I randomized, double-blind, placebo-controlled study toevaluate safety, tolerability, pharmacokinetics and target engagement of single intravenous and subcutaneous doses of GSK3858279 in healthy participants and to evaluate the efficacy of repeat subcutaneous doses in participants with osteoarthritis of the knee

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Division	:	Worldwide Development
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Title	:	Reporting and Analysis Plan for Study 207804: A two-part phase I randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, pharmacokinetics and target engagement of single intravenous and subcutaneous doses of GSK3858279 in healthy participants and to evaluate the efficacy of repeat subcutaneous doses in participants with osteoarthritis of the knee
Compound Number	:	GSK3858279
Study Number	:	207804
Effective Date	:	28-JUL-2022

Description:

The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report from Part A and Part B of Protocol 207804.

This RAP is intended to evaluate the:

- safety, tolerability, pharmacokinetics and target engagement of GSK3858279 in single intravenous and subcutaneous doses in healthy participants (Part A)
- safety, tolerability, efficacy, pharmacokinetics, target engagement and immunogenicity of repeat subcutaneous doses in participants with osteoarthritis of the knee (Part B).

This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverables.

Author	Date
PPD Study Statistician	28-JUL-2022
PPD CPMS Study Lead	

RAP Team Review Confirmations

(Method: E-mail)

Reviewer	Date
PPD Clinical Science Lead and Medical Monitor	11-JUL-2022
PPD CPMS Project Lead	12-JUL-2022
PPD Global Safety Representative	12-JUL-2022

Clinical Statistics Line Approvals

(Method: eSignature/email)

Approver	Date
PPD Project Statistician	21-JUL-2022
PPD Project Programming Leader	28-JUL-2022

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 207804:

Revision Chronology:		
Amendment 7	09-FEB-2022	TMF-14447953
Amendment 6	12-NOV-2021	TMF-11834237
Amendment 5	07-SEP-2020	2017N342035_05
Amendment 4	14-NOV-2019	2017N342035_04
Amendment 3	18-JUL-2019	2017N342035_03
Amendment 2	21-NOV-2018	2017N342035_02
Amendment 1	10-APR-2018	2017N342035_01
Original Protocol	02-FEB-2018	2017N342035_00

1.1. Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	01-MAR-2021	2017N342035_05 (07-SEP-2020)	Not Applicable	Original version.
SAP amendment 1	01-JUN-2021	2017N342035_05 (07-SEP-2020)	Part B sections	Part A, unmodified from previous version, and amended Part B.
SAP amendment 2	24-MAR-2022	TMF-14447953 (09-FEB-2022)	Part B Sections Programming notes for PK and TE outputs Adding additional Interim Analyses Information	Protocol was amended to account for two additional Interim Analyses.
SAP Amendment 3	28-JUL-2022	TMF-14447953 (09-FEB-2022)	Primary model update. Clarification on Intercurrent Events section. Additional outputs for IA4 and Part B SAC. Inclusion of safety tables (Part B 2.37-2.39)	Update to the model specification to avoid overparameterization by removal of the random subject intercept, and to include only data during the treatment period (i.e. up to week 8) in the primary analysis model. (Section 7)

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol 2017N342035_05 [(Dated: 07-Sep-2020)].

2.2. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Parts A and B To evaluate the safety and tolerability of escalating doses of GSK3858279 following single IV, single SC dosing in healthy participants and repeat SC dosing in OA participants.	Adverse Events (AE) and Serious Adverse Events (SAE). Clinical laboratory measurements, 12-lead electrocardiograms (ECG) and vital signs.
Part B To assess changes in pain in participants with OA of the knee following repeat SC dosing.	Change from baseline in average knee pain intensity at week 8. Change from baseline in worst knee pain intensity at Week 8.
Secondary	
To describe the pharmacokinetics (PK) of GSK3858279 following single IV, single SC in healthy participants and repeat SC dosing in OA participants.	CCI [redacted]
To evaluate the target engagement (TE) of CCL17 by GSK3858279 following single IV, single SC dosing in healthy participants and repeat SC dosing in OA participants.	CCI [redacted]
CCI [redacted]	

CCI

[redacted]

2.3. Study Design

This study will be a randomized, double-blind, placebo-controlled, two-part trial. A study diagram is included in Table 1.

Part A will be a single ascending dose escalation study to evaluate the safety, tolerability, PK, and target engagement of GSK3858279 in healthy participants. Single IV doses and a single SC dose will be investigated in separate cohorts of participants. Target engagement will be assessed both in blood and CCI [redacted] CCI Up to five single ascending IV dose levels of GSK3858279 will be investigated. A single SC dose of GSK3858279 will also be assessed to determine bioavailability, as future studies as well as the target product will likely involve SC administration.

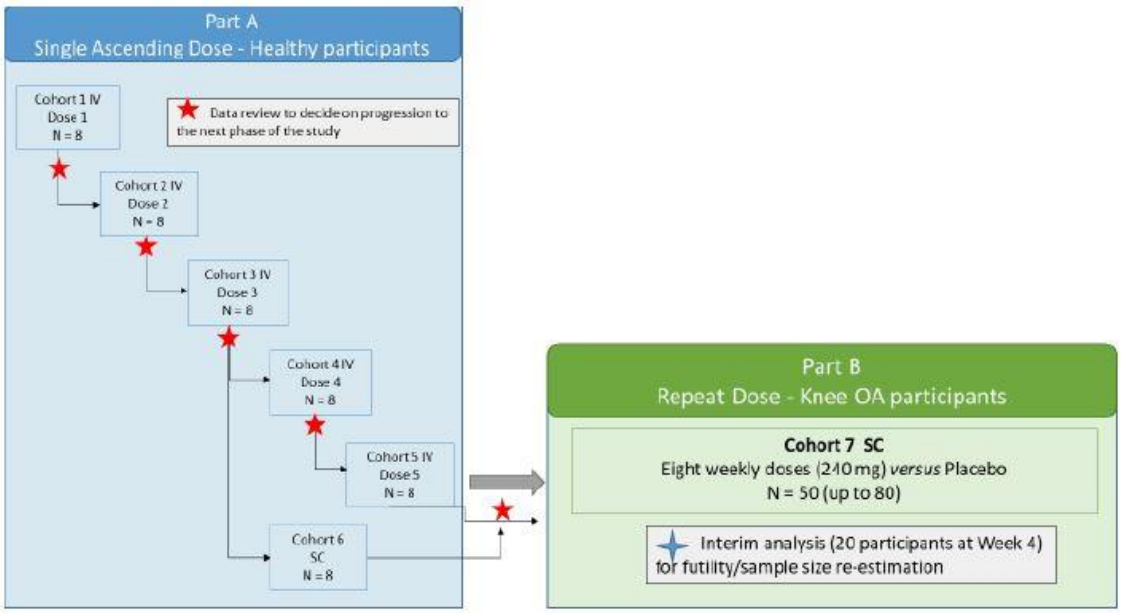
A Dose Escalation Committee (DEC) will review at least 15 days of safety and PK data prior to progression to the next dose level. The decision to progress the SC cohort will be based upon understanding the PK and TE data from some IV cohorts. Once sufficient safety, PK and target engagement data is collected from the top IV dose and SC cohorts, a data review will take place and a decision to proceed with Part B of the study may be made.

In Part A, sentinel participants will be used in each dosing cohort: two participants will be dosed first, one will be randomized to GSK3858279 and one to placebo. 48-hour post dose safety data from the sentinel participants will be reviewed by the investigator and the remainder of the cohort will then be dosed if deemed safe to do so.

Part B will investigate the safety, tolerability, clinical efficacy on pain (as primary endpoints), PK, target engagement and immunogenicity in participants with OA of the knee after weekly SC dosing for 8 weeks of GSK3858279 or placebo in a 1:1 ratio.

The table below provides an overview of the study design and the key features.

Table 1 Study Design

Study Design	
Figure 1: Parts A and B: Study Design  IV: intravenous; N: number of participants; OA: osteoarthritis; PK: pharmacokinetics; SC: subcutaneous	
Part A Design features	• Within each cohort, and hence at each dose level, GSK3858279 and placebo will be administered in a 3:1 ratio according to the randomisation schedule, in a blinded manner. • Of the eight participants within each cohort, six will receive GSK3858279 and two will receive placebo, as per the randomisation schedule. • Up to a maximum of 5 IV dose levels and 1 SC dose level will be studied in total in Part A. To mitigate a risk of adverse reactions, sequential dosing will be implemented. Two sentinel participants will receive study intervention first (one on active, one on placebo) per dosing cohort and will be monitored in the clinical unit for approximately 48 hours. • Assuming adequate safety from these two participants over the first 48 hrs post-dose, the remaining participants in the cohort can then be dosed. • Dose escalation data reviews will occur once sufficient safety and PK data is obtained from a cohort, and a dose escalation to the next planned dose may occur. • The decision to proceed to the next dose level of GSK3858279 will be made at a Dose Escalation Committee (DEC) meeting. Details are included in the Dose Escalation Plan (DEP). • Upon review of data from the 1 mg/kg IV cohort, the DEC may decide to trigger the SC cohort as well as the 3 mg/kg IV cohort, if data are satisfactory. • Once eight participants in the highest dose cohort in Part A have completed the Day 15 visit, the DEC will review all available safety, PK, target engagement (i.e, free and total CCL17 levels) in serum and decide whether to proceed with Part B of the study.

<table>
<tr><th colspan="2">Study Design</th></tr>
<tr><td></td><td>

In case of early dropouts, a minimum of 6 participants completing the Day 15 visit will be required for dose escalation data review [redacted]
Based on the emerging PK and TE data from Part A, a single IV dose up to 10 mg/kg is not suitable to test the mechanism in OA participants and hence a repeat SC dose of 240 mg is now considered more appropriate (Protocol Amendment #3, July 2019) and Protocol Amendment #5, Sept 2020 based on the observed TE of 3 mg/kg SC and predicted TE after repeat SC dosing.

</td></tr>
<tr><td>Part A Time & Events</td><td>

Refer to Appendix 2

</td></tr>
<tr><td>Part A Treatment sequences</td><td>Within each cohort, participants will be assigned to either GSK3858279 or placebo in a 3:1 ratio, where the intervention codes are as follows:
<table>
<tr><th>Intervention code</th><th>Intervention Description</th></tr>
<tr><td>A</td><td>0.1 mg/kg IV GSK3858279</td></tr>
<tr><td>B</td><td>0.3 mg/kg IV GSK3858279</td></tr>
<tr><td>C</td><td>1 mg/kg IV GSK3858279</td></tr>
<tr><td>D</td><td>3 mg/kg IV GSK3858279</td></tr>
<tr><td>E</td><td>10 mg/kg IV GSK3858279</td></tr>
<tr><td>F</td><td>SC GSK3858279</td></tr>
<tr><td>P</td><td>Placebo</td></tr>
</table>
</td></tr>
<tr><td>Part B Design Features</td><td>

In Part B, the total duration of the study (from 1st screening visit until final follow-up) for each participant will be up to 182 days (inclusive of a screening period of a maximum of 42 days).
Approximately 50 (up to a maximum of 80) participants with OA will be randomly assigned to GSK3858279 or placebo in a 1:1 ratio.
Each participant will receive weekly SC doses of either 240 mg GSK3858279 or placebo for 8 weeks.
Close in-stream safety review (AEs, clinical laboratory, vital signs, cardiac monitoring) is planned throughout for all participants (see Safety Management Plan).
An early detailed review of safety, PK, TE and ADA data following administration of repeat doses is intended for the first 8 participants (4 randomized to active treatment) when the 8th participant completes the Week 4 assessment.
A second detailed review of safety, PK, TE and ADA data is intended for the first 20 participants (10 randomized to active treatment) when the 20th participant completes the Week 4 assessment.
An interim analysis for futility will occur once approximately 20 participants have completed the Week 4 assessment.
A second interim analysis for an unblinded sample size re-estimation, including a futility assessment, may occur prior to enrolling the 50th participant, where the sample size could be decreased to a minimum of 20 or increased to a maximum of 80 participants enrolled if the observed SD of Change from baseline in the average knee pain intensity at week 8 is smaller or greater than 1.8 respectively. Sample size increase may also occur to account for participants who discontinue the treatment or study prior to Week 8. See Section 7.1.5.1 for more details
Additional interim analyses may occur for internal decision making and/or interaction with regulatory agencies as appropriate.

</td></tr>
</table>

<table>
<tr><th colspan="2">Study Design</th></tr>
<tr><td>Part B Time & Events</td><td>• Refer to Appendix 2</td></tr>
<tr><td>Part B Treatment sequences</td><td>• Participants will be assigned to either GSK3858279 or placebo in a 1:1 ratio, where the intervention codes are as follows:
<table>
<tr><th>Intervention code</th><th>Intervention Description</th></tr>
<tr><td>G</td><td>240 mg SC GSK3858279</td></tr>
<tr><td>P</td><td>Placebo</td></tr>
</table></td></tr>
</table>

2.4. Statistical Analyses

As the primary objective for part A of the study is safety and tolerability, and for part B is safety, tolerability and efficacy there are no formal hypotheses to be evaluated.

Part A: An assessment of dose proportionality will be conducted for selected pharmacokinetic endpoints (*i.e.* Cmax, and AUC(0-∞) and/or AUC(0-t)) following single IV dose. In addition, an exploratory comparison will be made between the IV and SC formulations at the dose level studied. This will be only done for the 3 mg/kg IV and SC doses.

Part B: A comparison between GSK3858279 and Placebo will be made on the pain numerical rating scale. An assessment will be made comparing GSK3858279 to placebo with respect to the change from baseline in average pain intensity at week 8. The change from baseline in worst pain intensity at week 8 will also be assessed.

3. PLANNED ANALYSES

3.1. Interim Analyses

Part A: No formal interim statistical analyses are planned. However, dose escalation meetings will occur at a relevant timepoint after each dose level; including between Parts A and B.

The decision to proceed to the next cohort, and next dose strength to be studied, will be made by the Dose Escalation Committee (DEC) based on assessment of safety and serum GSK3858279 pharmacokinetic data obtained in all participants at the prior dose level. Individual safety data (adverse events, laboratory safety tests, ECGs and vital signs) will be reviewed. In addition, immunogenicity data may be reviewed by the DEC during the study. Once sufficient safety, PK and target engagement data is collected from the top IV dose and SC cohorts, a data review will take place and a decision to proceed with Part B of the study may be made. Further details are included in the Dose Escalation Plan (DEP) Version 003 dated 19-Nov-2018.

Unblinded data from Part A may be reported out in full following the last subject last visit in this part of the study and prior to the conclusion of Part B.

Part B: The first interim analysis will occur once approximately 20 participants have completed the Week 4 assessment. A second interim analysis for an unblinded sample

size re-estimation may occur prior to enrolling the 50th participant, where the sample size could be decreased to a minimum of 20 or increased to a maximum of 80 participants.

Additional interim analyses may occur in order to inform internal decision making and/or for interaction with regulatory agencies as appropriate.

In addition to the interim analyses, two planned blinded safety data reviews as specified in the protocol will be carried out to decide upon dose adjustment, participant continuation/ discontinuation and if need be, to stop the study due to safety concerns. The necessary unblinded data will be summarised in a blinded fashion either by using dummy participant IDs or by presenting only group level data.

Further details of the part B interim analyses and safety reviews are outlined in the Interim Analysis Charter.

3.2. Final Analyses

The final planned analyses (Parts A and B) will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol (Section 4.5 End of Study Definition of the protocol): The end of the study is defined as the date of the last visit (including follow-up) of the last participant in the study (Parts A and B).
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management. The final delivery for Part A may be generated in its own reporting area prior to the completion of Part B of the study once Data Management has declared DBF for Part A. Parts A and B final deliveries may be generated and kept in separated reporting areas.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG and RAMOS NG procedures.

