Reporting and Analysis Plan

Study ID: 209973

Official Title of Study: Reporting and Analysis Plan for a randomized, double-blind, placebo-controlled, three-period two-treatment incomplete-block crossover study to investigate the effects of intravenous GSK3858279 on a battery of evoked pain tests in healthy participants.

EudraCT: 2019-002609-23

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Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for a randomized, double-blind, placebo-controlled, three-period two-treatment incomplete-block crossover study to investigate the effects of intravenous GSK3858279 on a battery of evoked pain tests in healthy participants.
Compound Number	:	GSK3858279
Effective Date	:	08-OCT-2021

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 209973
- This RAP will be provided to the study team members to convey the content of interim analyses and the Statistical Analysis Complete (SAC) and All Analysis Complete (AAC) deliverables.

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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 interim analyses and the Clinical Study Report for Protocol 209973:

Revision Chronology:		
2019N405625_00	25-JUL-2019	Original.
2019N405625_01	23-SEP-2019	Feedback from Scientific Review meeting, and the Ethics Committee, following protocol finalisation. Updates to SoA, Table 2 and Appendix 7 for clarity.
2019N405625_02	11-FEB-2020	Correction to certain exclusion criteria in order to streamline with the other related exclusion criteria. A minor correction to one of the objectives and endpoints, and washout period of few of the prohibited medications.
2019N405625_03	10-AUG-2020	Change to Analysis Populations. Populations are now UVB-MITT who undergo all assessments and MITT population who do not receive UVB irradiation (and not perform UVB heat pain detection assessment on irradiated skin). In addition, changes to expand age range and amendment of certain exclusion criteria in order to reduce volunteer burden and aid recruitment. Risk Benefit Analysis has also been amended in protocol amendment 03 to reflect changes made to the study design and new safety guidance available. As a result of the worldwide pandemic of COVID-19, throughout the protocol there have been addition of SARS-Cov2 screening and mitigation strategies to ensure the safety of the study participants.
2019N405625_04	25-MAY-2021	Amendment to the Interim Analysis sections. An interim analysis may be performed once the last UVB-MITT participant has completed their period 3 final day 15 PainCart assessments. Dependent on the results, the study could be stopped for futility.

1.1. Version History

RAP Version	**Approval Date**	**Protocol Version (Date) on which RAP is Based**	**Change**	**Rationale**
Original RAP	01-July-2021	TMF-13778634 (25-May-2021)	None	Original Version

RAP Version	Approval Date	Protocol Version (Date) on which RAP is Based	Change	Rationale
RAP Amendment 1	##-October-2021	TMF-13778634 (25-May-2021)	CPM Summary measure updated. Definition of Exposure updated. Reduced number of SAC displays. Removal of the Bayesian PainCart by Day sensitivity analyses. Inclusion of an All Analysis Complete (AAC) Milestone for exploratory endpoints.	Display is not analysed on the log scale, ratio to baseline is not suitable so change from baseline will be the summary measure. The volume of infusion will be presented to calculate exposure to study drug, along with start and stop date/time as a single dose study. Study has been terminated due to not meeting the futility threshold. A reduced SAC has been incorporated. The reduced SAC includes the removal of the Bayesian PainCart by Day sensitivity analyses. Due to the complex modelling structure in PROC MCMC, the low number of subjects compared to the amount of parameters, and that summary statistics and figures will be able to demonstrate the Period and Day effects, the analyses were removed. The AAC milestone has been incorporated to allow time for the analysis of all TLFs and not jeopardise the upper quartile performance targets and to report out the primary endpoints and AEs in a timely manner (SAC). This is due to the study terminating early and reporting the study 4 months ahead of the original SAC date.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the planned statistical analysis specified in protocol amendment 4 (2019N405625_04) are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
Section 9.3 Populations for Analyses	Removed population "Completers" Included UVB-ITT and UVB-Safety populations	The MITT and UVB-MITT is being utilised for the PainCart analyses instead. UVB-ITT and UVB-Safety populations will be used for UVB heat pain detection on irradiated skin summaries and safety displays.
Section 9.1.1.2	Update PK parameter table to include AUC(0-7) and tlast	AUC(0-7) may be used to assess whether there is any relationship between PK exposure and UVB Heat Pain AAUC(1-8). tlast needs to be output when AUC(0-t) is derived as per SOP_314000.
Section 7.3.1.2	Remove AUC(0-t) from TE parameter table for total CCL17	NCA will not be performed for total CCL17. TE parameters for total CCL17 will be determined directly from the observed total CCL17 levels in serum.
Section 12.11.11	Add exploratory Pharmacokinetic/Pharmacodynamic Figures	An exploratory graphical analysis will be performed to assess the relationship between primary endpoints of efficacy and PK exposure.
Section 9.1. Statistical Hypotheses	Removed references to hypothesis testing	The analysis is being perform in the Bayesian framework which does not involve hypothesis testing.

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the effects of IV administration of GSK3858279 in Ultraviolet B (UVB) burn inflammatory, cold pressor test and electrical pain test in the PainCart	• UVB heat pain detection (°C) • Cold pressor time to intolerable pain threshold (secs) • Electrical pain tolerance threshold (mA) - single stimulus
Safety Objectives	**Safety Endpoints**
• To evaluate the safety and tolerability of GSK3858279 following IV dosing	• Adverse Events (AE) and Serious Adverse Events (SAE) • Clinical laboratory measurements, 12-lead electrocardiograms (ECG) and vital signs that are considered of potential clinical importance.
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the pharmacokinetics (PK) of GSK3858279 following IV administration	• Serum PK concentrations and parameters including but not limited to: area under the concentration-time curve [AUC], maximum concentration [Cmax], tmax
• To evaluate the target engagement (TE) of CCL17 by GSK3858279 following IV administration	• Free and total CCL17 levels in serum
• To evaluate the effects of IV administration of GSK3858279 in additional endpoints in UVB test, cold pressor test and electrical pain test in the PainCart	• Heat pain detection on normal skin (°C) • Cold pressor time to pain detection (secs) • Electrical pain detection (mA) - single stimulus • Electrical pain detection and tolerance threshold (mA) - repeat stimulus • For each test Area Under the Curve (AUC)/Area Above the Curve (AAC) and post-test eVAS
• To evaluate the effects of IV administration of GSK3858279 in pressure pain test and Conditioned pain modulation (CPM) test of the PainCart	• Pressure pain (tolerance and detection) - KPa • CPM - (detection and tolerance thresholds) – mA • For each test AUC/AAC and post-test eVAS
• To assess the potential for anti-GSK3858279 antibody formation following IV dosing	• To include: incidence, titres, and, for samples with confirmed anti-drug antibodies (ADAs), neutralising activity

2.3. Study Design

This study will be a randomized, double-blind, placebo-controlled, three-period two-treatment incomplete-block crossover study in healthy participants to investigate the effects of IV GSK3858279 on evoked pain tests in the PainCart. The study will be performed in a single centre.

In each period participants will receive either GSK3858279 or placebo in a 1:1 ratio. During the trial participants will receive both treatments, participants will receive either two doses of GSK3858279 and one dose of placebo, or two doses of placebo and one dose of GSK3858279 with equal likelihood, the order of treatment assignments will be randomised.

The total duration of the study (from signing informed consent until final follow-up visit) for each participant will be approximately 6 months. Study participation may be prolonged in the event the study is on-hold. Screening period will be a maximum of 28 days prior to study procedures, each study period will be approximately 2 weeks with at least a 4-week wash-out period between dosing (i.e. Day 1) in each of the study periods, final follow-up visit will be at approximately 8 weeks after last dose.

Participants will arrive at the research unit either one or two days before dosing, for the non-UVB-MITT and UVB-MITT group respectively. After arrival, subjects will be tested for SARS-CoV-2. Urine will be screened for the presence of drugs and an alcohol breath test will be performed. For participants with a positive urine drug screen or alcohol breath test, the treatment occasion may be rescheduled at the discretion of the principal investigator and GSK medical monitor. UVB irradiation will be applied approximately 24 hours before dosing in the UVB-MITT population only. ECG and vital signs will also be performed.

Participants will be assigned to receive treatment and pain assessments during either morning or afternoon sessions. They will continue to receive treatment and pain assessments at approximately the same time of day throughout all three study periods.

Meals will be served at the site scheduled times. Safety, PK, PD and PainCart assessments will be performed as outlined in the SoA. Baseline measurements for PainCart (2 baseline measurements) are conducted at each study period prior to dosing.

Phone contact to assess the participant’s general health will be conducted as per the SoA, the investigator may invite the participant for a site visit at the investigator's discretion for additional follow-up, as required.

Overview of Study Design and Key Features

Figure 1 Study Design Schematic

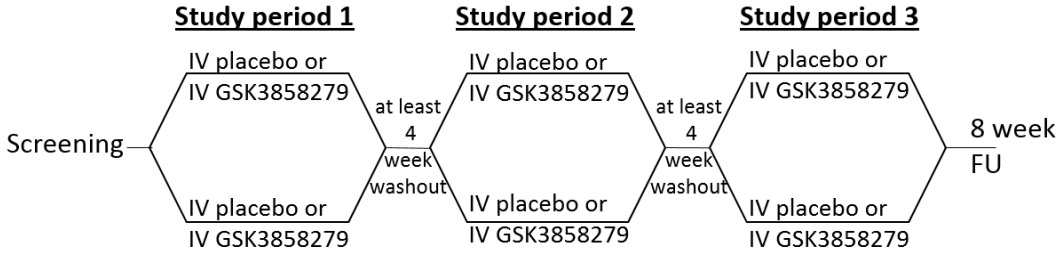


Figure 2 Visit schematic

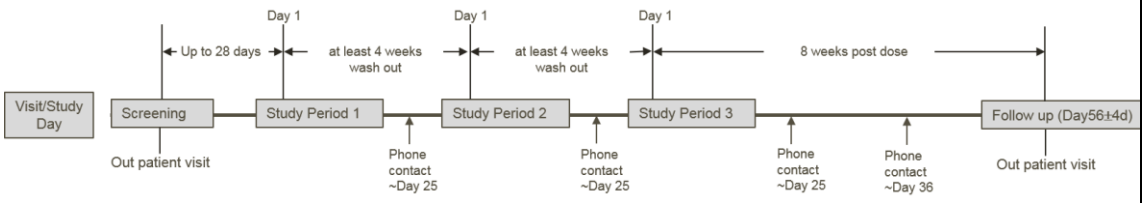
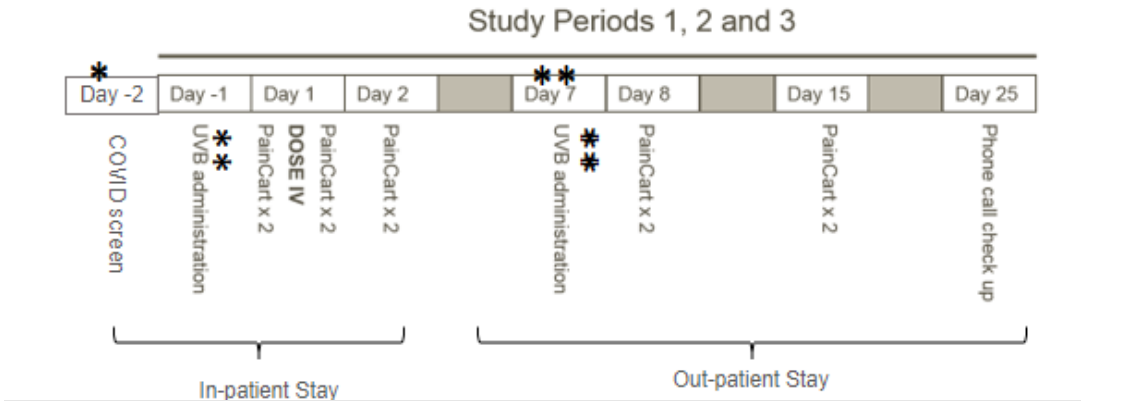