4. ANALYSIS POPULATIONS

4.1. Analysis Populations

4.1.1. Part A and B

Population	Description	Outputs
Screened	• All participants who were screened for eligibility	• Study Population (specific only)
Enrolled	• All participants who passed screening and entered the study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study are excluded from the Enrolled population as they did not enter the study.	• Study Population (Specific only)
Randomized	• All participants who were randomly assigned to treatment in the study. • This population will be based on the treatment the participant was randomized to.	• Study Population
Safety	• All randomized participants who received at least one dose of study treatment. • This population will be based on the treatment the participant received.	• Study Population (specific only) • Safety • PD
Pharmacokinetic	• All participants in the Safety population who had at least 1 reportable serum PK assessment. • This population will be based on the treatment the participant received. • Note: Non-quantifiable [NQ] values will be considered as reportable values	• PK

4.1.2. Part A only

Population	Description	Outputs
Blister	• All participants in the Safety population who had at least one blister assessment. • This population will be based on the treatment the participant received.	• PD
Blister Pharmacokinetic	• All participants in the Safety population who had at least 1 reportable blister PK assessment. • This population will be based on the treatment the participant received.	• PK

	• Note: Non-quantifiable [NQ] values will be	
CCI [redacted]		
Fully treated	• All participants in the Safety population who received at least 80% of planned study treatment*. • This population will be identified by review of protocol deviations	• PK, PD

*Part A has a single dose. Percentage of actual amount administered will be derived using the planned dose and the injected infusion volume.

4.1.3. Part B only

Population	Description	Outputs
Intent-to-Treat	• All randomized participants who received at least one dose of study treatment. • This population will be based on the treatment the participant was randomized to. Any participants who receive a treatment randomization number will be considered to have been randomized.	• Efficacy
Per Protocol	• All participants in the ITT population who comply with the protocol. • Protocol deviations that would exclude participants from the PP population are defined in Section 4.2 (Protocol Deviations) and Appendix 1: Exclusions from Per Protocol Population*).	• Efficacy (specific only)

* This population will be based on the treatment the participant was randomized to.

4.2. Protocol Deviations

Important protocol deviations (including but not limited to deviations related to study inclusion/exclusion criteria, and additionally in part B: prohibited medications, rescue medications, study medication and missing diary data) will be summarised and listed.

Important deviations which result in exclusion from the analysis population will also be summarised and listed.

Please refer to Appendix 1.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.

- This dataset will be the basis for the listings of protocol deviations.

A separate listing of all inclusion/exclusion criteria deviations will also be provided. This output will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. General

Separate outputs will be generated for both Part A and Part B.

5.2. Study Treatment Display Descriptors

In the Tables, Listings and Figures (TLF), treatment should be presented with placebo first, then in order of increasing dose by route of administration within each part.

Part A: Treatment group descriptions			
RandAll NG		Data displays for reporting	
Code	Description	Description	Order in TLF
A	0.1 mg/kg IV GSK3858279	0.1 mg/kg IV GSK3858279	2
B	0.3 mg/kg IV GSK3858279	0.3 mg/kg IV GSK3858279	3
C	1 mg/kg IV GSK3858279	1 mg/kg IV GSK3858279	4
D	3 mg/kg IV GSK3858279	3 mg/kg IV GSK3858279	5
E	10 mg/kg IV GSK3858279	10 mg/kg IV GSK3858279	6
F	SC GSK3858279	3 mg/kg SC GSK3858279	7
P	Placebo	Placebo	1

Part B: Treatment group descriptions			
RandAll NG		Data displays for reporting	
Code	Description	Description	Order in TLF
G	240 mg SC GSK3858279	240 mg SC GSK3858279	2
P	Placebo	Placebo	1

5.3. Baseline Definitions

The baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. Replicate assessments at a timepoint will be averaged, and the mean value will be used. Unless otherwise stated, if baseline data is missing, no derivation will be performed and baseline will be set to missing.

For the average and worst knee pain intensity, the mean of the scores in index knee over 7 days prior to dosing (Day -7 to Day -1) will be considered as baseline. Baseline should be calculated only if pain scores are recorded on at least 5 days out of 7. If pain scores are not recorded on at least 5 days, the baseline will be set to missing.

For Part B of the study, the CCL17 levels (free, total) baseline value will be derived by averaging the two pre-dose measurements (i.e., average of Day-4 and Day 1).

5.4. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices

Section	Component
Section 14.3	Appendix 3: Assessment Windows
Section 14.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
Section 14.5	Appendix 5: Data Display Standards & Handling Conventions
Section 14.6	Appendix 6: Derived and Transformed Data
Section 14.7	Appendix 7: Reporting Standards for Missing Data
Section 14.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

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

Study population analyses including analyses of participants' disposition, protocol deviations, demographic characteristics, prior and concomitant medications, baseline efficacy parameters, exposure, medical history and substance use will be based on GSK Core Data Standards.

Details of the planned displays are presented in Appendix 11.

7. EFFICACY ANALYSES – PART B ONLY

7.1. Co-primary Efficacy Analyses

7.1.1. Endpoint / Variables

The changes in pain in participants with OA of the knee following repeat SC administration are assessed using:

- Change from baseline in the average knee pain intensity at week 8.
- Change from baseline in the worst knee pain intensity at week 8.

7.1.2. Summary Measure

The primary summary measure will be the difference between treatments in mean change from baseline. The pain scores will be listed by participant and summarized descriptively by treatment.

7.1.3. Population of Interest

The analyses will be based on the Intent-to-Treat population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

There is one intercurrent event that is of interest:

1. Treatment Withdrawal (Participant discontinues the study treatment but continues to stay in the study)

No imputations would be carried out if there are missing data due to intercurrent events.

A hypothetical strategy will be used to estimate what the treatment effect would have been had the subject not experienced the intercurrent event. Data collected after the occurrence of the Intercurrent Event will be listed but not used in summary stats and stats analysis TFLs. Since the dosing interval in this study is 7 days, the date of occurrence of the treatment withdrawal intercurrent event will be defined as the date of the first missed dose of study treatment i.e. date of last dose of study treatment + 7 days. Pain scores are measured daily in the evening, therefore pain scores on or after the date of last dose of study treatment + 7 days will be considered as occurring after treatment withdrawal.

7.1.5. Statistical Analyses / Methods

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables

- Change from baseline in Average Knee Pain Intensity at Week 8
- Change from baseline in Worst Knee Pain Intensity at Week 8

Model Specification

- A Bayesian repeated measures model will be used to fit the change from baseline from Week 1 to Week 8.
- The endpoints will be assumed to follow a multivariate (MVN) normal distribution to model all repeated measurements within the same participant.
- Markov-Chain-Monte-Carlo (MCMC) method will be used to estimate the posterior distributions.
- A linear model for Change from Baseline at each Week (visit) will be constructed to model the within-participant covariance structures.
- Terms fitted in the model will include:
    - Categorical: Week (Week 1 to Week 8), Treatment (GSK3858279 and placebo), Treatment*Week Interaction, Baseline*Week Interaction
    - Continuous: Baseline
    - Repeated: Week

- The prior for the Variance Covariance Matrix will follow an Inverse Wishart Distribution.
- Vague priors (normal (0, var=1e6)) will be used for all other model parameters.
- Set simulation size at a minimum of 10000 and 1000 burn-in iterations. The simulation size and number of burn-in iterations could be updated during the convergence check.
- Refer to Appendix 6 - Bayesian Repeated Measures Model (PROC MCMC) for additional information
- Refer to Appendix 3 for details on visit computation.
- Refer to Appendix 9 for additional information

Model Checking & Diagnostics

- Bayesian Analyses: Refer to the relevant documentation (Bayesian Statistics Best Practice at GSK – Clinical Trials using Bayesian Inference).

- Refer to Appendix 9

Model Results Presentation

- Medians and 95% credible intervals will be produced by treatment group and for the difference between treatment groups, for each of the endpoints,
- The posterior distributions will be used to produce several probability statements:
    - P[True Difference (GSK3858279 – placebo) < X
    - where values of X to be generated are 0, -0.6, -0.8 and -1.0
- For all tables/figures presenting results from a statistical model, a footnote including model, prior distributions, covariates and a very brief mention of intercurrent events will be added.
- For all TFLs presenting efficacy endpoints, a footnote to state a range of the score for the endpoint specifying which direction of change is an improvement.

Interim Analysis 1

- A first interim analysis will occur once 20 participants reach Week 4
- The endpoint will be Change from baseline in average knee pain intensity at week 4

Interim Analysis 2

- A second interim analysis may occur once approximately 45 participants have been randomised (this estimated to happen when 28 participants reach Week 8) and will include a sample size re-estimation and a futility assessment. In addition to posterior probabilities, predictive probabilities of achieving criteria of interest at the end of the study will be estimated using a Bayesian Normal-Normal update. Vague priors for all modelling parameters will be used to compute the posterior distributions.
- Criteria of interest are:
  - P[True Difference (GSK3858279 – placebo) < X] where values of X to be generated are 0, -0.6, -0.8 and -1.0 and
  - Predictive probability > X%
- At the interim analysis an estimate of the standard deviation of the endpoint at week 8 will be estimated from the Bayesian Repeated Measures model. Details are given in Section 14.9.1. All data available at the time of the interim will be used for this purpose
- The ratio of the Estimated SD to Predicted SD (SD=1.8) for the change from baseline at Week 8 will be used to calculate the optimal sample size as follows:

$$SS_{optimal} = \left(\frac{SD_{estimated}}{1.8} \times \sqrt{50}\right)^2$$

- The optimal sample size must be within the range [# participants randomised, 80] subjects (i.e. if the optimal calculation is >80, the SS will be capped at 80/ if the optimal calculation is <50, the SS will be capped at # participants randomised). The number of participants resulting from the SS_optimal formula must be rounded up to the next even number.

Subgroup Analyses

- No subgroup analysis is planned for the study.

Sensitivity Analyses

- Refer to Section 14.9.2 for additional information.

Supportive Analyses

- The Bayesian Repeated Measures Model will be performed on the Per Protocol Population if the Per Protocol Population comprises 50 to 90% of the ITT population

7.2.2. Summary Measure

The difference in treatment mean change from baseline for WOMAC subscales scores and [redacted] will be analysed. In addition, the absolute and change from baseline values of WOMAC subscales scores, [redacted] and [redacted] (Individual and Overall) will be summarized descriptively by treatment. These scores will be also be listed by each participant and treatment.

Refer to Section 14.6.3 for details on calculation of WOMAC subscales scores.

The number of participants who took rescue medication will be summarised by treatment. In addition, the total weekly dose, average weekly dose and average rescue medication use will be summarized. A listing of rescue medication will be produced.

7.2.3. Population of Interest

The efficacy analyses will be based on the Intent-to-Treat population, unless otherwise specified.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

Intercurrent Events:

1. Treatment Withdrawal (Participant discontinues the study treatment but continues to stay in the study)

No imputations will be carried out if there are missing data due to intercurrent events.

A hypothetical strategy will be used to estimate what the treatment effect would have been had the subject not experienced the intercurrent event. Data collected after the occurrence of the Intercurrent Event will therefore not be used in the analysis. Since the dosing interval in this study is 7 days, the date of occurrence of the treatment withdrawal intercurrent event will be defined as the date of the first missed dose of study treatment

i.e. date of last dose of study treatment + 7 days. WOMAC, CCI [redacted] and PainDetect are measured pre-dose at each weekly visit, therefore assessments after the date of last dose of study treatment + 7 days will be considered as occurring after treatment withdrawal. Rescue Medication is assessed daily in the evening, therefore Rescue Medication on or after the date of last dose of study treatment + 7 days will be considered as occurring after treatment withdrawal.

7.2.5. Statistical Analyses / Methods

7.2.5.1. Statistical Methodology Specification

Endpoint / Variables
• WOMAC pain, stiffness and function subscales scores at Week 1,2,4,6,8 • CCI [redacted]
Model Specification

• A Bayesian repeated measures model will be used to fit the change from baseline from Week 1 to Week 8.
• The endpoints will be assumed to follow a multivariate (MVN) normal distribution to model all repeated measurements within the same participant.
• Markov-Chain-Monte-Carlo (MCMC) method in SAS will be used to estimate the posterior distributions of the endpoints.
• A linear model for Change from Baseline at each Week (visit) will be constructed to model the within-subject covariance structures.
• Terms fitted in the model will include:
  ○ Categorical: Week, Treatment (GSK3858279 and placebo), Treatment*Week Interaction, Baseline*Week Interaction
  ○ Continuous: Baseline
  ○ Repeated: Week
• The prior for the Variance Covariance Matrix will follow an Inverse Wishart Distribution.
• Set simulation size at a minimum of 10000 and 1000 burn-in iterations. The simulation size and number of burn-in iterations could be updated during the convergence check.
• The vague priors (normal (0, var=1e6)) will be used for the hyperparameters/all model parameters
• .
• Refer to Appendix 6 - Bayesian Repeated Measures Model (PROC MCMC) for additional information
• Refer to Appendix 3 for details on visit computation.
• Refer to Appendix 9 for additional information

Model Checking & Diagnostics
• Bayesian Analyses: Refer to the relevant documentation (Bayesian Statistics Best Practice at GSK – Clinical Trials using Bayesian Inference). • Refer to Appendix 9
Model Results Presentation
• Medians and 95% credible intervals will be produced by treatment group and for the difference between treatment groups each of the endpoints

• The posterior distributions will be used to produce several probability statements: • For WOMAC pain, stiffness and function subscales scores ▪ P[True Difference (GSK3858279 – placebo) < X] where values of X to be generated are 0, -0.6, -0.8 and -1.0 • For CCI [redacted] CCI [redacted] • For all tables/figures presenting results from a statistical model, a footnote including model, prior distributions, covariates and a very brief mention of intercurrent events will be added. • For all TFLs presenting efficacy endpoints, a footnote to state a range of the score for the endpoint specifying which direction of change is an improvement.
Subgroup Analyses
• No subgroup analyses is planned for the study.

8. SAFETY ANALYSES

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

8.1. Adverse Events Analyses

The definition of an AE is detailed in Appendix 3 of the protocol (Section 10.3).

Analyses of AEs will include those events that are on-treatment (Section 14.4.1).

Adverse events analyses including the analysis of Adverse Events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards.

Details of the planned displays are presented in Appendix 11.

8.2. Clinical Laboratory Analyses

Laboratory evaluations will be based on GSK Core Data Standards and will include:

- Hematology laboratory tests
- Chemistry laboratory tests
- Urinalysis
- Other screening tests

Details of the planned displays are presented in Appendix 11.

The laboratory assessments for each category are displayed in Table 2.

Table 2 Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1,2,3]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase	[2]Cardiac troponin T [3]NT-proBNP
Routine Urinalysis[1]	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination and laboratory quantification of proteinuria (if blood or protein is abnormal on dipstick) Part B: Alcohol			
Combined throat and nasopharyngeal swab	COVID-19 (SARS-CoV2) (see SRM for further details)			
Other Screening Tests	Blood (serum): Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) Serology (TB test, HIV antibody, HBsAg, HBcAb and hepatitis C virus antibody) QuantiFERON test Complement protein C3 and C4 Urine: Urine drug screen to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines. Urine albumin-creatinine ratio (UACR)			

Notes

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Protocol Section 7.2.1 and Appendix 6a and 6b of protocol. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which

may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2.Troponin T using high sensitivity test.
3.NT-proBNP (N-terminal pro B-type natriuretic peptide) at baseline and Day 57 visit only.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

8.3. Other Safety Analyses

The analyses of non-laboratory safety test results will be based on GSK Core Data Standards, unless otherwise specified.

The non-laboratory safety test results include:

- Vital Signs
- ECGs
- Echocardiogram
- Telemetry (for Part A only)
- Holter monitoring (for Part B only at Screening)

8.4. COVID-19 Pandemic Statistical Displays

A summary of the following COVID-19 assessments may be produced: Case Diagnosis, COVID-19, Test performed, and Results of the COVID-19 test. Additionally, a listing of all subjects with visits and assessments impacted by the pandemic may be produced. The listing will include:

1. Site Identifier
2. Treatment for parallel group studies
3. Unique Subject Identifier
4. Subject Identifier
5. Impacted Visit
6. Impact
7. Reason for Impact

Details of the planned displays are presented in Appendix 11.

9. PHARMACOKINETIC ANALYSES

9.1. Serum Pharmacokinetics

The PK analyses described below will be carried out for GSK3858279 in serum.

9.1.1. Endpoint / Variables

CCI [redacted]

9.1.1.1. Drug Concentration Measures

Refer to Appendix 5(Section 14.5.3).

9.1.1.2. Derived Pharmacokinetic Parameters

CCI [redacted]

NOTES:

CCI

[redacted]

9.1.1.2.2. Part B

CCI

[redacted]

NOTES:

Additional parameters may be included as required.

In the event that a robust and predictive population PK/TE model cannot be developed e.g. data limited by high levels of NR data, all parameters listed in the table will be derived directly from the observed data using standard non-compartmental analysis. In such case, PK parameters for subjects on sparse sampling schedule will be only calculated at weeks 1 and 8.

9.1.2. Summary Measure

Individual and mean/median concentration-time profiles of GSK3858279 in serum (stratified by treatment group in Part A) will be plotted and listed. Serum concentrations will be summarized descriptively. Derived serum PK parameters will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

9.1.3. Population of Interest

The serum pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified.

9.1.4. Strategy for Intercurrent (Post-Randomization) Events

Missing data would be considered as Missing at Random and no imputations for missing data would be carried out.

9.1.5. Statistical Analyses / Methods

Details of the planned displays are presented in Appendix 11 and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

9.1.5.1. Dose proportionality

Dose proportionality in Part A will be assessed by visual inspection of:

- Dose normalised AUC(0-∞) [or if not available AUC(0-t)] and Cmax values versus dose.

Dose proportionality may also be assessed using the power model described below.

Dose proportionality
Endpoints
• AUC(0-t), AUC(0-∞) and Cmax
Model specification
• Power model (log-log linear model): $y = \alpha \times dose^{\beta} \Leftrightarrow \log_e(y) = \log_e(\alpha) + \beta \times \log_e(dose)$ Where ○ y = endpoint of interest ○ dose = actual dose (mg) received under fasted condition ○ β = parameter associated to dose (slope)

○ α = subject-specific random effect (intercept) • Terms fitted in the power model: ○ Response: log transformation of the endpoint of interest $\log_e(y)$ ○ Fixed continuous covariates: $\log_e(dose)$ ○ Random: subject
Model checking & diagnostics
• Normality 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 there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data
Model results presentation
Table of the estimated slopes and 90% CI (slope close to 1 implies dose proportionality)

CCI

CCI

[redacted]

9.2.1. Endpoint / Variables

Blister concentrations of GSK3858279.

9.2.1.1. Drug Concentration Measures

Refer to Appendix 5 (Section 14.5.3).

9.2.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will not be calculated due to the sparsity of blister fluid samples.

The within subject and timepoint blister fluid:serum concentration ratio for GSK3858279 may be determined from the concentration-time data if data permit.

9.2.2. Summary Measure

Individual and mean/median concentration-time profiles of GSK3858279 in blister fluid (stratified by treatment group) will be plotted and listed. Blister fluid concentrations will be summarized descriptively.

9.2.3. Population of Interest

The blister pharmacokinetic analyses will be based on the Blister Pharmacokinetic population, unless otherwise specified.

9.2.4. Strategy for Intercurrent (Post-Randomization) Events

Missing data would be considered as Missing at Random and no imputations for missing data would be carried out.

9.2.5. Statistical Analyses / Methods

Details of the planned displays are presented in Appendix 11 and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

10. PHARMACODYNAMIC ANALYSES

10.1. Serum Target Engagement Analyses

The Target Engagement analyses described below will be carried out for Free and Total CCL17 in Serum.

10.1.1. Endpoint / Variables

Free and Total CCL17 levels in serum and derived Target Engagement parameters.

10.1.1.1. Target Engagement Concentration Measures

Refer to Appendix 5 (Section 14.5.4).

10.1.1.2. Derived Target Engagement Parameters

10.1.1.2.1. Part A

All Target Engagement parameters in Part A will be determined directly from the observed concentration-time data, as data permits. All calculations will be based on actual sampling times.

Target Engagement parameters that will be calculated for free CCL17 in Part A are listed below. Additional parameters may be included as required.

CCI

[redacted]

NOTES:
Additional parameters may be included as required.

Target engagement parameters that will be calculated for total CCL17 in Part A are listed below. Additional parameters may be included as required.

CCI

[redacted]

NOTES:
Additional parameters may be included as required.

10.1.1.2.2. Part B

All Target Engagement parameters in Part B will be calculated using a model based post-hoc analysis and the currently supported version of NONMEM. The model based post-hoc analysis is described in Section 11. All calculations will be based on actual sampling times.

Target Engagement parameters that will be calculated for free CCL17 in Part B are listed

CCI

[redacted]

CCI

[redacted]

NOTES:
Additional parameters may be included as required.
[1]In the event that a robust and predictive population PK/TE model cannot be developed e.g. data limited by high levels of NR data, TE parameters will be derived directly from the observed data.

Target engagement parameters that will be calculated for total CCL17 in Part B are listed below. Additional parameters may be included as required.

CCI

[redacted]

NOTES:
Additional parameters may be included as required.

[1]In the event that a robust and predictive population PK/TE model cannot be developed e.g. data limited by high levels of NR data, TE parameters will be derived directly from the observed data.

10.1.2. Summary Measure

Individual and median/mean concentration-time profiles of Free and Total CCL17 (stratified by treatment group in Part A) will be plotted and listed. Free and Total CCL17 concentrations in serum will be summarized descriptively.

Derived serum TE parameters will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

10.1.3. Population of Interest

The target engagement analyses will be based on the Safety population, unless otherwise specified.

10.1.4. Strategy for Intercurrent (Post-Randomization) Events

Missing data will not be imputed, regardless the reasons.

10.1.5. Statistical Analyses / Methods

Details of the planned displays are presented in Appendix 11 and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 10.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

CCI

The within subject and timepoint blister fluid:serum concentration ratio for free and total CCL17 may be determined from the concentration-time data if data permit. The free and total CCL17 concentrations will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

10.3. Immunogenicity

10.3.1. Summary Measure

The number and percentage of confirmed positive samples in each treatment group will be presented at each time assessed. Only binding antibody detection is collected in this study. Neutralising antibody detection is not collected.

10.3.2. Population of Interest

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

For the in-stream safety reviews 1 and 2, subject data will be anonymised as outlined in Appendix 6

11. PHARMACOKINETIC / TARGET ENGAGEMENT / PHARMACODYNAMIC (PK/TE/PD) ANALYSES

The primary goal of this analysis is to characterize the Pharmacokinetic / Target Engagement (PK/TE) relationship of GSK3858279 following IV and SC administration to healthy and OA participants. The influence of subject demographics and baseline characteristics, including disease activity, may be investigated. PK and TE data will be analysed using the currently supported version of NONMEM. Details of this analysis are described in a separate RAP [GSK Document number TMF-14343601.

The relationship between Pharmacokinetic / Target Engagement / Pharmacodynamic (PK/TE/PD) of GSK3858279 following repeat SC administration to OA participants may also be explored. Details of this analysis are described in a separate RAP GSK Document number TMF-14343601.

11.1. Pharmacokinetic / Target Engagement / Pharmacodynamic Dataset Specification

The dataset specification to support any PK/TE/PD analysis will be provided as a separate document.

The merging of PK, TE, treatment, demographic and efficacy data together with the creation of the NONMEM-specific dataset will be performed by, or under the direct auspices of, Clinical Statistics & Programming, GSK.

This dataset programming will be conducted in a HARP environment using the currently supported version of SAS.

12. BIOMARKER ANALYSES – PART A ONLY

12.1. Immune Cell Phenotypes

CCI [redacted]

12.1.2. Summary Measure

Two summary measures are of interest, the treatment effect (Placebo vs GSK3858279) and the difference between sample types (Blood vs Blister).

- Mean Treatment Difference in Change from baseline at all visits
- The within subject and timepoint ratio of Blister:Blood at all visits – only for blister induced cohorts of Part A

Measures of sample reliability (Blister Volume and Total White Blood Cell Count) will be listed only.

CCI [redacted]

12.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11 and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 10.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

12.1.4.1. Statistical Methodology Specification

Endpoint / Variables

- Percentage of Immune Cell Phenotypes

Model Specification

- Endpoints will be analyzed for each flow cytometry cell type using generalized linear mixed models (GLMM) with appropriate link functions or transformations performed as required.
- Terms in GLMM model will include:
    - categorical: baseline, treatment group, sample type, visit and two 3-way interactions
        - baseline with sample type with treatment group
        - visit with sample type with treatment group
    - Random effect: subject
- The Kenward 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.
- An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the RANDOM line.
    - In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS.
    - Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- LS Means for the Sample Type by Treatment by Visit will be calculated using the observed baseline mean for each sample type separately.

Model Checking & Diagnostics

- 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 there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.

Model Results Presentation

For summary measure 1 (mean treatment difference), for each sample type and each treatment group:

- Number of subjects in analyses
- Least Squares Mean of Change from Baseline with Standard Error

For all GSK3858279 arms

- Difference to Placebo, 95% Confidence Interval and p-value
- In addition for 3 mg SC:
- Difference to 3mg IV, 95% Confidence Interval.

For summary measure 2 (Mean Sample Type Difference), for each treatment group and overall (see note) and each sample type:

- Number of subjects in analyses
- Least Squares Mean of Change from Baseline with Standard Error

For Blister

- Difference to Blood, 95% Confidence Interval

Note: overall (treatment-independent) mean will be calculated for Blister and Blood, for each visit. Plots of LS Means (+/- SE) and Difference (95% CI) will be presented.
Sensitivity and Supportive Analyses
• A characterisation of the dose and/or exposure response may be carried out if data allows.

CCI

[redacted]

13. REFERENCES

GlaxoSmithKline Document Number 2017N342035_00. Study ID 207804: A two-part phase I randomized double blind (sponsor open) placebo controlled study to evaluate safety, tolerability, pharmacokinetics, target engagement and potential for efficacy of single intravenous and subcutaneous doses of GSK3858279 in healthy volunteers and participants with osteoarthritis of the knee.

GlaxoSmithKline Document Number 2017N342035_01. Study ID 207804: A two-part phase I randomized double blind (sponsor open) placebo controlled study to evaluate safety, tolerability, pharmacokinetics, target engagement and potential for efficacy of single intravenous and subcutaneous doses of GSK3858279 in healthy volunteers and participants with osteoarthritis of the knee.

GlaxoSmithKline Document Number 2017N342035_02. Study ID 207804: A two-part phase I randomized double blind (sponsor open) placebo controlled study to evaluate safety, tolerability, pharmacokinetics, target engagement and potential for efficacy of single intravenous and subcutaneous doses of GSK3858279 in healthy volunteers and participants with osteoarthritis of the knee.

GlaxoSmithKline Document Number 2017N342035_03. Study ID 207804: A two-part phase I randomized, double blind, placebo controlled study to evaluate safety, tolerability, pharmacokinetics and target engagement of single intravenous and subcutaneous doses of GSK3858279 in healthy participants and to evaluate the efficacy of repeat subcutaneous doses in participants with osteoarthritis of the knee.

GlaxoSmithKline Document Number 2017N342035_04. Study ID 207804: A two-part phase I randomized, double blind, placebo controlled study to evaluate safety, tolerability, pharmacokinetics and target engagement of single intravenous and subcutaneous doses of GSK3858279 in healthy participants and to evaluate the efficacy of repeat subcutaneous doses in participants with osteoarthritis of the knee.

GlaxoSmithKline Document Number 2017N342035_05. Study ID 207804: A two-part phase I randomized, double blind, placebo controlled study to evaluate safety, tolerability, pharmacokinetics and target engagement of single intravenous and subcutaneous doses of GSK3858279 in healthy participants and to evaluate the efficacy of repeat subcutaneous doses in participants with osteoarthritis of the knee.

GlaxoSmithKline Document Number TMF-11834237. Study ID 207804: A two-part phase I randomized, double blind, placebo controlled study to evaluate safety, tolerability, pharmacokinetics and target engagement of single intravenous and subcutaneous doses of GSK3858279 in healthy participants and to evaluate the efficacy of repeat subcutaneous doses in participants with osteoarthritis of the knee.

GlaxoSmithKline Document Number TMF- 14447953. Study ID 207804: A two-part phase I randomized, double blind, placebo controlled study to evaluate safety, tolerability, pharmacokinetics and target engagement of single intravenous and subcutaneous doses of GSK3858279 in healthy participants and to evaluate the efficacy of repeat subcutaneous doses in participants with osteoarthritis of the knee.

GlaxoSmithKline Document Number TMF-14343601 (v1.0). Project Data Analysis Plan for an Integrated Analysis of GSK3858279 Pharmacokinetic/Target Engagement/Pharmacodynamic relationship in Healthy Participants, Participants with Osteoarthritis of the Knee and other Indications. Effective Date 30-Dec-2021.

14. APPENDICES

14.1. Appendix 1: Protocol Deviation Management and Definitions for Fully Treated Population

14.1.1. Exclusions from Fully Treated Population (Part A) and Per Protocol Population (Part B)

Part A: A participant meeting any of the following criteria will be excluded from the Fully Treated population:

Exclusion Description
Patient did not receive ≥ 80% of planned medication*

*Part A has a single dose. Percentage of actual amount administered will be derived using the planned dose and the injected infusion volume. In case a subject didn't receive a full dose in PART A, the actual amount of drug administered (AMT) will be calculated as AMT [mg]= numerical part of treatment group [mg/kg] * WTBL [kg] * percentage of infusion volume / 100 when EXPOSURE.ACTTRT is "GSK3858279". In case a subject from the 3 mg/kg SC treatment group didn't receive a full dose and WTBL≥ 80 kg, then AMT [mg]= 240 [mg] * percentage of infusion volume / 100. The percentage of infusion volume (TVOLPCT) is assumed 100 for a full dose.

Part B: A participant who meets any of the below criteria will be excluded from the Per Protocol population:

Violation Category	Criterion Violated	Deviation
Inclusion/ Exclusion Criteria	Inclusion Criteria No. 7	Did not have OA of the index knee as defined by symptoms for ≥6 months with a clinical diagnosis of OA as per American College of Rheumatology (ACR) clinical diagnosis criteria
	Inclusion Criteria No. 8	Did not have an average of daily pain score ≥4 and ≤9 by the 11-point NRS (0-10) in index knee over 7 days prior to dosing (Day-7 to Day-1). Data should be recorded on at least 5 of 7 occasions by the participant to obtain a valid baseline value.
	Inclusion Criteria No. 9	Did not have a Kellgren and Lawrence (KL) score ≥2 on X-ray obtained during screening (Kellgren, 1957).
	Exclusion Criteria No. 39	Diagnosis of current inflammatory arthritis such as rheumatoid arthritis, autoimmune disorder affecting joints, seronegative spondyloarthritis, gout or pseudogout in any joint (defined as acute episodic attacks of swollen, painful joint in a patient with X-Ray chondrocalcinosis or calcium pyrophosphate dihydrate [CPPD] crystals). Note: asymptomatic CPPD crystals on X-ray are not an exclusion
	Exclusion Criteria No. 67	Underwent intra-articular therapy within 3 months prior to signing the informed consent.
	Exclusion Criteria No. 68	Intake of Immunosuppressants, including corticosteroids (parenteral within 3 months of screening; oral within 1 month of screening).
Prohibited Medications*		Any use of Systemic Corticosteriods from screening until the end of Week 8

Violation Category	Criterion Violated	Deviation
		Any use of Intra-articular therapy of the index joint from screening until the end of Week 8
		Any use of, opioids, NSAIDs, topical analgesics or anti-neuropathic agents 24 hours before a clinical visit on more than 1 visit during the first 8 weeks (Day 1 – Day 57)
		Any use of opioids, NSAIDs, topical analgesics or anti-neuropathic agents for more than 1 day per week on more than 1 visit during the first 8 weeks (Day 1 – Day 57)
CCI [redacted]		
Study Medication		Missing more than 1 dose out of 8 doses of study treatment
Missing Diary Data		Missing average knee pain or worst knee pain diary data for more than 2 days per week in more than 1 week out of the first 8 weeks (Day 1 – Day 57)
		Missing rescue medication (paracetamol) diary data for more than 2 days per week in more than 1 week out of the first 8 weeks (Day 1 – Day 57)

*Where medications listed above need to be identified programmatically, a list of dictionary codes from the GSK Drug dictionary will be defined with input from the study physician and coding dictionary analyst. The list will be created prior to unblinding and stored in a spreadsheet in refdata.