Figure 3 Study Period Details



* Required only in UVB-MITT population

** Optional assessments/study day applicable to UVB-MITT volunteers only

Design Features	• A screening visit can occur up to 28 days before study day 1. • A SARS-CoV-2 PCR test and temperature check will be performed at screening visit, prior to any other screening procedure. • Each study period lasts for approximately 4 weeks, with PainCart assessments occurring the first 2 weeks and wash out periods lasting approximately 4 weeks between treatment dosing in each period. • For each study period, UVB application (2 x MED) will be performed 24hr (±2hr) prior to start of infusion on Day 1 and Day 7 (24hr (±2hr) prior to start of PainCart assessment on Day 8, for those participants enrolled into the UVB group. The PainCart assessments are performed twice on Day 1 before start of infusion (baseline readings) and performed twice again on Day 1 at 1 and 3 hours post start

<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
<tr><td></td><td>of IV infusion. On days 2, 8 and 15, the PainCart assessment is performed twice, approximately 2 hours apart. On day 15 the UVB pain assessment will only be performed on normal skin, due to no UVB applied skin being applicable at that visit. The planned PainCart assessments on Day 2, 8 & 15 may be performed within a ± 24hr window.
• Participant replacements are permitted in the study.
• A follow up phone call is scheduled on day 36 of study period 3 (approximately 6 weeks post dose) and a final follow up out-patient visit scheduled on day 56 (approximately 8 weeks post dose).
• Participants will be stratified in to two strata based on whether they perform the PainCart assessments in the morning (AM) or the afternoon (PM). These strata will continue throughout the full duration of the study for the participant (e.g. if a participant performs their first PainCart assessment in the morning, they will perform their subsequent assessments in the morning too).</td></tr>
<tr><td>Dosing</td><td>• According to a participant's randomisation schedule, the dosing are as follows:
o 3 mg/kg IV GSK3858279, single dose
o Placebo, single dose
• All dosing occurs on Day 1 for each study period.</td></tr>
<tr><td>Time & Events</td><td>• Refer to Appendix 2: Schedule of Activities</td></tr>
<tr><td>Treatment Assignment</td><td>• GSK3858279 and placebo will be administered in a 1:1 ratio according to the randomisation schedule, in a blinded manner.
• A three period, cross over design, with participants receiving either two doses of GSK3858279 and one dose of placebo, or two doses of placebo and one dose of GSK3858279 with equal likelihood. The order of treatment assignments will be randomized.
• Approximately 30 healthy participants will be enrolled into the study, such that at least approximately 24 participants complete dosing and critical assessments in all three study periods.
• For the UVB-exposed population, approximately 18 participants are required to be enrolled to ensure that approximately 15 participants complete all UVB tests of the PainCart assessment on irradiated skin in all three study periods

<table><tr><th>Intervention code</th><th>Intervention Description</th></tr><tr><td>A</td><td>3 mg/kg IV GSK3858279</td></tr><tr><td>P</td><td>Placebo</td></tr></table></td></tr>
<tr><td>Interim Analysis</td><td>• Two interim analyses may be performed at the following timepoints:
o The final UVB-MITT participant in period 3 has completed the day 15 assessments of the PainCart tests. Dependent on the results observed, the study could be stopped for futility, based on pre-specified futility criteria. A secondary objective for the interim is to potentially use the analysis for internal decision-making purposes.

o The final participant in period 3 has completed the day 15 assessments of the PainCart tests. The interim analyses will be used for internal decision making only, no changes to the study can occur.</td></tr>
</table>

2.4. Statistical Analyses

The study will estimate the difference between GSK3858279 and placebo on the endpoints described: UVB heat pain detection test, cold pressor time to intolerable pain threshold test and electrical pain tolerance threshold test in the PainCart scale.

All participants will receive GSK3858279 and placebo during their course on the study, depending on their randomisation schedule.

The primary endpoints are:

- Ratio to Baseline in UVB heat pain detection (Celsius)
- Ratio to Baseline in cold pressor time to intolerable pain threshold (seconds)
- Ratio to Baseline in electrical pain tolerance – single stimulus (mA)

If ratio to baseline is not suitable due to the distribution of the parameters, change from baseline will be utilised instead.

3. PLANNED ANALYSES

3.1. Interim Analyses

Two interim analyses of the primary endpoints to inform internal decision making may be conducted during the study. The interim analyses may occur when:

- The final UVB-MITT participant (approx. 15 evaluable participants) to have completed the day 15 assessments of the PainCart assessments in study period 3 (final study period).
- The final randomised participant has completed the day 15 assessments of the PainCart assessments in study period 3 (final study period).

The table below details the endpoints that will be analysed/summarised at the interim:

Purpose of Interim	Endpoints
Interim Analysis 1 (Futility)	UVB heat pain detection (Celsius) • Absolute values (Summarised) • Change from baseline (Summarised) • Ratio to Baseline (Summarised) • AAUC of Ratio to Baseline (Analysed) Cold pressor time to intolerable pain threshold (seconds): • Absolute values (Summarised) • Change from baseline (Summarised) • Ratio to Baseline (Summarised) • AAUC of Ratio to Baseline (Analysed) Electrical pain tolerance – single stimulus (mA): • Absolute values (Summarised) • Change from baseline (Summarised) • Ratio to Baseline (Summarised) • AAUC of Ratio to Baseline (Analysed) Summary of Demographic Characteristics Summary of Derived Serum GSK3858279 Pharmacokinetic Parameters (non-transformed and log-transformed) Summary of Serum GSK3858279 Concentration-Time Data (ng/mL) Summary of Derived Free and Total CCL17 in Serum Target Engagement Parameters (non-transformed and log-transformed)

	Summary of Free & Total CCL17 in Serum Concentration-Time Data (pg/mL). Summary of All Adverse Events by System Organ Class and Preferred Term by Period (>=2 Subjects with the AE)
IA 2 – Internal Decision-Making Purposes	UVB heat pain detection (Celsius) • Absolute values (Summarised) • Change from baseline (Summarised) • Ratio to Baseline (Summarised) • AAUC of Ratio to Baseline (Analysed) Cold pressor time to intolerable pain threshold (seconds): • Absolute values (Summarised) • Change from baseline (Summarised) • Ratio to Baseline (Summarised) • AAUC of Ratio to Baseline (Analysed) Electrical pain tolerance – single stimulus (mA): • Absolute values (Summarised) • Change from baseline (Summarised) • Ratio to Baseline (Summarised) • AAUC of Ratio to Baseline (Analysed) Summary of Demographic Characteristics Summary of All Adverse Events by System Organ Class and Preferred Term by Period

Note: Ratio to baseline will only be produced if deemed suitable by the distribution of the parameters.
Note: AAUC = Analysis Area Under Curve. Derivation of AAUC is described in Section 12.6.3 Pharmacodynamic.

The statistical methods of the analyses are described in Section 7.1, Section 7.2 and Section 7.3.

The following functions will be unblinded to interim analysis data: Clinical Statistics, Clinical Programming and CPMS. Other members of GSK will be unblinded to group level summary data following the interim analyses (as documented in the Interim Charter).

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol.

2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG and RAMOS procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population • Safety
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 (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• Study Population
Randomized	• All participants who were randomly assigned to treatment in the study. • This population will be based on the treatment sequence 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 sequence the subject actually received. • Note: Participants who were not randomized but received at least one dose of study treatment should be included.	• Safety • PK/PD
Pharmacokinetic (PK)	• All participants in the Safety population who had at least 1 non-missing serum PK assessment. • Note: Non-quantifiable [NQ] values will be considered as non-missing values	• PK
Intent-To-Treat (ITT)	• All randomized participants who received at least one dose of study treatment. • This population will be based on the treatment sequence the subject was randomized to. • Any participants who receives a treatment randomization number will be considered to have been randomized.	• PainCart • Study Population
Modified Intent-to-Treat (MITT)	• All randomized participants who received at least one dose of study treatment and completed at least one PainCart assessment in at least two study periods. • This population will be based on the treatment sequence the subject was randomized to. • Any participants who receives a treatment randomization number will be considered to have been randomized.	• PainCart

Population	Definition / Criteria	Analyses Evaluated
UVB Safety	• Those in the Safety Population who also perform the UVB Heat Pain detection PainCart assessments on irradiated skin.	• Safety (UVB Sensitivity)
UVB Intent-to-Treat (UVB-ITT)	• Those in the ITT Population who also perform at least one UVB Heat Pain detection PainCart assessment on irradiated skin in at least one study period.	• PainCart UVB heat pain irradiated skin endpoint - summary
UVB Modified Intent-to-Treat (UVB-MITT)	• Those in the MITT Population who also perform at least one UVB Heat Pain detection PainCart assessment on irradiated skin in at least two study periods.	• PainCart UVB heat pain irradiated skin endpoint - analysis

Refer to Appendix 12: List of Data Displays which details the population used for each display.

A populations exclusion meeting will be held before unblinding of the data. The meeting minutes and list of participants excluded from the populations mentioned in Section 4: Analysis Populations will be documented and uploaded to eTMF. A summary and listing of the participants excluded from certain populations will be created.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, participant management or participant assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan Date: 05-Sept-2019, Version 1.0.

- 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 summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary 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. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	3 mg/kg IV GSK3858279	GSK3858279	2
P	Placebo	Placebo	1

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. GSK3858279 vs Placebo

For treatment sequence displays:

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A/P/P	3 mg/kg IV GSK3858279 – Placebo – Placebo	GSK3858279-Placebo-Placebo	2
P/A/A	Placebo – 3 mg/kg IV GSK3858279 – 3 mg/kg IV GSK3858279	Placebo- GSK3858279-GSK3858279	1
		Total	3

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. This study has three study periods, with each period having its own baseline which is the latest non-missing value prior to dosing in that period.

For the PainCart test, two assessments are performed at each visit except for visit Day 1 where two are performed prior to dose and two are performed after dose. The baseline value is defined as the mean of the two pre-dose assessments on Day 1 for each study period. If only one pre-dose assessment record is present on Day 1, then this value will be set as the baseline value.

For the PainCart analyses, baseline will compose of two variables:

- Subject level baseline = the mean of the three period baseline values for each subject.
- Period level baseline = Subject level baseline – Period specific baseline value.