14.2. Appendix 2: Schedule of Activities

14.2.1. Screening

PROCEDURE	**SCREENING PERIOD** Screening may be performed across one or more visits. **Part A:** up to 28 days before Day 1. **Part B:** from Day -42 to Day -5 (up to 42 days before Day 1)	NOTES
Informed consent	X	,
Inclusion and exclusion criteria	X	
Demography	X	
Full physical examination	X	
Medical/medication/drug/alcohol history	X	
Alcohol and tobacco screens	X	As per standard local practice. Smoking permitted only in Part B.
Urine drug screen	X	
HIV, Hepatitis B (HBsAg and HBcAb) and Hepatitis C (HepC antibody) screening	X	
Holter monitoring	X	24 hour for Part B only
12-lead ECG	Triplicate	
Vital signs	X	See SRM for details
Echocardiogram	X	
Haematology, clinical chemistry, urinalysis	X	Refer to Appendix 2. C3, C4 and BNP are included.
COVID-19 (SARS-CoV-2)	X	Documented negative COVID test within two days of initial screening OR test performed at the time of initial screening
TB Screening (QuantiFERON)	X	
FSH and estradiol (in WNCBP)	X	
Height and weight	X	
X-ray (K&L of index knee joint)	Part B	Inclusion Criterium. X ray performed *only* if ALL other inclusion and exclusion criteria were already met at initial screening (except NRS). Allow at least 7 calendar days for the X-ray result to be returned from central reading.
Daily pain scores (Digital Tool)	Part B (Day -7 to Day -1)	Scores will be recorded over the 7 consecutive evenings preceding dosing. Average result (Baseline value) will be evaluated for inclusion.
SAE assessment	X	From signing consent

14.2.2. Part A Cohorts Without Blister: 0.1 and 0.3 mg/kg IV

	Day												Early	Notes
Procedure	–1	1	2	3	8	15	22	29	43	57	85	113	**withdrawal**	Allowed visit windows are detailed in the SRM
Out-patient visit					X	X	X	X	X	X	X[1]	X[2]	X	[1] Final follow-up visit for 0.1 mg/kg cohort [2] Final follow-up visit for 0.3 mg/kg cohort
Admission in clinical unit	X													
Discharge from clinical unit				X										
Inclusion and exclusion criteria	X													
Brief physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	
Alcohol and tobacco screens	X													As per standard local practice
Urine drug screen	X													
Cardiac telemetry	X													Telemetry from at least 12 hrs before dosing until 12hrs post dose. Output to be reviewed for abnormalities prior to dosing on Day 1.
12-lead ECG	Triplicate	X[1]	X	X	X	X	X	X	X	X	X	X	X	On day -1 and day 1 ECGs may be generated from telemetry [1] On Day 1, pre dose then every 30 mins during infusion (i.e. 30 mins and 60mins after start of infusion) and then 1 hr post end of infusion.
Vital signs	X	X[1]	X	X	X	X	X	X	X	X	X	X	X	[1] On Day 1, pre dose then every 15 mins during infusion (i.e. 15, 30, 45 and 60mins post the start of infusion) and then 30 mins, 1, 2 and 4 hr post end of infusion.
Haematology, clinical chemistry, urinalysis	X		24hr post dose	48hr post dose	X	X	X	X	X	X	X	X	X	
Weight	X													Weight to be used to calculate the study treatment dose.
Randomization		Pre-dose												
CCI [redacted]														
Study treatment dosing		X												
AE assessment		<---------->											X	
SAE assessment	<---------->												X	
Concomitant medication review	<---------->												X	

14.2.3. Part A Cohorts With Blister: 1 mg/kg IV

	Day														Early	Notes
Procedure	–1	1	2	3	7	8	15	22	29	42	43	57	85	113	withdrawal	Allowed visit windows are detailed in the SRM
Out-patient visit							X	X	X			X	X	X	X	
Admission in clinical unit	X				X					X						
Discharge from clinical unit				X		X					X					
Inclusion and exclusion criteria	X															
Brief physical examination	X	X	X	X	X		X	X	X	X		X	X	X	X	
Alcohol and tobacco screens	X															As per standard local practice
Urine drug screen	X															
Cardiac telemetry	X															Telemetry from at least 12 hrs before dosing until 12hrs post dose. Review for abnormalities prior to dosing on Day 1.
12-lead ECG	Triplicate	X[1]	X	X	X		X	X	X	X		X	X	X	X	On Day -1 and Day 1 ECGs may be generated from telemetry [1] On Day 1, pre dose then every 30 mins during infusion (i.e. 30 mins and 60mins after start of infusion) and then 1 hr post end of infusion.
Vital signs	X	X[1]	X	X	X		X	X	X	X		X	X	X	X	[1] On Day 1, pre dose then every 15 mins during infusion (i.e. 15, 30, 45 and 60mins post the start of infusion) and then 30 mins, 1, 2 and 4 hr post end of infusion.
Haematology, clinical chemistry, urinalysis	X		24hr	48hr	X		X	X	X	X		X	X	X	X	
Weight	X															Weight to be used to calculate the study treatment dose.
Randomization		Pre-dose														
Induction of blister	X				X					X						
Aspiration of blister fluid		X				X					X					Aspiration 21 hours (+/- 3 hours) after induction of blister.
Blood sample for circulating immune cells		X				X					X					Cohort 3 only (not needed for Cohorts 1 and 2)
PK blood sample		X	24hr post dose	48hr post dose		X	X	X	X		X	X	X	X	X	D1 Samples to be taken at IV cohorts - pre-dose, 2 hr, 4 hr, 8 hr, and 12 hr post dose SC cohort - pre-dose and 8 hr post dose
CCI																
Study treatment dosing		X														
AE assessment	<----------													---------->	X	
SAE assessment	<----------													---------->	X	
Concomitant medication review	<----------													---------->	X	

14.2.4. Part A Cohorts With Blister: 3 and 10 mg/kg IV and SC

	Day														Early withdrawal	Notes
Procedure	–1	1	2	3	7	8	15	22	28	29	43	57	85	113	141		Allowed visit windows are detailed in the SRM
Out-patient visit							X	X		X		X	X	X[1]	X[2]	X	[1] Final follow-up visit for 3 mg/kg IV cohort [2] Final follow-up visit for 10 mg/kg IV and SC cohorts
Admission in clinical unit	X				X				X								
Discharge from clinical unit				X		X				X							
Inclusion and exclusion criteria	X																
Brief physical examination	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	
Alcohol and tobacco screens	X																As per standard local practice
Urine drug screen	X																
Cardiac telemetry	X																Telemetry from at least 12 hrs before dosing until 12hrs post dose. Review for abnormalities prior to dosing on Day 1.
12-lead ECG	Triplicate	X[1,2]	X	X	X		X	X	X	X	X	X	X	X	X	X	On Day -1 and Day 1 ECGs may be generated from telemetry [1] On Day 1, pre dose then every 30 mins during infusion (i.e. 30 mins and 60mins after start of infusion) and then 1 hr post end of infusion. [2] On Day 1, pre dose then 1 hr post injection.
Vital signs	X	X[1,2]	X	X	X		X	X	X	X	X	X	X	X	X	X	[1] On Day 1, pre dose then every 15 mins during infusion (i.e. 15, 30, 45 and 60mins post the start of infusion) and then 30 mins, 1, 2 and 4 hr post end of infusion. [2] On Day 1, pre dose then 1 hr post injection.
Haematology, clinical chemistry, urinalysis	X		24hr p.d.	24hr p.d.	X		X	X	X	X	X	X	X	X	X	X	
Weight	X																Weight to be used to calculate the study treatment dose.
Randomization		Pre-dose															
Induction of blister	X				X				X								
Aspiration of blister fluid		X				X				X							Aspiration 21 hours (+/- 3 hours) after induction of blister.
Blood sample for circulating immune cells		X				X				X							
CCI																	
Study treatment dosing		X															
AE assessment		<----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	X	
SAE assessment	<----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	X	
Concomitant medication review	<----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	X	

14.2.5. Part B

PROCEDURE	SCREEN	[a] TREATMENT PERIOD (8 Wks)														[b] FOLLOW-UP (~12 Wks)					Early withdrawal	See two footnotes. **NOTES a**) Treatment Period = Day 1 to 57. **b**) Follow-Up Period = Day 57 to 141. **c**) Day 141 (End of Study Visit) is ~13 wks since last dose on Day 50.
DAY	Day -4[1]	1	2	5	8	15	22	23	26	29	36	43	50	51	57	71	85	99	120	[c]141		**Visit Windows:** 1) *Within* 96 hours of Day 1 Days 15 to 71 (±1), Days 85 to 141 (±2).
Out-patient visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Tel.	X	X	**Tel** = telephone contact to check AEs and ConMeds (Day 120).
Discharge from clinical unit		X[1]			X[2]	X[2]	X[2]			X[2]	X[2]	X[2]	X[2]									1) Day 1: Discharge not sooner than 4 hours post-start of SC injections. 2) Remaining dosing days: discharge not sooner than 2 hours post-start SC injections.
Inc. & Exc Criteria	X	X																				Re-check clinical status before first dose.
Brief Phys. Exam.	X	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Alcohol and drug screen	X	X			X	X	X			X	X	X	X		X							Methods as per standard local practice
12-lead ECG (Triplicate)	X	(X)[1]	X		X[1]	X[1]	X[1]			X[1]	X[1]	X[1]	X[1]		X	X	X			X	X	1) On Dosing Days: pre-dose, and then 30 and 60 mins after post-start of dosing.
Vital signs	X	(X)[1]	X		X[2]	X[2]	X[2]			X[2]	X[2]	X[2]	X[2]		X	X	X			X	X	1) Day 1: pre-dose, and then 30 mins, 1, 2, 3 and 4 hrs post-start of dosing. 2) On other dosing days: pre-dose, 1 h and 2 hrs.
Haematology, clinical chemistry, urinalysis	(X)[1,2]		X		X	X	X			X	X	X	X		X[2]	X	X	X		X	X	Appendix 2. Samples taken prior to dosing, as appropriate. ADDITIONALLY: 1) Complement C3 & C4 (Screening only). 2) BNP (Screening & Day 57 only).
SARS-CoV-2 PCR Mandatory	X[1]														X					X	X	1) SARS-CoV-2 PCR NEGATIVE RESULT to be obtained prior to the 1st dose
SARS-CoV-2 PCR Optional						←[1]					←[1]											1) Recommended optional SARS-CoV-2 PCR test to be obtained ideally four days before the 3rd and 6th dose such that a result is available prior to dosing on those days
Daily Pain (Digital Tool)	See Screen	<----------Daily Pain---------->																				**N.B.** Pain recorded daily using a digital tool (Evenings of Day 1 to Day 84)
WOMAC		(X)			X	X				X		X			X	X	X	X		X	X[1]	WOMAC, PtGA (participant) & PhGA (Physician Global Assessments) completed prior to ALL other assessments and blood draws. 1) If withdrawal occurs earlier than Day 85.
PtGA & PhGA		(X)			X	X	X			X	X	X	X		X	X	X	X		X	X[1]	
Pain Detect (Digital Tool)		(X)													X		X				X	Perform PainDetect *after* completing WOMAC/Patient & Physician Global Assessment.
Randomization		X																				
Dosing (SC injections)		X			X	X	X			X	X	X	X									Allow at least 1 hour to thaw vials at room temp (or thaw 18 hours overnight at 2-8°C).
CCI	[redacted]																					
Concom. Medns	<---------->																				X	
Trial Questionnaire	(X)																			X	X	Optional trial-based questionnaire for participant completion.

All activities and blood samples are to be acquired *prior to dosing* (on dosing days), unless stated otherwise.

(X) denotes the Baseline Value.

14.3. Appendix 3: Assessment Windows

Acceptable time windows around the nominal time points for specific assessments will be included in the Study Reference Manual (SRM) and assessments performed within these time windows will not constitute a protocol deviation.

The table below describes the visit days for each week (Week 1-12). All available diary data in each of the weekly intervals will be used to calculate the Average Knee Pain Intensity, Worst Knee Pain Intensity and CCI [redacted] for that study week.

Study Week	Study Day	Phase
BL	-7 to -1	Baseline
1	1 to 7	Treatment
2	8 to 14	Treatment
3	15 to 21	Treatment
4	22 to 28	Treatment
5	29 to 35	Treatment
6	36 to 42	Treatment
7	43 to 49	Treatment
8	50 to 56	Treatment
9	57 to 63	Follow-up*
10	64 to 70	Follow-up
11	71 to 77	Follow-up
12	78 to 84	Follow-up

*Follow-up here means that the participant is no longer receiving the study medication/placebo, so only for informative purposes. Participants will be considered on treatment during the whole duration of the study (20 weeks).

All other assessments will use the nominal timepoints unless otherwise specified.

14.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

14.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to the first dose.

Study Phase	Definition
Pre-Treatment	Date/time < Study Treatment Start Date/time
On-Treatment	Study Treatment Start Date ≤ Date/time

Refer SOA in Appendix 2 for details of follow-up for each Cohort and Part.

14.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is >7 days prior to first dose.
Concomitant	Any medication that is not a prior

NOTE: Refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing

In addition, the following phase will also be calculated:

Study Phase	Definition
Prohibited Medication Phase	If medication has start date on or before Day 71 and is either ongoing or has end date on or after 7 days prior to first dose (Section 6.6 of the Protocol)

14.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	If AE start date >= Study Treatment Start Date

NOTES:

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

14.5. Appendix 5: Data Display Standards & Handling Conventions

14.5.1. Reporting Process

Software	
The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	UK1SALX00175
HARP Compound	\arprod\gsk3858279\mid207804
Analysis Datasets	
Analysis datasets will be created according to Legacy GSK A&R dataset standards	
Generation of RTF and PDF Files	
RTF and PDF files will be generated.	

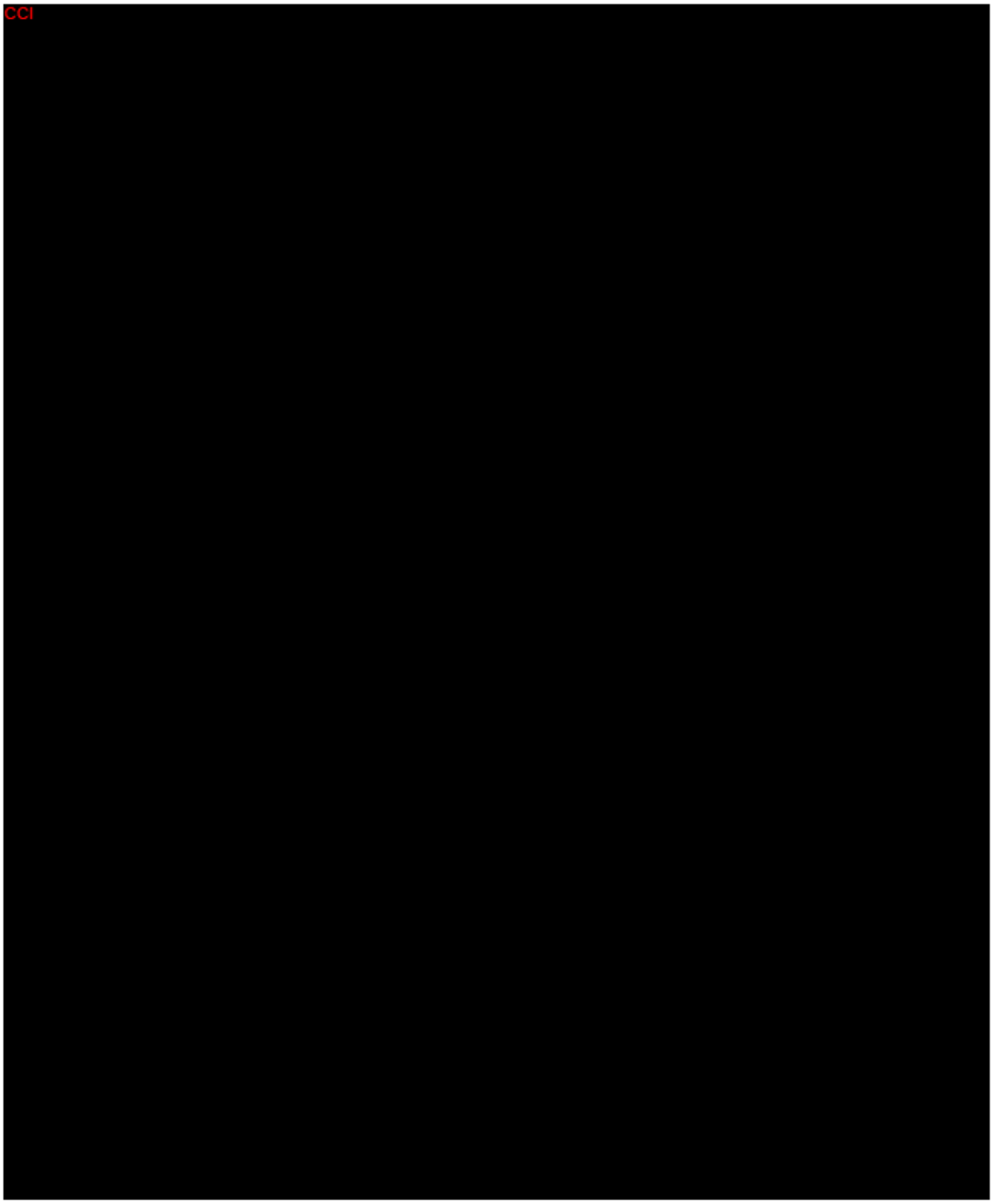
14.5.2. Reporting Standards

General	
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics • All data displays (Tables, Figures & Listings) will use the term "Subject" which reflects CDISC and GSK Data Display Standards terminology.	
Formats	
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DPs) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's. Actual values will be used in listings. The following criteria will be used in tables and figures: • For all Biomarkers , the following precision places will be applied: o Summary Statistics: 4 significant figures for Mean and Median, 5 significant figures for SD, 3 significant figures for Min and Max, in all cases but Blister Volume parameter. o For Blister Volume parameter: 2DP's, 3 DP's for Mean and Median, 4 DP's for SD, 3 DP's for Min and Max • For PD endpoints, which are blinded until DBF, determination of an appropriate presentation of significant figures will be made after unblinding in line with the IDSL principles	
Planned and Actual Time	
• Reporting for tables, figures and formal statistical analyses: o Planned time relative to the first dosing will be used in figures, summaries and planned time relative to the last dosing will be used in statistical analyses and calculation of any derived parameters, unless otherwise stated. o The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: o Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). o Unscheduled or unplanned readings will be presented within the subject's listings.	
Unscheduled Visits	
• Unscheduled visits will not be included in by-visit summary tables and figures. • All unscheduled visits will be included in listings and determination of worst-case values.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1 – do not report 95% CI unless otherwise specified.
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

14.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to VQD-GUI-000722 (6.0). Note: Concentration values will be imputed as per VQD-GUI-000722 (6.0).
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per VQD-GUI-000722 (6.0) for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/PK/TE/PD File	PK/TE/PD file (CSV format) for the PK/TE/PD analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in Section 11.1 Pharmacokinetic / CCI [redacted] / Pharmacodynamic Dataset Specification.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by CPMS	All PK parameters described in Section 9.1.1.2 (Part A and Part B).
PK Parameter to be Derived by Programmer	The following PK parameters will be derived by programmer for Part A: • Within subject and timepoint blister fluid: serum concentration ratio for GSK3858279.
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to SOP_314000.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to VQD-GUI-000722 (6.0).

CCI



14.6. Appendix 6: Derived and Transformed Data

14.6.1. General

Subject Number
• Participants will be assigned a unique identification number: study number concatenated subject ID number. In the case of a subject being enrolled multiple times, the first subject ID number will be used. For more details, see the AR data set specifications. Listings will include both subject ID and unique subject ID.
Multiple measurements at one analysis time point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Participants having both high and low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study day
• Calculated as the number of days from first dose date: o ref date = missing → study day = missing o ref date < first dose date → study day = ref date – first dose date o ref date ≥ first dose date → study day = ref date – (first dose date) + 1
Nominal Visit Day
• Nominal Visit Days were updated in protocol, however some visits may be recorded under the incorrect visit number/label for Part A only: o Day 112 and Day 113 will be collapsed under the Nominal Visit: Day 113. o Day 140 and Day 141 will be collapsed under the Nominal Visit: Day 141.

14.6.2. Study Population

Age

• Birth date will be presented in listings as 'YYYY'.
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  o Any participant with a missing day will have this imputed as day '15'.
  o Any participant with a missing date and month will have this imputed as '30th June'.
• Calculated based on the screening date

Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height $(m)^2$]
Race Category

• The five high level FDA race categories and designated Asian subcategories will be summarised along with all combinations of high level categories which exist in the data.
• The high level FDA race categories and designated Asian subcategories are:
  o AMERICAN INDIAN OR ALASKA NATIVE
  o ASIAN
  o CENTRAL/SOUTH ASIAN HERITAGE
  o JAPANESE HERTIAGE/EAST ASIAN HERITAGE/SOUTH EAST ASIAN HERITAGE
  o MIXED ASIAN RACE (only required if data exists)
  o BLACK OR AFRICAN AMERICAN
  o NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER
  o WHITE
• A subject who selects a combination of races will be counted in a row within "MULTIPLE" or within the "MIXED ASIAN RACE", not in each of the constituent terms.

Extent of Exposure

• Number of days of exposure to study drug in Part B will be calculated based on the formula:
  o Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1+18*5
  o Note: The half life of the drug is approximately 18 days. Hence 5*18 =~ 90 days is added in the equation of duration of exposure.
• Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure.
• The summary statistics based on the frequency of injections would be provided in the exposure display for Part B.

14.6.3. Efficacy

Derivations
WOMAC Osteoarthritis Index
• WOMAC questionnaire covers pain, stiffness and function related to osteoarthritis in the index knee. Participants will respond to each question using an 11-point NRS (0-10), with 0=CCI [redacted] and 10= CCI [redacted] • For each of the subscales – pain, stiffness and function, the average of all the scores within that subscale will be calculated for each subject at each timepoint such that the average lies within the range of 0 to 10. • The questions 1 to 5 constitute the subscale WOMAC pain, questions 6 and 7 constitute the subscale WOMAC stiffness, questions 8 to 24 constitute the subscale WOMAC function. • If any of the scores within a subscale is missing for a participant, then the subscale will not be computed and will be set to missing for that participant.
CCI [redacted]
Daily Pain NRS
• Average knee pain intensity: mean over the 7 days prior to each assessment visit • Worst knee pain intensity: mean over the 7 days prior to each assessment visit

14.6.4. Safety

ECG Parameters

RR Interval

- IF RR interval (msec) is not provided directly, then RR can be derived as:

  [1] If QTcB is machine read & QTcF is not provided, then :

$$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$

  [2] If QTcF is machine read and QTcB is not provided, then:

$$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$

- if both the QTcB and QTcF values are machine read and provided, RR will not be calculated.
- If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value, THEN do not derive.

Corrected QT Intervals

- When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements.
- IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as:

$$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

Worst Case Rules

Worst case finding based on the interpretation and the clinical significance:

- Count the subject as 'ABNORMAL' and 'CLINICALLY SIGNIFICANT', if any of the findings are 'ABNORMAL' and 'CLINICALLY SIGNIFICANT' during the time period/Post-Baseline.
- Else count the subject as 'ABNORMAL' and 'NOT CLINICALLY SIGNIFICANT', if any of the findings are 'ABNORMAL' and 'NOT CLINICALLY SIGNIFICANT' and none of the findings are 'ABNORMAL' and 'CLINICALLY SIGNIFICANT' during the time period/Post-Baseline.
- Else count the subject as 'NORMAL' if there is a finding of 'NORMAL' and none of the findings are 'ABNORMAL during the time period/Post-Baseline.
- Otherwise, do not count the subject during the time period/Post-Baseline, i.e. little n will reflect that the subject is not counted in the time period/Post-Baseline..

Laboratory Parameters

- All BLQ values will be imputed with ½ LLOQ.
- All ALQ values will be imputed with the ALQ + [smallest positive number with the same number of decimal places as the ALQ is reported with]
- Values reported as < x are assumed to have an LLOQ of x.
- Values reported as > x are assumed to have an ALQ of x.

14.6.5. Immunogenicity

A seed (5315) will be generated using code as outlined in Section 14.9.2. This will be saved in the refdata area.

- Using the generated seed, random numbers will be generated for all subjects that exist in the imgen dataset.

- These subjects will be ordered based on the random number and letters assigned sequentially (i.e. the patient with the smallest random number was ‘a’, the next patient ‘b’ and so on).

14.7. Appendix 7: Reporting Standards for Missing Data

14.7.1. Premature Withdrawals

Element	Reporting Detail
General	• A participant is considered to have completed the study if he/she has completed all phases of the study including the final follow-up visit • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

14.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a "blank" in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

14.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. • 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 or for specific analysis purposes.
Adverse Events	• Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings. • Partial dates for AE recorded in the CRF will be imputed using the following conventions:

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

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:
○ If year of start date = year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
▪ Else set start date = study treatment start date.
○ Else set start date = January 1.</td></tr>
<tr><td>Missing stop day</td><td>Last day of the month will be used.</td></tr>
<tr><td>Missing stop day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications</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 treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.
• Else if study treatment start date is not missing:
○ If month and year of start date = month and year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.
▪ Else set start date = study treatment start date.
○ Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:
○ If year of start date = year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
▪ Else set start date = study treatment 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
	<table><tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr><tr><td>Completely missing start/end date</td><td>No imputation</td></tr></table> • The recorded partial date will be displayed in listings.

14.8. Appendix 8: Values of Potential Clinical Importance

14.8.1. PCI Values for Part A

14.8.1.1. Vital Signs

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

14.8.1.2. Laboratory Values

Haematology				
Laboratory Parameter	Units	Category	Clinical Concern Range	
			Low Flag (< x)	High Flag (>x)
Hematocrit	Ratio of 1	Male	0.39	0.54
		Female	0.35	0.49
		Δ from BL	↓0.075	
Hemoglobin	g/L	Male	124	180
		Female	109	180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.75	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
White Blood Cell Count (WBC)	$x10^9$/ L		2.5	20

Clinical Chemistry				
Laboratory Parameter	Units	Category	Clinical Concern Range	
			Low Flag (< x)	High Flag (>x)
Albumin	g/L		30	
Calcium	mmol/L		2	2.75
Creatinine	umol/L			1.3 X ULN
Creatinine	umol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO_2	mmol/L		18	32
Creatinine Kinase	mg/dL			>1.6 X ULN
C-reactive Protein	mg/L			≥3.0
Troponin T	ng/L			14.1

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	IU/L	High	≥2xULN
AST/SGOT	IU/L	High	≥2xULN
AlkPhos	IU/L	High	≥2xULN
T Bilirubin	µmol/L	High	≥1.5xULN
T. Bilirubin + ALT	µmol/L IU/L	High	ALT≥3xULN AND bilirubin≥ 1.5xULN

14.8.1.3. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	**Upper**
Absolute			
Absolute QTc Interval	msec		>500
Absolute PR Interval	msec	<110	>220
Absolute QRS Interval	msec	<75	>120
Change from Baseline			
Increase from Baseline QTc	msec		>60

14.8.2. PCI Values for Part B

14.8.2.1. Vital Signs

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

14.8.2.2. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male	0.39	0.54
		Female	0.35	0.49
		Δ from BL	↓0.075	
Hemoglobin	g/L	Male	124	180
		Female	109	180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.75	4.5
Neutrophil Count	$x10^9$/ L		1.5	8.0
Platelet Count	$x10^9$/ L		100	550
White Blood Cell Count (WBC)	$x10^9$/ L		2.5	15

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Calcium	mmol/L		2	2.60
Creatinine	umol/L	Male		120
		Female		100
Creatinine	umol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	8
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Troponin T	ng/L			14.1
NT-pro BNP	ng/L			125.2

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	IU/L	High	≥1.5xULN
AST/SGOT	IU/L	High	≥1.5xULN
AlkPhos	IU/L	High	≥1.5xULN
T Bilirubin	µmol/L	High	≥1.5xULN
T. Bilirubin + ALT	µmol/L IU/L	High	ALT≥3xULN AND bilirubin≥ 1.5xULN

Immunology				
Test Analyte	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (<x)	**High Flag (>x)**
Complement C3	g/L	High	0.85	1.8
Complement C4	g/L	High	0.1	0.4

Virology			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
Hepatitis C Antibody	N/A	High	Reactive

14.8.2.3. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec	<350	>450
Absolute PR Interval	msec	<110	>220
Absolute QRS Interval	msec	<75	>120
Change from Baseline			
Increase from Baseline QTc	msec		>50

14.9. Appendix 9: Statistical Algorithms and Model Checking

14.9.1. Calculation of SD from Bayesian Repeated Measures model

1. Calculate the R Correlation matrix (correlation matrix for the repeated measures [in this case visit])

$$R_{corr} = \begin{bmatrix} 1 & \rho_{1,2} & \cdots & \rho_{1,8} \\ & 1 & \cdots & \rho_{2,8} \\ & & \cdots & \cdots \\ & & & 1 \end{bmatrix}$$

2. Calculate the number of subject contributing data up to each week (e.g. 32 subjects have up to week 8, a further 4 subjects contribute up to week 6 only, 3 more contribute data up to week 4 only.

$$\boldsymbol{n}_{cont} = \begin{bmatrix} n_{1,8} \\ n_{2,8} \\ \cdots \\ n_{7,8} \end{bmatrix} = \begin{bmatrix} n_1 \\ n_2 \\ \cdots \\ n_7 \end{bmatrix} - \begin{bmatrix} n_8 \\ n_8 \\ \cdots \\ n_8 \end{bmatrix}$$

$$ESS_8 = n_8 + \sum_{i=1,\ldots 7} \rho_{i,8} n_{i,8}$$

3. Calculate the SD

$$SD_{estimate,8} = SE_8 * \sqrt{ESS_8}$$

14.9.2. Model Checking & Diagnostics

Bayesian Repeated Measures Model

Seeds for all planned analyses will be determined using the following SAS code

```
data temp;
 do i=1 to #seed;
   number=round(10000*ranuni(207804),1); output;
 end;
run;
```

The following points are for guidance and illustration and do not guarantee a successful model convergence. They cannot cover all eventualities and do not remove the requirement to do what is best for the specific set of observed data being modelled.

Priors

Unless otherwise specified the following would be the default approach to selecting prior distributions:

- Vague priors of the form Normal(0, Var=1E6) would be assigned to each fixed effect in the proposed statistical model.

- Vague Inverse-gamma priors of the form IGamma(0.001,0.001) would be assigned to stand-alone variance parameters that are not expected to take values near zero (e.g. for the residual variance rather than a random effect variance component)
- For stand-alone variance parameters that may take values close to zero a noninformative prior of the form Uniform(0, XXX) may be assigned for the SD
- For repeated measures models Inverse-Wishart priors will be assigned for the Variance Covariance matrix (VCV). They would use degrees of freedom equal to the dimension of the VCV matrix and an Identity matrix (of the same dimension).
    - If there are issues with those variance parameters then the Identitity matrix may be replaced with a diagonal matrix that uses best guesses for the residual variance at each repeated measure time point (or the residual estimates from fitting simple models).
    - It is good practice to ensure that each prior distribution is visualised to ensure it appears sensible and allows clinically plausible response values, whilst not allowing impossible values to be drawn with high probability and that if it is intended to be non-informative it is doing so over the region of the likelihood function.

Checking convergence and other diagnostics

The key model diagnostic output is the MCSE/SD ratio for each parameter:

- Adequate values for the number of MCMC samples / thinning / number of burn in samples should be chosen to ensure that the MCSE/SD for the key parameters is below 0.01 (e.g. key parameters those associated with treatment, or as pre-specified comparisons of interest) in each final model.
- For other model parameters, try to get the MCSE/SD values as close to 0.01 as possible, but if there is significant autocorrelation then values below 0.05 would be considered acceptable.
- In addition, the number of tuning units and maximum number of tuning iterations may be increased to find a better multivariate normal approximation to the parameters, which in turn may reduce the MCSE/SD values
- Where possible the code should be written to allow the SAS compiler to identify and use conjugate sampling, since this can greatly reduce the corresponding MCSE/SD values
- Models selected with MCSE/SD values above 0.01 (for key parameters) or 0.05(for other parameters) would need a brief remark/justification added to the CSR to clarify why it was not possible to reach the targets and why it is believed the subsequent model still has utility.

Use of the default SAS PROC MCMC diagnostic plots should be made and where possible:

- Autocorrelation should decline rapidly and show no oscillation patterns
- Worm plots should show the chain appears to be stationary and mixing, i.e.
    - Constant mean, constant variance
    - Moving around the parameter space freely (not getting “stuck” at similar values for a large number of iterations before moving on again)
    - Moving rapidly between extremes
    - The posterior density should look reasonable for each parameter (e.g. for posterior parameters expected to follow a normal distribution the density plot should not

appear bi-modal, but for parameters acting as binary flags then bi-modal is acceptable)

- Correlation structures between relevant posterior parameters (and/or parameters in each PARMS block) should be explored using graphical methods. This can provide information about what potential issues may be and also what corrective action(s) may be worthwhile attempting.