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Efficacy				
PainCart Assessments			X	Mean of Day 1 (Pre-Dose) Assessments
Safety				
Vital Signs			X	Day 1 (Pre-Dose)
Haematology			X	Day 1 (Pre-Dose)
Chemistry			X	Day 1 (Pre-Dose)
ECG			X	Day 1(Pre-Dose) [Mean of triplicate measurements]
Urinalysis			X	Day 1 (Pre-Dose)

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

5.3. Multicentre Studies

This is a single centre study.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

The list of covariates and other strata may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses.

Category	Details
Strata	Time of Assessment (AM or PM)
Covariates	Baseline (of the analysis variable of interest), Study Period

5.5. Multiple Comparisons and Multiplicity

There are no planned adjustments for multiple comparisons or multiplicity.

5.6. 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
12.3	Appendix 3: Assessment Windows

Section	Component
12.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
12.5	Appendix 5: Data Display Standards & Handling Conventions
12.6	Appendix 6: Derived and Transformed Data
12.7	Appendix 7: Reporting Standards for Missing Data
12.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the population specified in Appendix 11: List of Data Displays, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications and exposure will be based on GSK Core Data Standards.

Details of the planned displays are presented in Appendix 12: List of Data Displays.

7. PHARMACODYNAMIC ANALYSES

7.1. Primary PainCart Analyses

7.1.1. Endpoint / Variables

The primary endpoints are

- UVB heat pain detection (Celsius)
- Cold pressor time to intolerable pain threshold (seconds)
- Electrical pain tolerance threshold (mA) – single stimulus

7.1.2. Summary Measure

For each of the three endpoints, the Analysis Area Under the Curve (AAUC) of the Ratio to Baseline will be the primary summary measure. The PainCart assessments will be log transformed in order to calculate the log change from baseline result which will be used for the primary analysis, and back transformed to obtain the ratio to baseline result. As default, summaries of Change from Baseline will also be calculated. If modelling assumptions are invalidated, then the results will not be presented. Ratio to baseline and change from baseline will be measured at each day where the assessment was performed. The AAUC is calculated via the trapezoidal method and will be normalised. Further details are referenced in Section 12.6.3 Pharmacodynamic.

7.1.3. Population of Interest

The primary analyses will be based on the MITT population for the cold pressor time to intolerable pain and electrical pain tolerance endpoints, and on the UVB-MITT for the UVB heat pain detection endpoint, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomisation) Events

Intercurrent current events (ICE) are defined as:

- Early withdrawal from study due to Covid-19
- Early withdrawal from study not due to Covid-19
- Use of prohibited medications
- Early discontinuation of study drug
- Use of COVID-19 vaccinations.

The “Hypothetical” strategy will be applied to handle the “Early withdrawal from study due to Covid-19”, “Early withdrawal from study not due to Covid-19 and “Early discontinuation of study drug” in the analysis for all endpoints. For the “Early withdrawal from study due to Covid-19” ICE, this strategy attempts to estimate treatment effects had the Covid-19 ICE not occurred. With COVID-19, the likelihood of participants withdrawing from the study is increasing (e.g. closure of the site, participants advised not

to leave homes etc.) which makes the Hypothetical strategy reasonable. The “Use of prohibited medications” and “Use of COVID-19 vaccinations” ICEs will implement a “Treatment Policy” strategy. The strategy implies direct use of data irrespective of the occurrence of the intercurrent events. The “Treatment policy” strategy is the same as de facto type estimand.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

Table 2: Primary PainCart Analyses details which of the primary endpoints are to be analysed and/or summarised.

Table 2 Primary PainCart Analyses

Estimand	Endpoint	Summary*	Primary Analysis – Bayesian AAUC Mixed ANCOVA	Listing
UVB Heat Pain	Detection (UVB Skin)	Yes	Yes (AAUC 1-8 days)	Yes (Inc. AAUC)
Cold Pressor	Tolerance	Yes	Yes (AAUC 1-15 days)	Yes (Inc. AAUC and eVAS)
Electrical pain – single stimulus (Pre-Cold Pressor)	Tolerance	Yes	Yes (AAUC 1-15 days)	Yes (Inc. AAUC and eVAS)

*The summary will include summary statistics for the summary measures, AAUC and post-test eVAS scores.

MMRM: Mixed Model Repeated Measures; ANCOVA: Analysis of Covariance; AAUC: Analysis Area Under Curve, BRM: Bayesian Repeated Measures

7.1.5.1. Statistical Methodology Specification

7.1.5.1.1. UVB heat pain detection (Celsius)

Endpoint / Variables
• Ratio to baseline (or change from baseline) in UVB heat pain detection (Celsius) AAUC(1-8 Days) • If ratio to baseline is deemed suitable due to the distribution of the parameters, the response will be log transformed. Any transformation of a response variable is also expected to be applied to the corresponding baseline variable. Final decisions on transformations will be based on the observed data and model diagnostics
Model Specification

The analysis will be performed on the AAUC (1-8 days) using a Bayesian Mixed Analysis of Covariance (ANCOVA) model.
 	
Refer to Section 12.6.3 Pharmacodynamic for the derivation of the AAUC via the trapezoidal method.
 	
Non-informative priors will be utilized for each model parameter as either a normal distribution with a mean = 0 and variance = 1e6 (very large variance), unless specified elsewhere.
The prior for the variance covariance matrix will follow an inverse Wishart distribution. An inverse Wishart prior on the covariance matrix is chosen as it ensures sampling efficiency with PROC MCMC using the conjugate sampler to draw the unstructured covariance.
 	
The random seed to use has been calculated prior to unblinding. Section 12.6 details the seed to use for the analyses in this RAP.
 	
The mixed model ANCOVA will be fitted using Bayesian techniques with PROC MCMC using the following approach:
 	
• Assume equal variances across treatment arms and use a pooled estimate of residual variability.
• Fit the following model:
  ○ M: Intercept + Treatment + Time of Assessment Stratum + Subject Level Baseline + Period Level Baseline + Study Period + Study Period*Period Level Baseline + Treatment*Study Period
  ○ Time of assessment stratum (AM, PM) may be removed from the model if model convergence issues arise.
 	
• For the model, use appropriate combinations of the model parameters (back transforming the combination if response variable is ratio to baseline) to obtain posterior distributions for the variables of interest. Binary flag variables can be used to evaluate the probability statements.

• The MCMC iterations are flagged if the posterior summary ratio > X, where X is various criteria. • The posterior probability is then calculated by summarising the number of flagged MCMC iterations / total number of MCMC iterations.
Model Checking & Diagnostics
• Refer to the relevant documentation (Bayesian Statistics Best Practice at GSK – Clinical Trials using Bayesian Inference).
Model Results Presentation
• The posterior ratio to baseline AAUC median for each treatment group will be presented along with the coefficient of variation (CV) (%) (calculated as $\sqrt{(\exp(sd^2) - 1)}$) and/or 95% credible intervals (CrI). The posterior treatment ratio to placebo, along with corresponding 95% Credible Intervals (CrI) and posterior probabilities that the true ratio is greater than 1 will be presented. • If the Ratio to Baseline is not suitable, the change from baseline AAUC in UVB heat pain detection will be compared between the treatment groups using a Bayesian mixed ANCOVA with the same model specification as above. All available post-baseline scheduled visits will be included in the analysis. Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised. An unstructured covariance matrix will be used to model the within-subject error.

7.1.5.1.2. Cold pressor time to intolerable pain & Electrical pain tolerance threshold – single stimulus

Endpoint / Variables
• Ratio to baseline in cold pressor time to intolerable pain threshold (seconds) (AAUC 1-15 days) • Ratio to baseline in electrical pain tolerance threshold (mA) – single stimulus (AAUC 1-15 days) • If ratio to baseline is deemed suitable due to the distribution of the parameters, the response will be log transformed. Any transformation of a response variable is also expected to be applied to the corresponding baseline variable. Final decisions on transformations will be based on the observed data and model diagnostics
Model Specification
• A Bayesian mixed ANCOVA model will be fitted to the ratio to baseline AAUC (1-15 days) for the electrical pain tolerance threshold endpoint and cold pressor time to intolerable pain endpoint, and used to estimate the ratio to placebo. • Refer to Section 7.1.5.1.1 Model Specification for more information
Model Checking & Diagnostics
• Refer to Section 7.1.5.1.1 Model Checking & Diagnostics for more information

Model Results Presentation
• Refer to Section 7.1.5.1.1 Model Results Presentation for more information
Interim Analysis 1
• The first interim analysis may occur once the final UVB-MITT participant in period 3 has completed their day 15 assessments of the PainCart tests. • In addition to posterior probabilities, predictive probabilities of achieving the criteria of interest at the end of the study if we were to randomise and analyse an additional 12 subjects will be estimated using a Bayesian Normal-Normal update. Vague priors for all modelling parameters will be used to compute the posterior distributions. • Further information is contained in the 209973 Interim Analysis Charter.

7.2. Exploratory PainCart Analyses

7.2.1. Endpoint / Variables

The exploratory endpoints are:

- Cold pressor time to pain detection threshold
- Electrical pain detection threshold– single stimulus
- Electrical pain tolerance threshold– repeat stimulus
- Electrical pain detection threshold– repeat stimulus
- Conditioned pain modulation (CPM) detection threshold
- Conditioned pain modulation (CPM) tolerance threshold
- Heat pain detection on normal skin
- Pressure pain tolerance threshold
- Pressure pain detection threshold

7.2.2. Summary Measure

For each of the exploratory PainCart endpoints apart from heat pain detection on normal skin, conditioned pain modulation and pressure pain thresholds, Ratio to Baseline will be the primary summary measure. As default, summaries of Change from Baseline will also be shown. For the conditioned pain modulation endpoint, the change from baseline will be the summary measure. If modelling assumptions are invalidated, then neither ratio to/change from baseline may be shown. For heat pain detection on normal skin and pressure pain thresholds only summary statistics (mean/geometric mean, SD/CV(%), Median, Min, Max) will be produced. Refer to Table 4 for further details.

7.2.3. Population of Interest

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

7.2.4. Strategy for Intercurrent (Post-Randomisation) Events

Refer to Section 7.1.4 Strategy for Intercurrent (Post-Randomisation) Events

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

Table 3 Exploratory PainCart Analyses

Estimand	Endpoint	Summary*	Analysis – Bayesian AAUC Mixed ANCOVA	Listing
Cold Pressor	Detection	Yes	Yes	Yes
Electrical pain – single stimulus	Detection	Yes	Yes	Yes
Electrical pain – repeat stimulus	Detection	Yes	Yes	Yes
	Tolerance	Yes	Yes	Yes
Conditioned pain modulation	Detection	Yes	Yes	Yes
	Tolerance	Yes	Yes	Yes
Heat Pain	Detection (Normal Skin)	Yes	No	Yes
Pressure Pain	Detection	Yes	No	Yes
	Tolerance	Yes	No	Yes

*The summary will include summary statistics for the summary measures, AAUC and post-test eVAS scores.

Note: ANCOVA analyses will be performed in the Bayesian framework only.