14.10. Appendix 10: Abbreviations & Trade Marks

14.10.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
AIC	Akaike's Information Criteria
AUC	Area Under the Concentration-Time Curve
A&R	Analysis and Reporting
BNP	N-terminal pro B-type natriuretic peptide
BUN	Blood urea nitrogen
CI	Confidence Interval
Cmax	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DEC	Dose Escalation Committee
DEP	Dose Escalation Plan
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
OA	Osteoarthritis
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PhGA	Physician Global Assessment
PK	Pharmacokinetics
PP	Per Protocol
CCI	[redacted]

Abbreviation	Description
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RBC	Red Blood Cell Count
SAC	Statistical Analysis Complete
SOA	Schedule of Activities
SOP	Standard Operation Procedure
TA	Therapeutic Area
TLF	Tables, Listings and Figures
WBC	Whole Blood Count
WOMAC	Western Ontario & McMaster Universities Osteoarthritis Index

14.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

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SAS
NONMEM

14.11. Appendix 11: List of Data Displays

14.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables		Figures	
	Part A	Part B	Part A	Part B
Safety Review	N/A	1	N/A	N/A
Sample Size Re-estimation	N/A	2	N/A	N/A
Study Population	1.01 to 1.09	1.10 to 1.28	N/A	N/A
Safety	2.01 to 2.16	2.17 to 2.39	N/A	N/A
Pharmacokinetic	3.01 to 3.06	3.07 to 3.08	3.01 to 3.06	3.07 to 3.09
Pharmacodynamic	4.01 to 4.05	4.06 to 4.08	4.01 to 4.03	4.04 to 4.06
[redacted]				
Efficacy	N/A	6.01 to 6.21	N/A	6.01 to 6.15

Section	Listings	
	Part A	Part B
ICH Listings	1 to 31, 64 to 65	32 to 63, 66
Other Listings	67 to 76	77 to 87

14.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated in a separate TFL Shells document.

Section	Figure	Table	Listing
Safety Review		SR_Tn	
Sample Size Re-estimation		SSR_Tn	
Study Population			
Safety		SAFE_Tn	
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Pharmacodynamic		PD_Tn	
[redacted]			
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln

14.11.3. Deliverables

Delivery	Description
Part A SAC	Part A Final Statistical Analysis Complete
Part B SR1	Safety Review 1
Part B SR2	Safety Review 2
Part B IA1	Interim Analysis 1
Part B IA2	Interim Analysis 2
Part B IA3	Interim Analysis 3
Part B IA4	Interim Analysis 4
Part B SAC	Part B Final Statistical Analysis Complete

14.11.4. Safety Review Table

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Immunogenicity – Part B					
1.	Safety	SR1	Part B: Summary of Immunogenicity		SR1, SR2

14.11.5. Sample Size Re-estimation table

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Sample Size Re-estimation – Part B					
2.	Safety	SSR_1	Part B: Summary of Sample Size Re-estimation		IA2

14.11.6. Study Population Tables

14.11.6.1. Part A

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Subject Disposition					
1.01.	Randomized	ES1	Part A: Summary of Subject Disposition for the Subject Conclusion Record	ICH E3, FDAAA, EudraCT	Part A SAC
1.02.	Screened	ES6	Part A: Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	Part A SAC
Protocol Deviation					
1.03.	Randomized	DV1	Part A: Summary of Important Protocol Deviations	ICH E3	Part A SAC
Population Analysed					
1.04.	Screened	SP1	Part A: Summary of Study Populations	IDSL. Include footnote with population definitions.	Part A SAC
Demographic and Baseline Characteristics					
1.05.	Randomized	DM1	Part A: Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	Part A SAC
1.06.	Enrolled	DM11	Part A: Summary of Age Ranges	EudraCT	Part A SAC
1.07.	Randomized	DM5	Part A: Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	Part A SAC
Prior and Concomitant Medications					
1.08.	Safety	CM1	Part A: Summary of Prior Medications	ICH E3	Part A SAC
1.09.	Safety	CM1	Part A: Summary of Concomitant Medications	ICH E3	Part A SAC

14.11.6.2. Part B

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Subject Disposition					
1.10.	Randomized	ES1	Part B: Summary of Subject Disposition for the Subject Conclusion Record		IA1, IA2, IA3, IA4, Part B SAC
1.11.	Randomized	SD1	Part B: Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		IA1, IA2, IA3, IA4, Part B SAC
1.12.	Screened	ES6	Part B: Summary of Screening Status and Reasons for Screen Failure		Part B SAC
1.13.	Enrolled	NS1	Part B: Summary of Number of Subjects by Country and Site ID		Part B SAC
COVID-19					
1.14.	Randomized	PAN1A	Part B: COVID-19 Case Diagnosis Events		Part B SAC
Protocol Deviation					
1.15.	Randomized	DV1	Part B: Summary of Important Protocol Deviations		Part B SAC
Population Analysed					
1.16.	Screened	SP1	Part B: Summary of Study Populations	Include footnote with population definitions.	Part B SAC
Demographic and Baseline Characteristics					
1.17.	Randomized	DM1	Part B: Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT Include KL scores	IA1, IA2, IA3, IA4, Part B SAC
1.18.	Randomized	POP_T1	Part B: Summary of Baseline Efficacy Parameters	Include Average & Worst Knee Pain Intensity, WOMAC, CCI [redacted] CCI [redacted] and Pain Detect	IA1, IA2, IA3, IA4, Part B SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
1.19.	Enrolled	DM11	Part B: Summary of Age Ranges	EudraCT	Part B SAC
1.20.	Randomized	DM5	Part B: Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	Part B SAC
Medical Conditions					
1.21.	Randomized	MH4	Part B: Summary of Past Medical Conditions	ICH E3	Part B SAC
1.22.	Randomized	MH4	Part B: Summary of Current Medical Conditions	ICH E3	Part B SAC
Prior and Concomitant Medications					
1.23.	Safety	CM1	Part B: Summary of Prior Medications	ICH E3	Part B SAC
1.24.	Safety	CM1	Part B: Summary of Concomitant Medications	ICH E3	Part B SAC
1.25.	Safety	CM1	Part B: Summary of Prior Osteoarthritis Medications	OA meds are captured on a specific CRF page	Part B SAC
1.26.	Safety	CM1	Part B: Summary of Osteoarthritis Concomitant Medications during Prohibited Medication Phase		Part B SAC
1.27.	Safety	CM1	Part B: Summary of Osteoarthritis Concomitant Medications		Part B SAC
Exposure					
1.28.	Safety	EX1	Part B: Summary of Exposure to Study Treatment	Provide statistics for the categories by number of injections received (4 injections, ≤ 3 injections)	Part B SAC

14.11.7. Safety Tables

14.11.7.1. Part A

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Adverse Events (AEs)					
2.01.	Safety	AE1CP	Part A: Summary of All Adverse Events by System Organ Class and Preferred Term		Part A SAC
2.02.	Safety	AE5A	Part A: Summary of All Adverse Events by System Organ Class and Preferred Term and Maximum Intensity		Part A SAC
2.03.	Safety	AE5A	Part A: Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity		Part A SAC
2.04.	Safety	AE15	Part A: Summary of All Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		Part A SAC
Vital Signs					
2.05.	Safety	VS1	Part A: Summary of Change from Baseline in Vital Signs	Includes Baseline values.	Part A SAC
2.06.	Safety	VS7	Part A: Summary of Worst Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline	Include all assessments post-baseline	Part A SAC
Laboratory: Hematology					
2.07.	Safety	LB1	Part A: Summary of Hematology Changes from Baseline	Includes baseline values.	Part A SAC
2.08.	Safety	LB17	Part A: Summary of Worst Case Hematology Results by PCI Criteria Post-Baseline Relative to Baseline	Include all assessments post-baseline	Part A SAC
Laboratory: Chemistry					
2.09.	Safety	LB1	Part A: Summary of Chemistry Changes from Baseline	ICH E3	Part A SAC
2.10.	Safety	LB17	Part A: Summary of Worst Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline	ICH E3 Include all assessments post-baseline	Part A SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Laboratory: Urinalysis					
2.11.	Safety	UR1	Part A: Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline		Part A SAC
ECG					
2.12.	Safety	EG1	Part A: Summary of ECG Findings		Part A SAC
2.13.	Safety	EG10	Part A: Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	Use QTcB and QTcF intervals	Part A SAC
2.14.	Safety	EG2	Part A: Summary of Change from Baseline in ECG Values by Visit	Use QTcB and QTcF intervals	Part A SAC
2.15.	Safety	EG11	Part A: Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	Use QTcB and QTcF intervals	Part A SAC
Telemetry – Part A					
2.16.	Safety	EG1	Part A: Summary of Telemetry Findings		Part A SAC

14.11.7.2. Part B

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Adverse Events (AEs) – Part B					
2.17.	Safety	CP_AE1p	Part B: Summary of All Adverse Events by System Organ Class and Preferred Term		IA3, Part B SAC
2.18.	Safety	AE5A	Part B: Summary of All Adverse Events by System Organ Class and Preferred Term and Maximum Intensity		IA3, Part B SAC
2.19.	Safety	AE3	Part B: Summary of Common (≥5%) Adverse Events by Overall Frequency		Part B SAC
2.20.	Safety	AE5A	Part B: Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity	Include Total column.	IA3, Part B SAC
2.21.	Safety	AE15	Part B: Summary of All Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		IA3, Part B SAC
2.22.	Safety	AE15	Part B: Summary of Common (≥5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		Part B SAC
Serious and Other Significant Adverse Events					
2.23.	Safety	AE16	Part B: Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		IA3, Part B SAC
2.24.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term		IA3, Part B SAC
2.25.	Safety	AE3	Summary of Serious Drug-Related Adverse Events by Overall Frequency		IA3, Part B SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Vital Signs					
2.26.	Safety	VS1	Part B: Summary of Change from Baseline in Vital Signs	Include Baseline	IA3, Part B SAC
2.27.	Safety	VS7	Part B: Summary of Worst Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline		IA3, Part B SAC
Laboratory: Hematology					
2.28.	Safety	LB1	Part B: Summary of Hematology Changes from Baseline	Include Baseline	IA3, Part B SAC
2.29.	Safety	LB17	Part B: Summary of Worst Case Hematology Results by PCI Criteria Post-Baseline Relative to Baseline		IA3, Part B SAC
Laboratory: Chemistry					
2.30.	Safety	LB1	Part B: Summary of Chemistry Changes from Baseline		IA3, Part B SAC
2.31.	Safety	LB17	Part B: Summary of Worst Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline		IA3, Part B SAC
Laboratory: Urinalysis					
2.32.	Safety	UR1	Part B: Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline		IA3, Part B SAC
ECG					
2.33.	Safety	EG1	Part B: Summary of ECG Findings		IA3, Part B SAC
2.34.	Safety	EG10	Part B: Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	Use QTcB and QTcF intervals	IA3, Part B SAC
2.35.	Safety	EG2	Part B: Summary of Change from Baseline in ECG Values by Visit	Use QTcB and QTcF intervals	IA3, Part B SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
2.36.	Safety	EG11	Part B: Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	Use QTcB and QTcF intervals	IA3, Part B SAC
Immunogenicity					
2.37.	Safety	AE1CP	Part B: Summary of Treatment-Emergent Adverse Events by Highest Post-Baseline ADA Result	Split table by Positive/ Negative ADA status	Part B SAC
Injection Site Reactions					
2.38.	Safety	SAFE_T1	Part B: Summary of Injection Site Reactions as per specified AE Term list	Safety to provide list of HLT / Preferred Terms. Add a footnote explaining that this table was created using a pre-specified subset of MedDra AE Terms	Part B SAC
2.39.	Safety	ESI1	Part B: Summary of Characteristics of Injection Site Reactions as per specified AE Term list	Safety to provide list of HLT / Preferred Terms. Add a footnote explaining that this table was created using a pre-specified subset of MedDra AETerms	Part B SAC

14.11.8. Pharmacokinetic Tables

14.11.8.1. Part A

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Serum GSK3858279					
3.01.	PK	PK01	Part A: Summary of Serum GSK3858279 Concentration-Time Data (ng/mL)	Please only present the median, min, max, sd (log), geometric mean and 95% CI, back-transformed from the log_e scale.	Part A SAC
3.02.	PK	PK06	Part A: Summary of Derived Serum GSK3858279 Pharmacokinetic Parameters (non-transformed and log-transformed)	Include Cmax, tmax, AUC(0-t), AUC(0-∞), t½, CL, Vss. Please note that tmax should not be log_e-transformed and 95% CI should not be presented. Please add the following footnote: CL= systemic clearance for IV, apparent systemic clearance for SC.	Part A SAC
3.03.	PK	PK_T1	Part A: Summary of Serum GSK3858279 Pharmacokinetic Dose Proportionality		Part A SAC
3.04.	PK	PK_T2	Part A: Summary of SC:IV GSK3858279 Pharmacokinetic Comparison		Part A SAC
Blister GSK3858279					

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
CCI [redacted]					

14.11.8.2. Part B

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Serum GSK3858279					
CCI [redacted]					

14.11.9. Pharmacokinetic Figures

14.11.9.1. Part A

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Serum GSK3858279					
CCI [redacted]					

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
3.02.	PK	PK17	Part A: Mean Serum GSK3858279 Concentration-Time Plots (Linear and Semi-log)	Add the following footnotes: Note: LLOQ=100 ng/mL. Note: Concentrations below LLOQ have been set to zero and included in the summary statistic calculations. Note: Any single mid-profile non-quantifiable (NQ) concentrations have been omitted. Note: Zero concentration values have been set to missing in the log-linear plot. Note: Samples have been excluded where results were missing or quantifiable pre-dose concentrations.	Part A SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
3.03.	PK	PK18	Part A: Median Serum GSK3858279 Concentration-Time Plots (Linear and Semi-log)	Add the following footnotes: Note: LLOQ=100 ng/mL. Note: Concentrations below LLOQ have been set to zero and included in the summary statistic calculations. Note: Any single mid-profile non-quantifiable (NQ) concentrations have been omitted. Note: Zero concentration values have been set to missing in the log-linear plot. Note: Samples have been excluded where results were missing or quantifiable pre-dose concentrations.	Part A SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
CCI	[redacted]				

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
CCI [redacted]					

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
CCI					

14.11.9.2. Part B

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Serum GSK3858279					
CCI [redacted]					