7.2.5.1. Statistical Methodology Specification

Endpoint / Variables
• The endpoints will be analysed as detailed in Section 7.1.5.1.
Model Specification
• Refer to Section 7.1.5.1.2 Model Specification for more information
Model Checking & Diagnostics
• Refer to Section 7.1.5.1.2 Model Checking and Diagnostics for more information
Model Results Presentation
• Refer to Section 7.1.5.1.2 Model Results Presentation for more information

7.3. Serum Target Engagement Analyses

The Target Engagement analyses described below will be carried out for Free and Total CCL17 in Serum. The target engagement analyses will be based on the Safety population, unless otherwise specified.

7.3.1. Endpoint / Variables

7.3.1.1. Target Engagement Concentration Measures

Refer to Appendix 5 Section 12.5.4 Reporting Standards for Target Engagement.

7.3.1.2. Derived Target Engagement Parameters

All calculations will be based on actual sampling times.

Target engagement parameters listed below will be determined from the observed free CCL17 levels in serum. Additional parameters may be included as required.

Parameter	Parameter description
Cmin	• Minimum observed concentration • Determined directly from the concentration-time data
tmin	• Time to reach Cmin • Determined directly from the concentration-time data
BL	• Baseline (as defined in Section 5.2)
Percentage reduction	• Percentage of free CCL17 reduced by the presence of GSK3858279 • Calculated by time point as: (BL-concentration)*100/BL
Maximum Percentage reduction	• Maximum Percentage of free CCL17 reduced by the presence of GSK3858279 • Calculated as: (BL-Cmin)*100/BL

NOTES:
Additional parameters may be included as required.

Target engagement parameters listed below will be determined from the observed total CCL17 levels in serum. Additional parameters may be included as required.

Parameter	Parameter description
Cmax	• Maximum observed concentration • Determined directly from the concentration-time data
tmax	• Time to reach Cmax • Determined directly from the concentration-time data
BL	• Baseline (as defined in Section 5.2)
Fold increase	• Ratio of total CCL17 concentration to baseline • Calculated by time point as: Concentration/BL • Determined directly from the concentration-time data
Maximum Fold increase	• Ratio of maximum concentration of total CCL17 to baseline • Calculated as: Cmax/BL • Determined directly from the concentration-time data

NOTES:
Additional parameters may be included as required.

7.3.2. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.3.1 will be summarised using descriptive statistics by treatment and study period, graphically presented (where appropriate) and listed.

7.4. Immunogenicity

7.4.1. Summary Measure

The number and percentage of confirmed positive samples in each treatment group and period will be presented at each time assessed.

7.4.2. Population of Interest

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

7.4.3. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.4.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

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. Any reported skin reactions will be recorded as Adverse Events as mentioned in the protocol.

Analyses of AEs will only include those events that are on-treatment as defined in Appendix 4: Study Phases and Treatment Emergent Adverse Events (Section 12.4).

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

The details of the planned displays are provided in Appendix 12: List of Data Displays.

8.2. Clinical Laboratory Analyses

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

- Haematology laboratory tests
- Chemistry laboratory tests
- Urinalysis
- Other screening tests

Clinical laboratory analyses will include all assessments post-baseline.

Details of the planned displays are presented in Appendix 11: List of Data Displays

The laboratory assessments for each category are displayed below (Table 2 of the protocol):

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count RBC Count Haemoglobin Haematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin

Laboratory Assessments	Parameters			
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase	[3]Complement protein C3 and C4
Routine Urinalysis[2]	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Breath alcohol test • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B core antibody [HbcAb] and hepatitis C virus antibody) • QuantiFERON test • Urine albumin-creatinine ratio (UACR) The results of each test must be entered into the medical notes.			
Other screening and follow up tests	• Troponin-T (high sensitivity) • NT-proBNP			

NOTES:
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 5 of the 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. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
3. Complement protein C3 and C4 to be performed (as baseline).

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

The details of the planned displays are presented in Appendix 12: List of Data Displays.

9. PHARMACOKINETIC ANALYSES

9.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 12.5.3 Reporting Standards for Pharmacokinetic).

9.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations will be based on actual sampling times.

Pharmacokinetic parameters listed below will be determined from the serum GSK3858279 concentration-time data, as data permits. Additional parameters may be included as required.

Parameter	Parameter Description
AUC(0-t)	• Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) • Calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-7)	• Area under the concentration-time curve from time zero (Day 1) to 7 days post-dose (Day 8) • Calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid
Cmax	• Maximum observed concentration • Determined directly from the concentration-time data.
tmax	• Time to reach Cmax • Determined directly from the concentration-time data
tlast	• Time of occurrence of last quantifiable concentration • Determined directly from the concentration-time data

NOTES:
Additional parameters may be included as required.

9.3. Population of Interest

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

9.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.2 will be summarised using descriptive statistics by study period, graphically presented (where appropriate) and listed.

10. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

The primary goal of this analysis is to characterize the pharmacokinetic / pharmacodynamic (PK/PD) relationship of GSK3858279 administered IV in healthy participants.

The PK and TE data may also be integrated with ongoing and planned studies to develop a Population PK/TE model for GSK3858279. Details of this integrated analysis will be described in a separate PDAP.

10.1. Statistical Analyses / Methods

A summary of the planned PK/PD analyses is outlined below:

- An exploratory graphical analysis will be performed to assess the relationship between observed measures of nociception and individual PK or TE data. If the exploratory graphical analysis suggests a relationship and data permits, direct or indirect response models may be developed and linked with the previous popPK/TE model to characterise the relationship between different modalities of nociception and PK or TE. Details of this analysis, if required, will be described in a separate SAP.

- To support this analysis, a PK/PD dataset will be generated. The details for the dataset specifications are provided in Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses.
- S&P will deliver 6 PK/PD figures, as detailed in Section 12.11.11: Pharmacokinetic / Pharmacodynamic Figures as part of the AAC package.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

The full list of protocol deviations collected on the eCRF is in the Protocol Deviation Management Plan (PDMP). Please refer to this document for current guidance.

12.1.1. Exclusions from Per Protocol Population

There is no Per Protocol population in this study.

12.2. Appendix 2: Schedule of Activities

12.2.1. Protocol Defined Schedule of Events

12.2.1.1. Screening and Follow-Up

Procedure	Screening (up to 28 days before Day 1)		Follow-up check 36±4 days post last dose	Final follow-up 56±4 days post-last dose	Notes
	Part 1	Part 2			
Out-patient visit	X	X		X	Optional in-clinic stay for participants at the discretion of investigator.
Phone call			X		AE collection - may be out-patient visit at discretion of Investigator for additional checks
Informed consent	X				
Severe acute respiratory syndrome SARS-CoV-2 PCR test	X			X	
Temperature check	X	X		X	
Inclusion and exclusion criteria	X				Recheck clinical status before randomization and/or 1st dose of study intervention.
Demography	X				
Full physical examination including height and weight.	X				Weight at screening is used for determination of dose
Fitzpatrick Skin Type	X				Assessments for UVB-MITT population only Assessment to determine applying MED application
Echocardiogram	X				
Medical history (includes substance usage)	X				Substances: Drugs, Alcohol, tobacco and caffeine
Current medical conditions	X				
HIV, Hepatitis B and C	X				
Haematology, clinical chemistry (include liver chemistries) and urinalysis	X			X	Including Troponin-T (hs)
NT-proBNP	X			X	
UrDrug, BrAlc	X			X	
12-lead ECG	T			X	T = Triplicate X = Single
Vital signs	X			X	

Procedure	Screening (up to 28 days before Day 1)		Follow-up check 36±4 days post last dose	Final follow-up 56±4 days post-last dose	Notes
	Part 1	Part 2			
PainCart training	[X]	[X]			May be performed during either part 1 or part 2 (not both)
Minimal Erythema Dose (MED) application	X				Assessments for UVB-MITT population only. Exposure to pre-determined 6 ascending doses of UVB radiation. MED application will be the final assessment on Part 1 of Screening and will only be completed after confirmation of eligibility from available results, e.g. lab data, echocardiogram results may not be available.
MED assessment		X			Assessments for UVB-MITT population only. 24 hours (±2 hours) after UV exposure
AE/SAE review	X	X	X	X	

- An echocardiogram performed within 3 months prior to first dosing is acceptable for enrolment into the study

- MED determination performed within 6 weeks prior to first dosing is acceptable for enrolment into the study

12.2.1.2. Study periods 1, 2, 3 and Early Withdrawal

When the following assessments are scheduled to be performed at the same time-point, the order will be as follows:

ECG > vital signs > PK and PD sampling > PainCart

Procedure	Study periods 1, 2, 3 (Days)								Early Withdrawal	Notes
	-2	–1	1	2	7	8	15	25		Allowed visit windows are detailed in the Study Reference Manual (SRM)
Out-patient visit					X*	X	X		X	Optional in-clinic stay for participants at the discretion of investigator. *Day 7 is optional for those participants not receiving UVB.
Admission in clinical unit	X**									Optional in-clinic stay for participants at the discretion of investigator. ** If subjects are not UVB-MITT participants, optional admission will be on Day-1 with Day-2 completed on Day-1.
Discharge from clinical unit				X						Except if, the participant needs to remain in the Unit longer for medical reasons.
Phone Call								X		AE collection - may be out-patient visit at discretion of Investigator for additional checks
Brief Physical Examination			X	X		X	X		X	
Haematology, clinical chemistry (include liver chemistries) and urinalysis		X	X	X		X	X		X	Troponin T to be assessed on Day -1, 8, 15 (and EW if needed). **C3/C4 on Day -1 only**
UrDrug, BrAlc		X			X*		X			*for volunteers who do not receive UVB application, the Day 7 Assessments may be performed on Day 8 prior to PainCart
SARS-CoV-2 PCR test	X**								X	

Procedure	Study periods 1, 2, 3 (Days)								Early Withdrawal	Notes
	-2	–1	1	2	7	8	15	25		Allowed visit windows are detailed in the Study Reference Manual (SRM)
12-lead ECG		T	X			X	X		X	Day 1: pre-dose (T), 0.5hr, 1hr post start of infusion. On other days a single measure taken prior to 1st PainCart assessment. T = Triplicate X = Single
Vital signs (including temperature)	X**	X	X	X	X-t	X	X		X	Day 1: pre-dose, 0.5hr, 1hr, 2hr post start of infusion. X-t: temperature assessment on Day 7 for UVB-MITT population only On other days a single measure taken prior to 1st PainCart assessment.
Randomization			X							Study period 1 only
Drug/placebo IV infusion			X							Continuous infusion over 1 hour
PainCart			X	X		X	X			Day 1 pre-dose performed twice (baseline) Day 1 performed at 1 and 3 hours post start of IV infusion. Other days performed twice ~2 hours apart at approximately the same time of day in each study period. Day 15 - heat pain detection assessment associated with UVB test performed on normal skin only. Participants not receiving UVB application will not undergo UVB heat pain detection test on irradiated skin. All other PainCart assessments including heat pain detection performed on normal skin will still be assessed. See Appendix 7 of protocol for details of testing
UVB application		X			X					UVB application (2 x MED) will be performed 24hr (±2hr) prior to start of infusion on Day 1. UVB application (2 x MED) on Day 7 will be performed 24hr (±2hr) prior to PainCart assessment on Day 8. UVB application only applies to those in the UVB-MITT population.

Procedure	Study periods 1, 2, 3 (Days)								Early Withdrawal	Notes
	-2	–1	1	2	7	8	15	25		Allowed visit windows are detailed in the Study Reference Manual (SRM)
AE review	X**	X	←==========→						X	
SAE review	X**	X	←==========→						X	
Concomitant medication review	X**	X	←==========→						X	
Blood samples for PK and PD			X	X		X	X		X	Day 1: pre-dose, 1hr, 3hr post-start of IV infusion. On other days samples taken prior to 1st PainCart assessment.
Blood sample for immunogenicity			X				X		X	Day 1: pre-dose. Day 15: prior to 1st PainCart assessment.

** If subjects are not UVB-MITT participants, optional admission will be on Day-1 with Day-2 assessments completed on Day-1.

- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic assessments may be altered during the course of the study based on newly available data to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.
- The planned study assessments on Day 7 (UVB-MITT population only), 8, 15 and 25 may be performed within a ± 24hr window.
- A questionnaire related to COVID-19 is part of each visit and included in the AE review.

12.3. Appendix 3: Assessment Windows

12.3.1. General

Clinic visits are scheduled to take place as specified in Appendix 2: Schedule of Activities. Measurements will be reported based on the visits they are assigned to in the study database without adjustment. Measurements outside visit windows will not be excluded from analyses and may constitute an important protocol deviation upon further review.

If a circumstance should arise where multiple measurements have been collected and recorded against the same scheduled visit and timepoint, for which only one measurement should have been collected, then the first valid value will be used for that timepoint.

12.3.2. PainCart Assessment Window

During each study period, all participants will be assessed on the various PainCart tests for measuring different modalities of nociception. The PainCart assessments are performed multiple times during each study period and taken multiple times during each clinical visit.

The following information in Table 4: PainCart Assessment Windows displays which PainCart assessments relate to which day, and how they are summarised at each visit. As a note, the AAUC analysis for the PainCart endpoints will utilise the individual assessments instead of the summarised daily assessments detailed below.

Table 4 PainCart Assessment Windows

PainCart Assessment Windows		
Analysis Day	**Analysis Period**	
	Timepoint	**Summarised**
Baseline	Day 1 (Randomisation, Pre-Dose)	Two assessments are performed pre-dosing. Baseline is defined as the mean value prior to dosing in each study period. If only one pre-dose assessment record is present on Day 1, then this value will be set as the baseline value
Day 1	Day 1 (Randomisation, Post-Dose)	Two assessments are performed at 1 and 3 hours post start of IV infusion. The analysis day value is defined as the mean value of the two assessments. If only one post-dose assessment is performed on Day 1, then that value will be set as the analysis day value..

PainCart Assessment Windows		
Analysis Day	**Analysis Period**	
	Timepoint	**Summarised**
Day 2, 8 and 15	Day 2, 8 and 15 from day of randomisation	Two assessments are performed at approximately 2 hours apart at roughly the same time of day in each study period. The analysis day value is defined as the mean value of the two assessments. If only one assessment is performed on the day, then that value will be set as the analysis day value. The planned PainCart assessments on day 2, 7 (MED application), 8 & 15 may be performed within a ± 1-24hr window.

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

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

12.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to the start date of the study treatment.

Study Phase	Definition
Pre-Treatment	Date/Time < Study Treatment Dose Date/Time (Period 1)
On-Treatment	Study Treatment Dose Date/Time (Period 1) ≤ Date/Time

12.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 7 days prior to screening visit
Concomitant	Any medication that is not a prior For period specific concomitant medications, Refer to Section 12.6.1 for period definitions

NOTES:

- Please 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.

12.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If the AE is on-treatment, then the AE is treatment emergent. • Refer to Section 12.6.1 for period definitions.

NOTES:

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

12.5. Appendix 5: Data Display Standards & Handling Conventions

12.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used. R may be used for Stage 2 QC purposes.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Compound	: arenv/arprod/gsk3858279/mid209973/
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards.	
Generation of RTF Files	
• RTF files will be generated for Interim SAC (if performing) and final SAC/AAC tables.	

12.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) 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.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • 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:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and/or figures. • All unscheduled visits will be included in listings and determination of PCIs.
Descriptive Summary Statistics
Continuous Data: Refer to IDSL Statistical Principle 6.06.1

Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

12.5.3. 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/Pop PK File	Not applicable.
NONMEM/PK/PD File	PK/PD file (CSV format) for the PK/PD analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in Section 12.9.1 Pharmacokinetic/Pharmacodynamic Dataset Specification.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by CPMS	The following PK parameters will be derived by CPMS: • AUC(0-t), AUC(0-7), Cmax, tmax and tlast.
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).

12.5.4. Reporting Standards for Target Engagement

Target Engagement Concentration Data	
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. NQ values for Free CCL17 will be set to ½ LLQ and subsequent valid concentrations will be retained. Median will be imputed for missing baseline values. LLQ value will be imputed for baseline values equal to zero.

Target Engagement Parameter Derivation	
TE Parameter to be Derived by CPMS	• None
TE Parameter to be Derived by Programmer	The following TE parameters will be derived by programmer: • Cmin, tmin, BL, percentage reduction, maximum percentage reduction for free CCL17 • Cmax, tmax, BL, fold increase, maximum fold increase for total CCL17
Target Engagement 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).

12.6. Appendix 6: Derived and Transformed Data

12.6.1. General

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 Period
• The start date of Period [1/2/3] is the dosing Day 1 date for that period. • The end date of Period [1/2] is the Day -1 date for the subsequent period. • The end date for Period 3 and Period[1/2] if no subsequent period follows, will be the final follow up visit date, or if applicable, study withdrawal date, whichever date is earlier.
Study Day / Period Day

• Study day is derived with respect to the very first dose date (Period 1):
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Dose Date → Study Day = Ref Date – Dose Date
  • Ref Data ≥ Dose Date → Study Day = Ref Date – (Dose Date) + 1
• Period day is derived with respect to the dose date during that period:
  • Ref Date = Missing → Period Day = Missing
  • Ref Date < Period Start Date → Period Day = Ref Date – Period Dose Start Date
  • Ref Data ≥ Period Start Date → Period Day = Ref Date – (Period Dose Start Date) + 1

12.6.2. Study Population

Extent of Exposure
• This is a single dose per period study, the volume of infusion will be recorded, as will the start and stop date/time of infusion. • Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Date of Subsequent/Last Dose – (Date of First Dose) +1+ 18*5** • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure.
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:
  ○ Any subject with a missing day will have this imputed as day '15'.
  ○ Any subject with a missing date and month will have this imputed as '30th June'.
• Calculated based on the screening date
• Completely missing dates of birth will remain as missing, with no imputation applied. Consequently, the age of the participant will not be calculated and will remain missing.

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

Race Category

- The five high level Food and Drug Administration (FDA) race categories and designated Asian subcategories are:
  1. African American/African Heritage
  2. American Indian or Alaska Native
  3. Asian
     a) Central/South Asian Heritage
     b) Japanese/East Asian Heritage/South East Asian Heritage
     c) Mixed Asian Heritage (only required if data exists)
  4. Native Hawaiian or other Pacific Islander
  5. White
- These categories and subcategories will be summarized along with all combinations of high level categories which exist in the data. All five of the high level race categories and the two Asian subcategories must appear on the display even if there are no participants in a particular category, but combinations that do not exist in the data do not need to be represented. Combinations will be represented as the concatenation of the high level category terms, e.g., "White & Asian." The designated Asian subcategories will not be summarized as combinations with other categories.
- In addition, the standard race categories collected per IDSL will be summarized along with categories for mixed race. The categories are:
  1. African American/African Heritage
  2. American Indian or Alaska Native
  3. Asian - Central/South Asian Heritage
  4. Asian – East Asian Heritage
  5. Asian – Japanese Heritage
  6. Asian – South East Asian Heritage
  7. Asian – Mixed Race
  8. Native Hawaiian or other Pacific Islander
  9. White – Arabic/North African Heritage
  10. White – White/Caucasian/European Heritage
  11. White – Mixed Race
  12. Mixed Race
- "Asian – Mixed Race" is only used if more than one Asian category is selected, but no non-Asian races. Similarly, "White – Mixed Race" is only used if both of the White categories are selected, and no non-White races. If multiple races of different types are selected, then the overall "Mixed Race" category is used.
- A participant will only be represented in a single category. A participant who selects a combination of races will be counted as "Asian – Mixed Race," "White – Mixed Race," or "Mixed Race," but not in each of the constituent terms. Therefore, the counts will add up to the total number of participants with a response, and the percentages will add to 100%.

12.6.3. Pharmacodynamic

PainCart Assessments

General

- For PainCart assessments, baseline is defined as the mean value of the two assessments taken prior to dosing in each session (Day 1).

- The following PainCart endpoints will be assessed utilising all available individual assessments recorded during the study periods (AAUC: Analysis area under the curve, PDT = pain detection threshold, PTT = pain tolerance threshold):

  - UVB Heat: PDT AAUC
  - Cold Pressor: PDT, PTT AAUC
  - Electrical stair (pre-cold pressor): PDT, PTT AAUC
  - Electrical burst: PDT, PTT, AAUC
  - Conditioned pain modulation (CPM): PDT, PTT AAUC

- The following PainCart endpoints will be assessed at Baseline, Day 1, Day 2, Day 8 and Day 15 (AAC: Area above the curve from eVAS, AUC = area under the curve from eVAS, PDT = pain detection threshold, PTT = pain tolerance threshold, (e)VAS = ((electronic) visual analogue scale):

  - UVB Heat Pain Detection – Normal Skin
  - Cold Pressor: PDT, PTT, post-test VAS
  - Electrical stair (pre-cold pressor): PDT, PTT, post-test VAS
  - Electrical stair (post-cold pressor): PDT, PTT, post-test VAS (for use in calculation for CPM)
  - Electrical burst: PDT, PTT, AUC, post-test VAS
  - Pressure Pain: PDT, PTT, AUC, post-test VAS

- The UVB heat pain endpoint on irradiated skin will be assessed at all timepoints mentioned above except for Day 15.