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
CCI					

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
CCI					

14.11.10. Pharmacodynamic Tables

14.11.10.1. Part A

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Serum Target Engagement					
4.01.	Safety	PD_T1	Part A: Summary of Free & Total CCL17 in Serum Concentration-Time Data (pg/mL)	Please only present the median, min, max, sd (log), geometric mean and 95% CI back-transformed from the $\log_e$ scale. Apply logit transformation for % reduction parameter and present median, min, max, sd (logit), geometric mean and 95% CI, back-transformed from the logit scale. If % reduction ≤0, set to 0.1. If % reduction ≥100, set to 99.9. These imputations are needed for logit transformation. Use Student's t-distribution for CI. Add the following footnotes: Note: Free CCL17 values below the LLOQ have been imputed to ½* LLOQ. Total CCL17 values below the LLOQ have been imputed to 0. Values equal to zero at baseline have been imputed to LLOQ whilst missing baseline values have been imputed to the median of the non-missing baseline values. Note: Free CCL17 and Total CCL17 exceeding the upper limit of quantification (ULOQ) have been excluded from the summary statistics (ULOQ Free CCL17: 3600 pg/mL, ULOQ Total CCL17: 50000 pg/mL). Note: If more than 30% of values have been imputed at any timepoint for a treatment group, then the standard deviation is not displayed. Note: Percentage reduction values <= 0 are imputed to be 0.1 and values >= 100 are imputed to be 99.9. Note: The percentage reduction parameter was logit transformed, summarised, and back-transformed using the logistic function to obtain the geometric summary statistics. The 95% CI of the geometric mean was calculated using Student's t distribution.	Part A SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.02.	Safety	PD_T2	Part A: Summary of Derived Free and Total CCL17 in Serum Target Engagement Parameters (non-transformed and log-transformed)	Please only present the median, min, max, sd (log), geometric mean and 95% CI back-transformed from the log_e scale. Please note that tmax and tmin should not be log_e-transformed and 95% CI should not be presented. Apply logit transformation for maximum % reduction parameter and present median, min, max, sd (logit), geometric mean and 95% CI back-transformed from the logit scale. If maximum % reduction ≤0, set to 0.1. If maximum % reduction ≥100, set to 99.9. These imputations are needed for logit transformation. Use Student's t-distribution for CI. Add the following footnote: Note: Percentage reduction values <= 0 are imputed to be 0.1 and values >= 100 are imputed to be 99.9. Note: The maximum percentage reduction parameter was logit transformed, summarised, and back-transformed using the logistic function to obtain the geometric summary statistics. The 95% CI of the geometric mean was calculated using Student's t distribution.	Part A SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Blister Target Engagement					
4.03.	Blister	PD_T1	Part A: Summary of Free & Total CCL17 in Blister Fluid Concentration-Time Data (pg/mL)	Please only present the median, min, max, sd (log), geometric mean and 95% CI back-transformed from the $\log_e$ scale. Apply logit transformation for % reduction parameter and present median, min, max, sd (logit), geometric mean and 95% CI back-transformed from the logit scale. If % reduction ≤0, set to 0.1. If % reduction ≥100, set to 99.9. These imputations are needed for logit transformation. Use Student's t-distribution for CI. Add the following footnotes: Note: Free CCL17 values below the LLOQ have been imputed to ½*LLOQ. Total CCL17 values below the LLOQ have been imputed to 0. Values equal to zero at baseline have been imputed to LLOQ whilst missing baseline values have been imputed to the median of the non-missing baseline values. Note: Free CCL17 and Total CCL17 exceeding the upper limit of quantification (ULOQ) have been excluded from the summary statistics (ULOQ Free CCL17: 3600 pg/mL, ULOQ Total CCL17: 50000 pg/mL). Note: If more than 30% of values have been imputed at any timepoint for a treatment group, then the standard deviation is not displayed. Note: Percentage reduction values <= 0 are imputed to be 0.1 and values >= 100 are imputed to be 99.9. Note: The percentage reduction parameter was logit transformed, summarised, and back-transformed using the logistic function to obtain the geometric summary statistics. The 95% CI of the geometric mean was calculated using Student's t distribution.	Part A SAC
4.04.	Blister	PD_T1	Part A: Summary of Derived Blister	Please only present the median, min, max, sd (log), geometric mean and 95% CI back-transformed from the $\log_e$ scale. Apply logit transformation for % reduction parameter and present median, min, max,	Part A SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
			Fluid:Serum Free & Total CCL17 concentration ratio	sd (logit), geometric mean and 95% CI back-transformed from the logit scale. If % reduction ≤0, set to 0.1. If % reduction ≥100, set to 99.9. These imputations are needed for logit transformation. Use Student's t-distribution for CI. Please only present the median, min, max, sd (log), geometric mean and 95% CI back-transformed from the loge scale. Apply logit transformation for % reduction parameter and present median, min, max, sd (logit), geometric mean and 95% CI back-transformed from the logit scale. If % reduction ≤0, set to 0.1. If % reduction ≥100, set to 99.9. These imputations are needed for logit transformation. Use Student's t-distribution for CI. Add the following footnotes: Note: Free CCL17 values below the LLOQ have been imputed to ½*LLOQ. Total CCL17 values below the LLOQ have been imputed to 0. Values equal to zero at baseline have been imputed to LLOQ whilst missing baseline values have been imputed to the median of the non-missing baseline values. Note: Free CCL17 and Total CCL17 exceeding the upper limit of quantification (ULOQ) have been excluded from the summary statistics (ULOQ Free CCL17: 3600 pg/mL, ULOQ Total CCL17: 50000 pg/mL). Note: If more than 30% of values have been imputed at any timepoint for a treatment group, then the standard deviation is not displayed. Note: Percentage reduction values <= 0 are imputed to be 0.1 and values >= 100 are imputed to be 99.9. Note: The percentage reduction parameter was logit transformed, summarised, and back-transformed using the logistic function to obtain the geometric summary statistics. The 95% CI of the geometric mean was calculated using Student's t	

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
				distribution.	
Immunogenicity					
4.05.	Safety	IMM1	Part A: Summary of Immunogenicity		Part A SAC

14.11.10.2. Part B

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Serum Target Engagement					

4.06.	Safety	PD_T1	Part B: Summary of Free & Total CCL17 in Serum Concentration-Time Data (pg/mL)	Please only present the median, min, max, sd (log), geometric mean and 95% CI back-transformed from the log_e scale. Apply logit transformation for % reduction parameter. If % reduction ≤0, set to 0.1. If % reduction ≥100, set to 99.9. These imputations are needed for logit transformation. Use Student's t-distribution for CI. Please only present the median, min, max, sd (log), geometric mean and 95% CI back-transformed from the log_e scale. Apply logit transformation for % reduction parameter and present median, min, max, sd (logit), geometric mean and 95% CI back-transformed from the logit scale. If % reduction ≤0, set to 0.1. If % reduction ≥100, set to 99.9. These imputations are needed for logit transformation. Use Student's t-distribution for CI. Add the following footnotes: Note: Free CCL17 values below the LLOQ have been imputed to ½*LLOQ. Total CCL17 values below the LLOQ have been imputed to 0. Values equal to zero at baseline have been imputed to LLOQ whilst missing baseline values have been imputed to the median of the non-missing baseline values. Note: Free CCL17 and Total CCL17 exceeding the upper limit of quantification (ULOQ) have been excluded from the summary statistics (ULOQ Free CCL17: 3600 pg/mL, ULOQ Total CCL17: 50000 pg/mL). Note: If more than 30% of values have been imputed at any timepoint for a treatment group, then the standard deviation is not displayed. Note: Baseline is the mean of the Day -4 and Day 1 Pre-Dose assessments. Note: Percentage reduction and fold increase parameters were calculated using a model based post-hoc analysis. Note: Percentage reduction values <= 0 are imputed to be 0.1 and values >= 100 are imputed to be 99.9.	Part B SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
				Note: The percentage reduction parameter was logit transformed, summarised, and back-transformed using the logistic function to obtain the geometric summary statistics. The 95% CI of the geometric mean was calculated using Student's t distribution.	
4.07.	Safety	PD_T2	Part B: Summary of Model-Derived Free and Total CCL17 in Serum Target Engagement Parameters (non-transformed and log-transformed)	Please only present the median, min, max, sd (log), geometric mean and 95% CI back-transformed from the $\log_e$ scale. Please note that tmin and tmax should not be $\log_e$-transformed and 95% CI should not be presented. Apply logit transformation for % reduction and maximum % reduction parameters. If % reduction ≤0, set to 0.1. If % reduction ≥100, set to 99.9. These imputations are needed for logit transformation. Use Student's t-distribution for CI. Add the following footnotes: Note: All Target Engagement parameters were calculated using a model based post-hoc analysis. Note: Percentage reduction values <= 0 are imputed to be 0.1 and values >= 100 are imputed to be 99.9. Note: The percentage reduction and maximum percentage reduction parameters were logit transformed, summarised, and back-transformed using the logistic function to obtain the geometric summary statistics. The 95% CI of the geometric mean was calculated using Student's t distribution.	IA3, Part B SAC
Immunogenicity					
4.08.	Safety	IMM1	Part B: Summary of Immunogenicity	Add extra row for Part B SAC - "Highest post-baseline" result. This would be #participants with at least one post-baseline positive result / # participants with at least one post baseline sample.	IA3, Part B SAC

14.11.11. Pharmacodynamic Figures

14.11.11.1. Part A

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Serum Target Engagement					
4.01.	Safety	PK16	Part A: Individual Free & Total Serum CCL17 Concentration-Time Plots (Linear and Semi-log)	One panel per dose group. Add the following footnotes: Note: Free CCL17 LLOQ = 2.93 pg/mL, ULOQ = 3600 pg/mL. Note: Total CCL17 LLOQ = 13.11 pg/mL, ULOQ = 50000 pg/mL. Note: The baseline value is presented at an actual relative time of 0 days. Note: Any non-quantifiable (NQ) Free CCL17 concentration values have been set to ½*LLOQ. Note: Any NQ Total CCL17 concentration values before the first measurable concentration have been set to 0 and have been included in the linear plot. Note: Any single NQ values have been omitted. Note: Any multiple mid-profile NQ concentrations of Free CCL17 and Total CCL17 have been set to ½*LLOQ and 0, respectively, and the subsequent measurable concentrations have been retained. Note: Percentage reduction values <= 0 are imputed to be 0.1 and values >= 100 are imputed to be 99.9	Part A SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.02.	Safety	PK17	Part A: Mean Free & Total Serum CCL17 Concentration-Time Plots (Linear and Semi-log)	Apply logit transformation for % reduction parameter. If % reduction ≤0, set to 0.1. If % reduction ≥100, set to 99.9. These imputations are needed for logit transformation. Use Student's t-distribution for CI. Add the following footnotes: Note: Free CCL17 LLOQ = 2.93 pg/mL, ULOQ = 3600 pg/mL. Note: Total CCL17 LLOQ = 13.11 pg/mL, ULOQ = 50000 pg/mL. Note: Free CCL17 and Total CCL17 concentrations below LLOQ have been set to ½*LLOQ and 0, respectively, and have been included in the summary statistic calculations. Note: Any single mid-profile non-quantifiable (NQ) concentrations have been omitted. Note: Measurable Total CCL17 concentrations following more than one consecutive mid-profile NQ have been omitted. Note: Zero Total CCL17 concentration values have been set to missing in the log-linear plot. Note: The geometric mean is plotted as the data is not normally distributed. Note: Percentage reduction values <= 0 are imputed to be 0.1 and values >= 100 are imputed to be 99.9. Note: The percentage reduction parameter was logit transformed, summarised, and back-transformed using the logistic function to obtain the geometric summary statistics.	Part A SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.03.	Safety	PK18	Part A: Median Free & Total Serum CCL17 Concentration-Time Plots (Linear and Semi-log)	.Add the following footnotes: Note: Free CCL17 LLOQ = 2.93 pg/mL, ULOQ = 3600 pg/mL. Note: Total CCL17 LLOQ = 13.11 pg/mL, ULOQ = 50000 pg/mL. Note: Free CCL17 and Total CCL17 concentrations below LLOQ have been set to ½*LLOQ and 0, respectively, and have been included in the summary statistic calculations. Note: Any single mid-profile non-quantifiable (NQ) concentrations have been omitted. Note: Measurable Total CCL17 concentrations following more than one consecutive mid-profile NQ have been omitted. Note: Zero Total CCL17 concentration values have been set to missing in the log-linear plot.	Part A SAC

14.11.11.2. Part B

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Serum Target Engagement					
4.04.	Safety	PK16	Part B: Individual Free & Total Serum CCL17 Concentration-Time Plots (Linear and Semi-log)	One panel per dose group. Add the following footnotes: Note: Free CCL17 LLOQ = 2.93 pg/mL, ULOQ = 3600 pg/mL. Note: Total CCL17 LLOQ = 13.11 pg/mL, ULOQ = 50000 pg/mL. Note: The baseline value is presented at an actual relative time of 0 days. Note: Any non-quantifiable (NQ) Free CCL17 concentration values have been set to ½*LLOQ. Note: Any NQ Total CCL17 concentration values before the first measurable concentration have been set to 0 and have been included in the linear plot. Note: Any single NQ values have been omitted. Note: Any multiple mid-profile NQ concentrations of Free CCL17 and Total CCL17 have been set to ½*LLOQ and 0, respectively, and the subsequent measurable concentrations have been retained. Note: Percentage reduction values <= 0 are imputed to be 0.1 and values >= 100 are imputed to be 99.9.	Part B SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.05.	Safety	PK17	Part B: Mean Free & Total Serum CCL17 Concentration-Time Plots (Linear and Semi-log)	Apply logit transformation for % reduction parameter. If % reduction ≤0, set to 0.1. If % reduction ≥100, set to 99.9. These imputations are needed for logit transformation. Use Student's t-distribution for CI. Add the following footnotes: Note: Free CCL17 LLOQ = 2.93 pg/mL, ULOQ = 3600 pg/mL. Note: Total CCL17 LLOQ = 13.11 pg/mL, ULOQ = 50000 pg/mL. Note: Free CCL17 and Total CCL17 concentrations below LLOQ have been set to ½*LLOQ and 0, respectively, and have been included in the summary statistic calculations. Note: Any single mid-profile non-quantifiable (NQ) concentrations have been omitted. Note: Measurable Total CCL17 concentrations following more than one consecutive mid-profile NQ have been omitted. Note: Zero Total CCL17 concentration values have been set to missing in the log-linear plot. Note: The geometric mean is plotted as the data is not normally distributed. Note: Percentage reduction values <= 0 are imputed to be 0.1 and values >= 100 are imputed to be 99.9. Note: The percentage reduction parameter was logit transformed, summarised, and back-transformed using the logistic function to obtain the geometric summary statistics.	Part B SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.06.	Safety	PK18	Part B: Median Free & Total Serum CCL17 Concentration-Time Plots (Linear and Semi-log)	Add the following footnotes: Note: Free CCL17 LLOQ = 2.93 pg/mL, ULOQ = 3600 pg/mL. Note: Total CCL17 LLOQ = 13.11 pg/mL, ULOQ = 50000 pg/mL. Note: Free CCL17 and Total CCL17 concentrations below LLOQ have been set to ½*LLOQ and 0, respectively, and have been included in the summary statistic calculations. Note: Any single mid-profile non-quantifiable (NQ) concentrations have been omitted. Note: Measurable Total CCL17 concentrations following more than one consecutive mid-profile NQ have been omitted. Note: Zero Total CCL17-concentration values have been set to missing in the log-linear plot.	Part B SAC

14.11.12. Biomarker Tables

14.11.12.1. Part A

No.	Population	IDSL/ Example Shell	Title	Programming Notes	Deliverable
Immune Cell Phenotype					
5.01.	Biomarker	BIO_T1	Part A: Summary of Immune Cell Phenotypes		Part A SAC
5.02.	Biomarker	BIO_T2	Part A: Analyses of Immune Cell Phenotypes: Treatment		Part A SAC
5.03.	Biomarker	BIO_T3	Part A: Analyses of Immune Cell Phenotypes: Sample Type		Part A SAC