Conditioned Pain Modulation (CPM)

- CPM is the activation of the pain-modulatory mechanism, as part of the descending endogenous analgesia system. The degree of CPM is assessed by comparing the electrical pain thresholds for the single stimulus paradigm before and after the cold pressor task. i.e.
- CPM = Post-Cold Pressor electrical stair threshold – Pre-Cold electrical stair threshold

Derivation of AAUC for PainCart Assessments

- The following analysis AAUC's for the PainCart assessments will be calculated as follows:

Assessment	AAUC's Calculated	Derivation Details
Heat Pain Detection on UVB skin	AAUC (1-8 Days)	➢ Baseline = Day 1 (Pre-Dose)

PainCart Assessments

Cold Pressor Detection and Tolerance	AAUC (1-15 Days)	➢ Baseline = Day 1 (Pre-Dose)
All other PainCart assessments	AAUC (1-15 Days)	➢ Baseline = Day 1 (Pre-Dose)

- The weighted mean AAUC parameters will be derived by calculating the area under the curve (AUC) using the trapezoidal rule, and then dividing by the actual relevant time interval (i.e. t_f - t_l):

$$\boldsymbol{Weighted\ Mean\ AAUC(t_f - t_l)} = \frac{\frac{1}{2}\sum_{i=1}^{l-1}(t_{i+1} - t_i)(y_{i+1} + y_i)}{tl - tf}$$

Where (example provided for UVB heat pain detection AUC(1-8 Days):

- y_i = Value of endpoint at i^{th} time point
- t_i = The i^{th} actual time point (days) for UVB heat pain detection:
  - t values will be calculated as the actual time recorded in the SAS dataset in the SAS datetime format. For baseline, the timepoint will be calculated as the midpoint of the two pre-dose assessments.
- *tf* = Actual time point of first non-missing obs
- *tl* = Actual time point of last non-missing obs
- *l* = Number of time points used in the AAUC calculation

Seeds for PainCart Analyses – PROC MCMC

- Seeds for all planned analyses were determined in advance using the following SAS code (analysis_seed.SAS) and documented within this RAP prior to unblinding:

```
data temp;
  do i = 1 to 15;
   number=round(100000*ranuni(0),1);
  output;
 end;
run;
proc print;
run;
```

Endpoint	Test	Analysis	Macro Seed
Heat Pain	Detection	Mixed ANCOVA	57743

PainCart Assessments			
Cold Pressor	Tolerance	Mixed ANCOVA	95933
	Detection	Mixed ANCOVA	55572
Electrical Pain – single stimulus (Pre-cold pressor)	Tolerance	Mixed ANCOVA	01749
	Detection	Mixed ANCOVA	19282
Conditioned Pain Modulation (CPM)	Detection	Mixed ANCOVA	46555
	Tolerance	Mixed ANCOVA	33042
Electrical Pain – repeated stimulus	Tolerance	Mixed ANCOVA	80088
	Detection	Mixed ANCOVA	73186

12.6.4. Safety

Adverse Events

- Adverse events will be coded using the current MedDRA coding dictionary at the time of reporting providing a Preferred Term (PT) and a System Organ Class (SOC) for analysis and reporting.

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 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 participant as 'ABNORMAL' and 'CLINICALLY SIGNIFCANT', if any of the findings are 'ABNORMAL' and 'CLINICALLY SIGNIFCANT' during the time period/Post-Baseline.
- Else count the participant as 'ABNORMAL' and 'NOT CLINICALLY SIGNIFCANT', if any of the findings are 'ABNORMAL' and 'NOT CLINICALLY SIGNIFCANT' and none of the findings are 'ABNORMAL' and 'CLINICALLY SIGNIFCANT' during the time period/Post-Baseline.
- Else count the participant 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 participant 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.

12.7. Appendix 7: Reporting Standards for Missing Data

12.7.1. Premature Withdrawals

Element	Reporting Detail
General	• A participant is considered to have completed the study if they have completed all phases and periods of the study including the last visit. • Withdrawn participants may be replaced (as detailed in Section 2.3) in the study in order to ensure sufficient participants complete the study. Replacement participants will be assigned to the same treatment sequence as the participant they are replacing, at the discretion of the Sponsor and in consultation with the Principal Investigator. • 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. • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

12.7.2. 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: ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
MMRM Analysis	• All the available assessments taken at scheduled visits will be included in the repeated measures models in which missing data are not explicitly imputed but the correlation between visits for all participants is used to adjust the estimate of treatment effect considering any missing data.

12.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

Element	Reporting Detail

Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	• The recorded partial date will be displayed in listings.

12.8. Appendix 8: Values of Potential Clinical Importance

12.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Haematocrit	Ratio of 1	Male	0.39	0.54
		Δ from BL	↓0.075	>10%
Haemoglobin	g/L	Male	124	180
		Δ from BL	↓25	>10%
Lymphocytes	$x10^9$/ L		0.75	4.5
Neutrophil Count	$x10^9$/ L		1.5	8.0
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		2.5	15

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	g/L		30	
Calcium	mmol/L		2.00	2.75
Creatinine	µmol/L			1.3 X ULN
		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

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

12.8.2. 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

12.8.3. 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

12.9. Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses

An exploratory graphical analysis of the total drug on the primary endpoints of efficacy will be performed by generating the PK/PD plots as presented in Appendix 12.

If the exploratory graphical analysis suggests a relationship and data permits, a PopPK/TE model may be developed from the final PK and TE data from the first-time in human study 207804 and may be fitted to the current data using the nonlinear mixed effects modelling software NONMEM. In this case, data relative to the primary measures of efficacy will be used to model the PD effect. Direct and indirect response models may be developed from all available PD data and linked with the PK/TE to characterise the relationship between different modalities of nociception and PK or TE.

The appropriateness of the PopPK/PD model will be assessed by the OFV, successful convergence, covariance estimation, shrinkage, parameter uncertainty, standard GoF and simulation-based diagnostic plots e.g. VPC.

The GoF plots may include, but are not limited to:

- Population and individual predictions versus observations
- Conditional weighted residuals versus population predictions and time

If a VPC is a performed, this will be based on 1000 simulations with the model and the design structure of the observed data (i.e. dose level and time, time of PK/PD sampling and individual values of model covariates, if any). The median and the 10^{th} and 90^{th} will be compared to the observed data.

If any PK/PD modelling is conducted, it will be reported in a separate CPMS modelling report, after reporting of this study.

12.9.1. Pharmacokinetic / Pharmacodynamic Dataset Specification

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

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

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

12.10. Appendix 10: Abbreviations & Trade Marks

12.10.1. Abbreviations

Abbreviation	Description
AAC	All Analysis Complete
AAUC	Analysis Area Under the Curve
ADAs	Anti-Drug Antibodies
AE	Adverse Event
AIC	Akaike's Information Criteria
ANCOVA	Analysis of Covariance
A&R	Analysis and Reporting
AUC	Area Under the Curve
CDISC	Clinical Data Interchange Standards Consortium
CHDR	Centre for Human Drug Research
CI	Confidence Interval
CrI	Credible Interval
CPM	Conditioned Pain Modulation
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
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
eVAS	Electronic Visual Analogue Scale
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GoF	Goodness-of-Fit
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
LS	Least Squares
mA	Milliamp
MCMC	Markov Chain Monte Carlo
MITT	Modified Intent to Treat

Abbreviation	Description
MMRM	Mixed Model Repeated Measures
OFV	Objective Function Value
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Posterior Probability
PopPK	Population PK
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
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SD	Standard Deviation
SDSP	Study Data Standardization Plan
SE	Standard Error
SEC	Seconds
SOP	Standard Operation Procedure
SP	Study Period
TA	Therapeutic Area
TE	Target Engagement
TFL	Tables, Figures & Listings
UVB	Ultraviolet B

12.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM version 7.3
PainCart
R / RStudio
SAS
WinNonLin

12.11. Appendix 11: List of Data Displays

12.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.01 to 1.17	N/A
Pharmacodynamic	2.01 to 2.25	2.01 to 2.09
Safety	3.01 to 3.24	N/A
Pharmacokinetic	4.01 to 4.02	4.01 to 4.03
Pharmacokinetic / Pharmacodynamic	N/A	5.01 to 5.06
Section	**Listings**	
ICH Listings	1 to 31	
Other Listings	32 to 40	

12.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 12: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population		POP_Tn	
Pharmacodynamic	PD_Fn	PD_Tn	PD_Ln
Safety			
Pharmacokinetic			
Pharmacokinetic / Pharmacodynamic	PKPD_Fn		

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

12.11.3. Deliverables

Delivery [Priority] [1]	Description
IA 1 SAC [X]	Interim Analysis 1 Statistical Analysis Complete
IA 2 SAC [X]	Interim Analysis 2 Statistical Analysis Complete
SAC [X]	Final Statistical Analysis Complete
AAC [X][2]	Final All Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort
2. The displays listed as Delivery AAC may be delivered for the SAC milestone depending on availability of the displays.

12.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.01.	Randomised	ES1xo	Summary of Subject Status and Subject Disposition for the Study Conclusion Record by Relationship to COVID-19 Pandemic	ICH E3, FDAAA, EudraCT Present by: Overall, Related to COVID-19, Not Related to COVID-19	AAC [1]
1.02.	Screened	ES6	Summary of Screen Status and Reasons for Screen Failure	Journal Requirements	AAC [1]
1.03.	ITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment by Relationship to COVID-19 Pandemic	ICH E3 Present by: Overall, Related to COVID-19, Not Related to COVID-19	AAC [1]
1.04.	ITT	ES4	Summary of Subject Disposition at Each Study Period	ICH E3	AAC [1]
1.05.	ITT	ES11	Summary of Outcome of Adverse Events Which Led to Study Withdrawal at Each Study Period	EMA mandated clinical trial results registry	AAC [1]
1.06.	ITT	ES5	Summary of Reason for Withdrawal at Each Period	FDAAA, EMA Only if the withdrawal at each period is collected.	AAC [1]
1.07.	ITT	POP_T1	Summary of Attendance at Each Day		AAC [1]
1.08.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID Relative to COVID-19 Pandemic Measures	EudraCT/Clinical Operations Present Total column only. Present Overall, and by Before and After implementation of Pandemic Measures	AAC [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Protocol Deviation					
1.09.	ITT	DV1	Summary of Important Protocol Deviations by relationship to COVID-19 Pandemic	ICH E3 Present only Total column Present by: Overall, Related to COVID-19, Not Related to COVID-19	AAC [1]
Population Analysed					
1.10.	Screened	SP1	Summary of Study Populations	IDSL	AAC [1]
Demographic and Baseline Characteristics					
1.11.	Randomised	DM1xo	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT Programming Note: Include BMI summary Present by COVID-19 Pandemic Measures Subgroup: Overall, Before, After	IA 1 [1], IA 2 [2], AAC [3]
1.12.	Enrolled	DM11xo	Summary of Age Ranges	EudraCT	AAC [1]
1.13.	Randomised	DM6xo	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	AAC [1]
Medical Conditions					
1.14.	Safety	MH1	Summary of Past Medical Conditions (Cardiovascular Risk Factors)	ICH E3 Present total column only, as per IDSL crossover recommendation.	AAC [1]
1.15.	Safety	MH1	Summary of Current Medical Conditions (Cardiovascular Risk Factors)	ICH E3 Present total column only, as per IDSL crossover recommendation.	AAC [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prior and Concomitant Medications					
1.16.	Safety	CM8	Summary of Prior Concomitant Medications	ICH E3	AAC [1]
1.17.	Safety	CM8	Summary of Concomitant Medications by Period	ICH E3 Present by period	AAC [1]

12.11.5. Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PainCart					
UVB Heat Detection Assessment					
2.01.	UVB-ITT	PD_T1	Summary of UVB Heat Pain Detection (Celsius) on UVB Skin	NVSCATCD=0015 and NVTESTCD=AF001 Programming Note: Repeat for Treatment: GSK3858279; Period: 2 and 3. Geometric Mean and CV (%) Presented for Ratio to Baseline. Day 15 not recorded for UVB heat pain UVB skin assessments	IA 1 [1], IA 2 [2], SAC [3]
2.02.	UVB-MITT	PD_T3	Bayesian Statistical Analysis of Ratio to Baseline Analysis Area Under the Curve (AAUC 1-8 Days) in UVB Heat Pain Detection (Celsius*Day)	Programming note: Include footnotes for the final model fitted, including priors used and interpretations of the direction of effect.	IA 1 [1], IA 2 [2], SAC [3]