14.11.13. Biomarker Figures

14.11.13.1. Part A

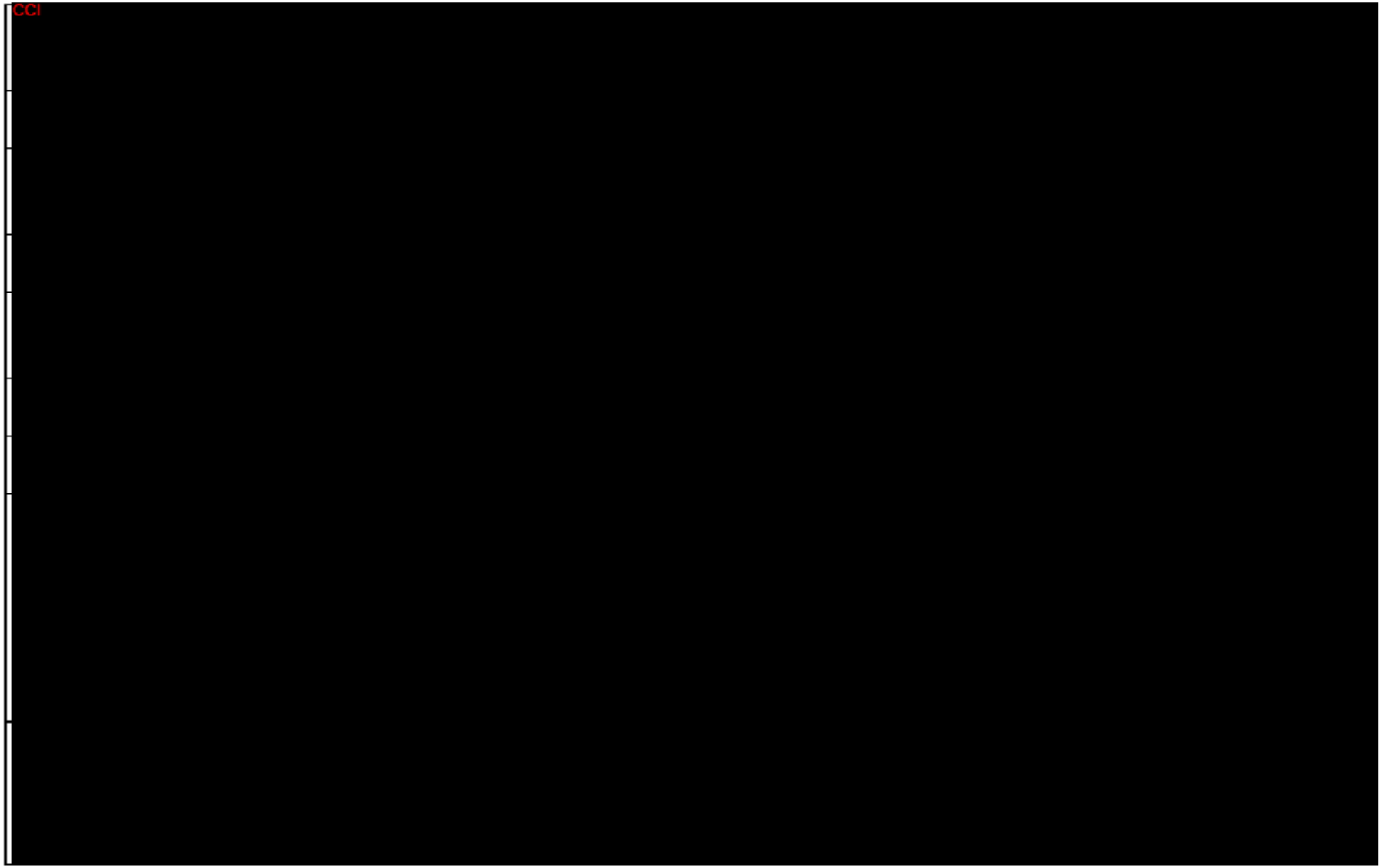
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Immune Cell Phenotype					
5.01.	Biomarker	BIO_F1	Part A: LS Mean Change from Baseline (+/- SE) of Immune Cell Phenotypes: Treatments by Visit		Part A SAC
5.02.	Biomarker	BIO_F2	Part A: Differences and 95% CI of Immune Cell Phenotypes: Treatments by Visit		Part A SAC
5.03.	Biomarker	BIO_F1	Part A: LS Mean Change from Baseline (+/- SE) of Immune Cell Phenotypes: Sample Type by Visit		Part A SAC
5.04.	Biomarker	BIO_F2	Part A: Differences and 95% CI of Immune Cell Phenotypes: Sample Type by Visit		Part A SAC

14.11.14. Efficacy Tables

14.11.14.1. Part B

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Primary Efficacy					
6.01.	ITT	EFF_T10	Part B: Summary of Pain Intensity Data	Frequency table showing at each visit, how many subjects had how many days of knee pain intensity data (presented by trt group).	IA1, IA2, Part B SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
6.02.	ITT	EFF_T1	Part B: Summary of Absolute Values and Change from Baseline in Average Knee Pain Intensity		IA1, IA2, IA3, IA4, Part B SAC
6.03.	ITT	EFF_T2	Part B: Bayesian Analysis of Change from Baseline in Average Knee Pain Intensity		IA1, IA2, IA3, IA4, Part B SAC
6.04.	PP	EFF_T1	Part B: Summary of Absolute Values and Change from Baseline in Average Knee Pain Intensity		Part B SAC
6.05.	PP	EFF_T2	Part B: Bayesian Analysis of Change from Baseline in Average Knee Pain Intensity		Part B SAC
6.06.	ITT	EFF_T1	Part B: Summary of Absolute Values and Change from Baseline in Worst Knee Pain Intensity		IA3, IA4, Part B SAC
6.07.	ITT	EFF_T2	Part B: Bayesian Analysis of Change from Baseline in Worst Knee Pain Intensity		IA3, IA4, Part B SAC
CCI [redacted]					


CCI

CCI [redacted]

14.11.15. Efficacy Figures

14.11.15.1. Part B

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Primary Efficacy					
6.01.	ITT	EFF_F1	Part B: Plot of Posterior Median and 95% CI of Average Knee Pain Intensity		Part B SAC
6.02.	ITT	EFF_F1	Part B: Plot of Posterior Median and 95% CI of Change from Baseline in Average Knee Pain Intensity		IA1, IA2, IA3, IA4, Part B SAC
6.03.	ITT	EFF_F1	Part B: Plot of Posterior Median and 95% CI of Worst Knee Pain Intensity		Part B SAC
6.04.	ITT	EFF_F1	Part B: Plot of Posterior Median and 95% CI of Change from Baseline in Worst Knee Pain Intensity		Part B SAC
6.05.	PP	EFF_F1	Part B: Plot of Posterior Median and 95% CI of Average Knee Pain Intensity		Part B SAC
6.06.	PP	EFF_F1	Part B: Plot of Posterior Median and 95% CI of Change from Baseline in Average Knee Pain Intensity		Part B SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
CCI	[redacted]				

14.11.16. ICH Listings

14.11.16.1. Part A

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Subject Disposition					
1.	Screened	ES7	Part A: Listing of Reasons for Screen Failure		Part A SAC
2.	Screened	ES9	Part A: Listing of Subjects who were Rescreened		Part A SAC
3.	Enrolled	ES2	Part A: Listing of Reasons for Study Withdrawal		Part A SAC
4.	Randomized	BL1	Part A: Listing of Subjects for Whom the Treatment Blind was Broken		Part A SAC
5.	Randomized	TA1	Part A: Listing of Planned and Actual Treatments		Part A SAC
Protocol Deviations					
6.	Enrolled	DV2	Part A: Listing of Important Protocol Deviations		Part A SAC
7.	Enrolled	IE3	Part A: Listing of Subjects with Inclusion/Exclusion Criteria Deviations		Part A SAC
Populations Analysed					
8.	Enrolled	SP3	Part A: Listing of Subjects Excluded from Any Population		Part A SAC
Demographic and Baseline Characteristics					
9.	Randomized	DM2	Part A: Listing of Demographic Characteristics		Part A SAC
10.	Randomized	DM9	Part A: Listing of Race		Part A SAC
Medical History					
11.	Safety	MH2	Part A: Listing of Current and Past Medical Conditions		Part A SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Concomitant Medications					
12.	Safety	CP_CM3	Part A: Listing of Prior and Concomitant Medications		Part A SAC
Exposure					
13.	Safety	POP_L01	Part A: Listing of Exposure Data		Part A SAC
Adverse Events					
14.	Safety	AE8CP	Part A: Listing of All Adverse Events		Part A SAC
15.	Safety	AE7	Part A: Listing of Subject Numbers for Individual Adverse Events		Part A SAC
16.	Safety	AE2	Part A: Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		Part A SAC
Serious and Other Significant Adverse Events					
17.	Safety	AE8CPa	Part A: Listing of Serious Adverse Events (Fatal and Non-Fatal)		Part A SAC
18.	Safety	AE14	Part A: Listing of Reasons for Considering as a Serious Adverse Event		Part A SAC
19.	Safety	AE8CP	Part A: Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment		Part A SAC
20.	Safety	AE8CP	Part A: Listing of Other Significant Adverse Events		Part A SAC
Vital Signs					
21.	Safety	VS4	Part A: Listing of Vital Signs of Potential Clinical Importance		Part A SAC
22.	Safety	VS4	Part A: Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance		Part A SAC
Laboratory: All					
23.	Safety	LB5	Part A: Listing of Laboratory Values of Potential Clinical Importance		Part A SAC
24.	Safety	LB5	Part A: Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Importance		Part A SAC
25.	Safety	LB14	Part A: Listing of Laboratory Data with Character Results		Part A SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
26.	Safety	UR2A	Part A: Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance		Part A SAC
ECG					
27.	Safety	EG3	Part A: Listing of ECG Values of Potential Clinical Importance		Part A SAC
28.	Safety	EG3	Part A: Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		Part A SAC
29.	Safety	EG5	Part A: Listing of Abnormal ECG Findings		Part A SAC
30.	Safety	EG5	Part A: Listing of All ECG Findings for Subjects with an Abnormal ECG Finding		Part A SAC
Telemetry					
31.	Safety	EG5	Part A: Listing of Abnormal Telemetry Findings	.	Part A SAC

14.11.16.2. Part B

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Subject Disposition					
32.	Screened	ES7	Part B: Listing of Reasons for Screen Failures		Part B SAC
33.	Screened	ES9	Part B: Listing of Subjects who were Rescreened		Part B SAC
34.	Enrolled	ES2	Part B: Listing of Reasons for Study Withdrawal		Part B SAC
35.	Randomized	BL1	Part B: Listing of Subjects for Whom the Treatment Blind was Broken		Part B SAC
36.	ITT	SD2	Part B: Listing of Reasons for Study Treatment Discontinuation		Part B SAC
37.	Randomized	TA1	Part B: Listing of Planned and Actual Treatments		Part B SAC
Protocol Deviations					
38.	Enrolled	DV2	Part B: Listing of Important Protocol Deviations		Part B SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
39.	Enrolled	IE3	Part B: Listing of Subjects with Inclusion/Exclusion Criteria Deviations		Part B SAC
Populations Analysed					
40.	Enrolled	SP3	Part B: Listing of Subjects Excluded from Any Population		Part B SAC
Demographic and Baseline Characteristics					
41.	Randomized	DM2	Part B: Listing of Demographic Characteristics		Part B SAC
42.	Randomized	DM9	Part B: Listing of Race		Part B SAC
Medical Conditions					
43.	Safety	MH2	Part B: Listing of Current and Past Medical Conditions		Part B SAC
Concomitant Medications					
44.	Safety	CP_CM3	Part B: Listing of Prior and Concomitant Medications		Part B SAC
45.	Safety	CP_CM3	Part B: Listing of Prior and Concomitant Osteoarthritis Medications	OA con-meds are captured on a specific CRF page	Part B SAC
Exposure					
46.	Safety	EX3	Part B: Listing of Exposure Data	Include number of injections received	Part B SAC
Adverse Events					
47.	Safety	AE8CP	Part B: Listing of All Adverse Events		Part B SAC
48.	Safety	AE7	Part B: Listing of Subject Numbers for Individual Adverse Events		Part B SAC
49.	Safety	AE2	Part B: Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		Part B SAC
Serious and Other Significant Adverse Events					
50.	Safety	AE8CPa	Part B: Listing of Serious Adverse Events (Fatal and Non-Fatal)		Part B SAC
51.	Safety	AE14	Part B: Listing of Reasons for Considering as a Serious Adverse Event		Part B SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
52.	Safety	AE8CP	Part B: Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment		IA3, Part B SAC
53.	Safety	AE8CP	Part B: Listing of Other Significant Adverse Events		Part B SAC
Vital Signs					
54.	Safety	VS4	Part B: Listing of Vital Signs of Potential Clinical Importance		Part B SAC
55.	Safety	VS4	Part B: Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance		Part B SAC
Laboratory: All					
56.	Safety	LB5	Part B: Listing of Laboratory Values of Potential Clinical Importance		IA3, Part B SAC
57.	Safety	LB5	Part B: Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Importance		IA3, Part B SAC
58.	Safety	LB14	Part B: Listing of Laboratory Data with Character Results		Part B SAC
59.	Safety	UR2A	Part B: Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance		Part B SAC
ECG					
60.	Safety	EG3	Part B: Listing of ECG Values of Potential Clinical Importance		Part B SAC
61.	Safety	EG3	Part B: Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		Part B SAC
62.	Safety	EG5	Part B: Listing of Abnormal ECG Findings		Part B SAC
63.	Safety	EG5	Part B: Listing of All ECG Findings for Subjects with an Abnormal ECG Finding		Part B SAC

14.11.17. ICH Conditional Listings

The following listings will only be produced if a liver event is observed within the trial.

14.11.17.1. Part A

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Hepatobiliary (Liver)					
64.	Safety	MH2	Part A: Listing of Medical Conditions for Subjects with Liver Stopping Events	Conditional on liver event being seen	Part A SAC
65.	Safety	SU2	Part A: Listing of Substance Use for Subjects with Liver Stopping Events	Conditional on liver event being seen	Part A SAC

14.11.17.2. Part B

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Hepatobiliary (Liver)					
66.	Safety	MH2	Part B: Listing of Medical Conditions for Subjects with Liver Stopping Events	Conditional on liver event being seen	Part B SAC
67.	Safety	MH2	Part B: Listing of Substance Use for Subjects with Liver Stopping Events	Conditional on liver event being seen	Part B SAC

14.11.18. Non-ICH Listings

14.11.18.1. Part A

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Substance Use					
68.	Safety	SU2	Part A: Listing of Substance Use	Include columns: Smoking history, Currently Smoke, Last Smoked, Drink Alcohol, Units per Week, Currently using Illicit Drugs	Part A SAC
Pharmacokinetics					
69.	PK	PK07	Part A: Listing of Serum GSK3858279 Concentration-Time Data (ng/mL)		Part A SAC
70.	PK	PK13	Part A: Listing of Derived Serum GSK3858279 Pharmacokinetic Parameters	Add a footnote saying that NQ means non-quantifiable and LLQ=100 ng/mL	Part A SAC
CCI					

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Pharmacodynamic					
72.	Safety	PK07	Part A: Listing of Free & Total CCL17 in Serum Concentration-Time Data (pg/mL)	Including Percentage Inhibition/Fold Increase Add a footnote saying that NQ means non-quantifiable and Free CCL17 LLOQ=2.93 pg/mL and Total CCL17 LLOQ=13.11 pg/mL.	Part A SAC
73.	Safety	PK13	Part A: Listing of Derived Free CCL17 in Serum Target Engagement Parameters		Part A SAC
74.	Safety	PK13	Part A: Listing of Derived Total CCL17 in Serum Target Engagement Parameters		Part A SAC
75.	Blister	PK07	Part A: Listing of Free & Total CCL17 in Blister Fluid Concentration-Time Data (pg/mL)	Including Blister/Serum Ratio	Part A SAC
76.	Safety	IMM2	Part A: Listing of Immunogenicity		Part A SAC
Biomarker					
77.	Biomarker	BIO_L1	Part A: Listing of Immune Cell Phenotypes		Part A SAC

14.11.18.2. Part B

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Substance Use					
78.	Safety	SU2	Part B: Listing of Substance Use	Include columns: Smoking history, Currently Smoke, Last Smoked, Drink Alcohol, Units per Week, Currently using Illicit Drugs	Part B SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Pharmacokinetics					
79.	PK	PK07	Part B: Listing of Serum GSK3858279 Concentration-Time Data (ng/mL)	Add a footnote saying that NQ means non-quantifiable and LLOQ=100 ng/mL	Part B SAC
80.	PK	PK13	Part B: Listing of Model-Derived Serum GSK3858279 Pharmacokinetic Parameters	Add a footnote saying that "All Pharmacokinetic parameters were calculated using a model based post-hoc analysis".	Part B SAC
Pharmacodynamic					
81.	Safety	PK07	Part B: Listing of Free & Total CCL17 in Serum Concentration-Time Data (pg/mL)	Add a footnote saying that LLOQ means lower limit of quantification and ULOQ means upper limit of quantification. LLOQ for free CCL17= 2.93 pg/mL. LLOQ for total CCL17= 13.11 pg/mL.ULOQ for free CCL17= 3600 pg/mL. ULOQ for total CCL17= 50000 pg/mL.	Part B SAC
82.	Safety	PK13	Part B: Listing of Derived Free CCL17 in Serum Target Engagement Parameters	Including Percentage Inhibition/Fold Increase. Add a footnote saying "All Target Engagement parameters were calculated using a model based post-hoc analysis.".	Part B SAC
83.	Safety	PK13	Part B: Listing of Derived Total CCL17 in Serum Target Engagement Parameters	Add a footnote saying "All Target Engagement parameters were calculated using a model based post-hoc analysis.".	Part B SAC
84.	Safety	IMM2	Part B: Listing of Immunogenicity	For IA3, include only participants with at least one positive confirmation assay result.	IA3, Part B SAC
Primary Efficacy					
85.	ITT	EFF_L01	Part B: Listing of Average and Worst Knee Pain Intensity	Include the number of records which make up the average	IA1, IA2, Part B SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
CCI [redacted]					
COVID-19					
88.	Randomized	PAN7	Part B: Listing of All Subjects with Visits and Assessments Impacted by COVID-19 Pandemic		Part B SAC