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.03.	ITT	PD_T1	Summary of UVB Heat Pain Detection (Celsius) on Normal Skin	NVSCATCD=0014 and NVTESTCD=AF001 Programming Note: Repeat for Treatment: GSK3858279; Period: 2 and 3. Geometric Mean and CV (%) Presented for Ratio to Baseline.	AAC [1]
Cold Pressor Assessment					
2.04.	ITT	PD_T1	Summary of Cold Pressor Time to Intolerable Pain Threshold (Seconds)	NVSCATCD=0011 and NVTESTCD=AF004 Programming Note: Repeat for Treatment: GSK3858279; Period: 2 and 3. Geometric Mean and CV (%) Presented for Ratio to Baseline.	IA 1 [1], IA 2 [2], SAC [3]
2.05.	MITT	PD_T3	Bayesian Statistical Analysis of Ratio to Baseline Analysis Area Under the Curve (AAUC 1-15 Days) in Cold Pressor Time to Intolerable Pain Threshold (Seconds*Day)	Programming note: Include footnotes for the final model fitted, including priors used and interpretations of the direction of effect.	IA 1 [1], IA 2 [2], SAC [3]
2.06.	ITT	PD_T1	Summary of Cold Pressor Time to Pain Detection Threshold (Seconds)	NVSCATCD=0011 and NVTESTCD=AF003 Programming Note: Repeat for Treatment: GSK3858279; Period: 2 and 3. Geometric Mean and CV (%) Presented for Ratio to Baseline.	AAC [1]
2.07.	MITT	PD_T3	Bayesian Statistical Analysis of Ratio to Baseline in Cold Pressor Time to Pain Detection Threshold (Seconds) – Area Under Curve	Programming note: Include footnotes for the final model fitted, including priors used and interpretations of the direction of effect.	AAC [1]

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Electrical Stimulation Assessment					
2.08.	ITT	PD_T1	Summary of Electrical Pain Tolerance Threshold (mA) – Single Stimulus	NVSCATCD=0013 and NVTESTCD=AF004 Programming Note: Repeat for Treatment: GSK3858279; Period: 2 and 3. Geometric Mean and CV (%) Presented for Ratio to Baseline.	IA 1 [1], IA 2 [2], SAC [3]
2.09.	MITT	PD_T3	Bayesian Statistical Analysis of Ratio to Baseline Analysis Area Under the Curve (AAUC 1-15 Days) in Electrical Pain Tolerance Threshold – Single Stimulus (mA*Day)	Programming note: Include footnotes for the final model fitted, including priors used and interpretations of the direction of effect.	IA 1 [1], IA 2 [2], SAC [3]
2.10.	ITT	PD_T1	Summary of Electrical Pain Detection Threshold (mA) – Single Stimulus	NVSCATCD=0013 and NVTESTCD=AF003 Programming Note: Repeat for Treatment: GSK3858279; Period: 2 and 3. Geometric Mean and CV (%) Presented for Ratio to Baseline.	AAC [1]
2.11.	MITT	PD_T3	Bayesian Statistical Analysis of Ratio to Baseline Analysis Area Under the Curve (AAUC 1-15 Days) in Electrical Pain Detection Threshold – Single Stimulus (mA*Day)	Programming note: Include footnotes for the final model fitted, including priors used and interpretations of the direction of effect.	AAC [1]
2.12.	ITT	PD_T1	Summary of Electrical Pain Tolerance Threshold (mA) – Repeat Stimulus	NVSCATCD=0012 and NVTESTCD=AF004 Programming Note: Repeat for Treatment: GSK3858279; Period: 2 and 3. Geometric Mean and CV (%) Presented for Ratio to Baseline.	AAC [1]

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.13.	MITT	PD_T3	Bayesian Statistical Analysis of Ratio to Baseline Analysis Area Under the Curve (AAUC 1-15 Days) in Electrical Pain Tolerance Threshold – Repeat Stimulus (mA*Day)	Programming note: Include footnotes for the final model fitted, including priors used and interpretations of the direction of effect.	AAC [1]
2.14.	ITT	PD_T1	Summary of Electrical Pain Detection Threshold (mA) – Repeat Stimulus	NVSCATCD=0012 and NVTESTCD=AF003 Programming Note: Repeat for Treatment: GSK3858279; Period: 2 and 3. Geometric Mean and CV (%) Presented for Ratio to Baseline.	AAC [1]
2.15.	MITT	PD_T3	Bayesian Statistical Analysis of Ratio to Baseline Analysis Area Under the Curve (AAUC 1-15 Days) in Electrical Pain Detection Threshold – Repeat Stimulus (mA*Day)	Programming note: Include footnotes for the final model fitted, including priors used and interpretations of the direction of effect.	AAC [1]
Conditioned Pain Modulation (CPM)					
2.16.	ITT	PD_T1	Summary of Conditioned Pain Modulation Detection Threshold (mA)	Programming Note: Repeat for Treatment: GSK3858279; Period: 2 and 3. Geometric Mean and CV (%) Presented for Ratio to Baseline.	AAC [1]
2.17.	MITT	PD_T3	Bayesian Statistical Analysis of Ratio to Baseline Analysis Area Under the Curve (AAUC 1-15 Days) in Conditioned Pain Modulation Detection Threshold (mA*Day)	Programming note: Include footnotes for the final model fitted, including priors used and interpretations of the direction of effect.	AAC [1]
2.18.	ITT	PD_T1	Summary of Conditioned Pain Modulation Tolerance Threshold (mA)	Programming Note: Repeat for Treatment: GSK3858279; Period: 2 and 3. Geometric Mean and CV (%) Presented for Ratio to Baseline.	AAC [1]

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.19.	MITT	PD_T3	Bayesian Statistical Analysis of Ratio to Baseline Analysis Area Under the Curve (AAUC 1-15 Days) in Conditioned Pain Modulation Tolerance Threshold (mA*Day)	Programming note: Include footnotes for the final model fitted, including priors used and interpretations of the direction of effect.	AAC [1]
Pressure Pain Assessment					
2.20.	ITT	PD_T1	Summary of Pressure Pain Detection Threshold (kPa)	NVSCATCD=0016 and NVTESTCD=AF003 Programming Note: Repeat for Treatment: GSK3858279; Period: 2 and 3. Geometric Mean and CV (%) Presented for Ratio to Baseline.	AAC [1]
2.21.	ITT	PD_T1	Summary of Pressure Pain Tolerance Threshold (kPa)	NVSCATCD=0016 and NVTESTCD=AF004 Programming Note: Repeat for Treatment: GSK3858279; Period: 2 and 3. Geometric Mean and CV (%) Presented for Ratio to Baseline.	AAC [1]
Serum Concentration					
2.22.	Safety	PD_T5	Summary of Free & Total CCL17 in Serum Concentration-Time Data (pg/mL)	By treatment & study period.	IA 1 [1], AAC [2]
Target Engagement					
2.23.	Safety	PD_T7	Summary of Derived Free and Total CCL17 in Serum Target Engagement Parameters (non-transformed and log-transformed)	By treatment & study period.	IA 1 [1], AAC [2]
2.24.	Safety	PD_T7	Summary of Derived Free and Total CCL17 in Serum Target Engagement Parameters - Percent Reduction and Fold Increase (non-transformed and log-transformed)	By treatment & study period. Include a column Planned Time Point.	IA 1 [1], AAC [2]

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Immunogenicity					
2.25.	Safety	IMM1	Summary of Immunogenicity	Present by Period. Drop Planned Time Column. Include a Total Column. Footnote: "Note: Percentage is calculated as (x/n)*100 where x = the number of subjects with a positive sample and n = the number of subjects for whom a sample was collected."	AAC [1]

12.11.6. Pharmacodynamic Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PainCart					
2.01.	UVB-MITT	PD_F1	Ratio to Baseline in UVB Heat Pain Detection	Programming note: Include footnote on how the ratio to baseline was derived. State original unit of pain assessment.	SAC [1]
2.02.	MITT	PD_F1	Ratio to Baseline in Cold Pressor Time to Intolerable Pain Threshold	Programming note: Include footnote on how the ratio to baseline was derived. State original unit of pain assessment.	SAC [1]
2.03.	MITT	PD_F1	Ratio to Baseline in Electrical Pain Tolerance Threshold – Single Stimulus	Programming note: Include footnote on how the ratio to baseline was derived. State original unit of pain assessment.	SAC [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.04.	UVB-ITT	PD_F1	Individual Ratio to Baseline in UVB Heat Pain Detection	Programming note: Include footnote on how the ratio to baseline was derived. State original unit of pain assessment.	SAC [1]
2.05.	ITT	PD_F1	Individual Ratio to Baseline in Cold Pressor Time to Intolerable Pain Threshold	Programming note: Include footnote on how the ratio to baseline was derived. State original unit of pain assessment.	SAC [1]
2.06.	ITT	PD_F1	Individual Ratio to Baseline in Electrical Pain Tolerance Threshold – Single Stimulus	Programming note: Include footnote on how the ratio to baseline was derived. State original unit of pain assessment.	SAC [1]
Target Engagement Concentrations					
2.07.	Safety	PK16A	Individual Free & Total Serum CCL17 Concentration-Time Plots (Linear and Semi-log)	IDSL. By participant, endpoint and treatment sequence Period is presented on the same plot, with linear and semi-logarithmic scale side by side	AAC [1]
2.08.	Safety	PK17	Mean Free & Total Serum CCL17 Concentration-Time Plots (Linear and Semi-log) by Treatment	IDSL. By endpoint and treatment sequence. Period is presented on the same plot, with linear and semi-logarithmic scale side by side.	AAC [1]
2.09.	Safety	PK18	Median Free & Total Serum CCL17 Concentration-Time Plots (Linear and Semi-log) by Treatment	IDSL. By endpoint and treatment sequence. Period is presented on the same plot, with linear and semi-logarithmic scale side by side.	AAC [1]

12.11.7. Safety Tables

Safety: Tables – All Safety Tables will be presented by Period unless stated otherwise.					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.01.	Safety	AE1xo	Summary of All Adverse Events by System Organ Class and Preferred Term by Period	ICH E3 Present by Period Programming note: For interim analysis present AEs SOCs and PTs which have more than 2 subjects overall per period. i.e. at least two unique subjects in the Total column per period. Include footnote: Note: For interim, only AEs occurring in two or more subjects by period are reported.	IA 1 [1], IA 2 [2], SAC [3]
3.02.	UVB-Safety	AE1xo	Summary of All Adverse Events by System Organ Class and Preferred Term by Period – UVB Participants Only	ICH E3 Present by Period	SAC [1]
3.03.	Safety	AE1xo	Summary of All Adverse Events by System Organ Class and Preferred Term - Overall	ICH E3 Present Placebo, GSK3858279, Total Columns	SAC [1]
3.04.	Safety	AE5A	Summary of All Adverse Events by System Organ Class and Preferred Term and Maximum Intensity by Period	ICH E3	SAC [1]
3.05.	Safety	AE1xo	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term by Period	ICH E3	SAC [1]
3.06.	Safety	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity by Period	ICH E3	SAC [1]
3.07.	Safety	AE3	Summary of Non-Serious Drug-Related Adverse Events by Overall Frequency by Period	PLS Requirement	SAC [1]

Safety: Tables – All Safety Tables will be presented by Period unless stated otherwise.					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.08.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences) by Period	FDAAA, EudraCT	SAC [1]
Serious and Other Significant Adverse Events					
3.09.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences) by Period	FDAAA, EudraCT Produce if more than 5 SAEs are reported.	SAC [1]
3.10.	Safety	AE3	Summary of Serious Drug-Related Adverse Events by Overall Frequency by Period	PLS Requirement	SAC [1]

Safety: Tables – All Safety Tables will be presented by Period unless stated otherwise.					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Chemistry					
3.11.	Safety	LB1	Summary of Chemistry Changes from Baseline by Period	ICH E3 Present by Period	AAC [1]
3.12.	Safety	LB17	Summary of Worst-Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline by Period	ICH E3 Present by period	AAC [1]
Laboratory: Haematology					
3.13.	Safety	LB1	Summary of Haematology Changes from Baseline by Period	ICH E3 Present by Period	AAC [1]
3.14.	Safety	LB17	Summary of Worst Case Haematology by PCI Criteria Post-Baseline Relative to Baseline by Period	ICH E3 Present by Period	AAC [1]
Laboratory: Urinalysis					
3.15.	Safety	LB1	Summary of Urine Concentration Changes from Baseline by Period	ICH E3 Present by Period	AAC [1]
3.16.	Safety	UR1	Summary of Worst-Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline by Period	ICH E3 Present by Period	AAC [1]
ECG					
3.17.	Safety	EG1	Summary of ECG Findings by Period	IDSL	AAC [1]
3.18.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category by Period	IDSL	AAC [1]

Safety: Tables – All Safety Tables will be presented by Period unless stated otherwise.					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.19.	Safety	EG2	Summary of Change from Baseline in ECG Values by Day by Period	IDSL	AAC [1]
3.20.	[Safety]	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category by Period	IDSL	AAC [1]
Vital Signs					
3.21.	Safety	VS1	Summary of Change from Baseline in Vital Signs by Period	ICH E3	AAC [1]
3.22.	Safety	VS7	Summary of Worst-Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline by Period	IDSL	AAC [1]
Laboratory: Hepatobiliary (Liver)					
3.23.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting by Period	IDSL Programming Note: Subjects should be recorded under the treatment they are receiving at the time the liver monitoring/stopping event is reported, or if the liver monitoring/stopping event was reported during a washout period, under the last study treatment received. Only produce if there is a liver event	AAC [1]

Safety: Tables – All Safety Tables will be presented by Period unless stated otherwise.					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
COVID-19					
3.24.	Safety	PAN1A	Summary of COVID-19 Assessments for Subjects with Suspected, Probable or Confirmed COVID-19 Adverse Events by Period	Present by Period. Treatment columns as: Placebo and GSK3858279 COVID-19 recommended display	AAC [1]

12.11.8. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentrations					
4.01.	PK	PK01	Summary of Serum GSK3858279 Concentration-Time Data (ng/mL)	IDSL. Include 95% Confidence Interval for the mean. Present by period.	IA[1], AAC [2]
4.02.	PK	PK06	Summary of Derived Serum GSK3858279 Pharmacokinetic Parameters (non-transformed and log-transformed)	IDSL. Include Cmax, tmax, tlast, AUC(0-t), AUC(0-7). tmax and tlast should not be log-transformed. Present by period	IA 1 [1], AAC [2]

12.11.9. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentrations					
4.01.	PK	PK16A	Individual Serum GSK3858279 Concentration-Time Plots (Linear and Semi-log)	IDSL. By participant and treatment sequence. Legend by study period in the plot with linear and semi-logarithmic scale side by side.	AAC [1]
4.02.	PK	PK17	Mean Serum GSK3858279 Concentration-Time Plots (Linear and Semi-log)	IDSL. By Treatment sequence. Legend by study period in the plot with linear and semi-logarithmic scale side by side	AAC [1]
4.03.	PK	PK18	Median Serum GSK3858279 Concentration-Time Plots (Linear and Semi-log)	IDSL. By Treatment.sequence. Legend by study period in the plot with linear and semi-logarithmic scale side by side	AAC [1]

12.11.10. Pharmacokinetic / Pharmacodynamic Tables

No PK/PD tables are currently detailed to be produced by S&P.

If any PK/PD modelling analysis is conducted by CPMS, it will be reported in a separate CPMS modelling report, after reporting of this study. Any PK/PD Tables generated by CPMS will be included in the CPMS modelling report.

12.11.11. Pharmacokinetic / Pharmacodynamic Figures

Pharmacokinetic / Pharmacodynamic Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.01	PK	PKPD_F1	Individual UVB Heat Pain Detection Threshold AAUC(1-8) versus GSK3858279 AUC(0-7) Plot (Linear) by Period		AAC [1]
5.02	PK	PKPD_F1	Individual Cold Pressor Time to Intolerable Pain Threshold AAUC(1-15) versus GSK3858279 AUC(0-t) Plot (Linear) by Period		AAC [1]
5.03	PK	PKPD_F1	Individual Electrical pain (single stimulus) Pain Tolerance Threshold AAUC(1-15) versus GSK3858279 AUC(0-t) Plot (Linear) by Period		AAC [1]
5.04	PK	PKPD_F1	Time Matched Individual UVB Heat Pain Detection Threshold (Celsius) versus GSK3858279 Serum Concentrations Plot (Linear) by Period	Colour-coded per time point. Pre-Dose, 1HR, 3HR, Day 2, Day 8, Day 15. Include a legend for Period.	AAC [1]
5.05	PK	PKPD_F1	Time Matched Individual Cold Pressor Time to Intolerable Pain Threshold (Seconds) versus GSK3858279 Serum Concentrations Plot (Linear) by Period	Colour-coded per time point. Pre-Dose, 1HR, 3HR, Day 2, Day 8, Day 15. Include a legend for Period.	AAC [1]
5.06	PK	PKPD_F1	Time Matched Individual Electrical pain (single stimulus) Pain Tolerance Threshold (Milliamps) versus GSK3858279 Serum Concentrations Plot (Linear) by Period	Colour-coded per time point. Pre-Dose, 1HR, 3HR, Day 2, Day 8, Day 15. Include a legend for Period.	AAC [1]

The figures listed in Section 12.11.11. will be produced by S&P.

If any PK/PD modelling analysis is conducted by CPMS, it will be reported in a separate CPMS modelling report, after reporting of this study. Any PK/PD figures generated by CPMS will be included in the CPMS modelling report.

12.11.12. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	AAC [1]
2.	Screened	ES9	Listing of Subjects who were Rescreened		AAC [1]
3.	Enrolled	ES2xo	Listing of Reasons for Study Withdrawal	ICH E3	AAC [1]
4.	ITT	SD2xo	Listing of Reasons for Study Treatment Discontinuation	ICH E3	AAC [1]
5.	ITT	BL2	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	AAC [1]
6.	ITT	TA2	Listing of Planned and Actual Treatments	IDSL	AAC [1]
Protocol Deviations					
7.	Enrolled	DV2xo	Listing of Important Protocol Deviations	ICH E3	AAC [1]
8.	Enrolled	DV2xo	Listing of Non-Important COVID-19 related Protocol Deviations	COVID-19 recommended display	AAC [1]
9.	Enrolled	IE4	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	AAC [1]
Populations Analysed					
10.	Enrolled	SP3a	Listing of Subjects Excluded from Any Population	ICH E3	AAC [1]
Demographic and Baseline Characteristics					
11.	ITT	DM2xo	Listing of Demographic Characteristics	ICH E3	AAC [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
12.	ITT	DM9xo	Listing of Race	ICH E3	AAC [1]
Prior and Concomitant Medications					
13.	ITT	CM10xo	Listing of Current and Past Concomitant Medications	IDSL	AAC [1]
Prior and Concomitant Medications					
14.	ITT	MH2xo	Listing of Current and Past Medical Conditions	IDSL	AAC [1]
Exposure					
15.	ITT	EX3xo	Listing of Exposure Data	ICH E3	AAC [1]
Adverse Events					
16.	Safety	AE8CPxo	Listing of All Adverse Events	ICH E3	SAC [1]
17.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC [1]
18.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC [1]
Serious and Other Significant Adverse Events					
19.	Safety	AE8CPxo	Listing of Serious Adverse Events	ICH E3 Include column for Fatal/Non-Fatal	SAC [1]
20.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC [1]
21.	Safety	AE8CPxo	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC [1]
22.	Safety	AE8CPxo	Listing of Other Significant Adverse Events	ICH E3	SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
All Laboratory					
23.	Safety	LB5xo	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance	ICH E3	AAC [1]
24.	Safety	LB5xo	Listing of All Laboratory Data		AAC [1]
25.	Safety	UR2xo	Listing of Urinalysis Data for Participants with Any Value of Potential Clinical Importance	ICH E3	AAC [1]
26.	Safety	UR2xo	Listing of All Urinalysis Data		AAC [1]
ECG					
27.	Safety	EG3xo	Listing of ECG Values	IDSL	AAC [1]
28.	Safety	EG5xo	Listing of ECG Findings	IDSL	AAC [1]
Vital Signs					
29.	Safety	VS4xo	Listing of All Vital Signs	IDSL	AAC [1]
Hepatobiliary (Liver)					
30.	Safety	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	IDSL (Conditional on liver event being seen)	AAC [1]
31.	Safety	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL (Conditional on liver event being seen)	AAC [1]

12.11.13. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PainCart Assessments					
32.	ITT	EFF_L1	Listing of PainCart Assessments		SAC [1]
33.	ITT	EFF_L2	Listing of PainCart Visual Analogue Scale Scores		AAC [1]
Pharmacokinetics					
34.	Safety	PK07xo	Listing of Serum GSK3858279 Concentration-Time Data (ng/mL)		AAC [1]
35.	Safety	PK13xo	Listing of Derived Serum GSK3858279 Pharmacokinetic Parameters		AAC [1]
Pharmacodynamics					
36.	Safety	PK07xo	Listing of Free & Total CCL17 in Serum Concentration-Time Data (pg/mL)	Include Percentage reduction / Fold Increase Present by Endpoint: Free CCL17, Total CCL17	AAC [1]
37.	Safety	PK13xo	Listing of Derived Free CCL17 in Serum Target Engagement Parameters		AAC [1]
38.	Safety	PK13xo	Listing of Derived Total CCL17 in Serum Target Engagement Parameters		AAC [1]
39.	Safety	IMM2	Listing of Immunogenicity		AAC [1]
COVID-19					
40.	Safety	PAN7	Listing of All Subjects with Visits and Assessments Impacted by COVID-19 Pandemic		AAC [1]

12.12. Appendix 12: Mock Shells

Data Display Specification will be made available on request

Signature Page for 209973 TMF-14046943 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 08-Oct-2021 15:41:29 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 12-Oct-2021 16:51:57 GMT+0000

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