Information Type: Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A multicenter randomized, double-blind, placebo-controlled Phase 2 study to evaluate efficacy, safety, tolerability, pharmacokinetics, and target engagement of GSK3858279 in adult participants with chronic Diabetic Peripheral Neuropathic Pain (DPNP)

Study Number: 214221

Compound Number: *GSK3858279*

Acronym: NEPTUNE-17

Sponsor Name: GlaxoSmithKline Research & Development Limited

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	26 Sep 2023	Original and Amendment 1 (24 July 2023)	Not Applicable	Original version
SAP amendment 1	30 Aug 2024	Original and Amendment 1, 2 (26 March 2024)	Minor edits/corrections throughout	Improve clarity and align with protocol amendments
			Update to main analytical approach in Section 4.2.2 and Section 4.2.4	Improve estimation of the primary and additional estimands
			Remove fixed baseline sensitivity analysis in Section 4.2.3	Result would be the same as the primary analysis since mean value of imputed values is zero in both approaches.
			Addition of updated strategy for DER analysis in Section 4.6.3	Align strategy with the population modelling approach
			Addition of Section 4.6.5	Include regional analyses per updated SAP template
			Addition of details of early access in Section 4.7.1	Clarity around ADaM datasets to be provided.
			Insertion of appendix 6.1	To include full details of bayesian MMRM
			Addition of Table 6 in Section 6.2.3	To define list of criteria leading to

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				exclusion from per-protocol population
			Addition of Section 6.3	Include eCOA compliance per updated SAP template
			Addition of assessments windows in Section 6.4.4	Clarity around derivation of weekly pain score and weekly use of rescue/prohibited pain therapy
SAP amendment 2	30 Jan 2025	Original and Amendment 1, 2 (26 March 2024)	Removal of summary/analysis of tertiary/exploratory endpoints, sensitivity analyses for all endpoints, all regional analyses, per-protocol analysis, all summaries of eCOA compliance other than overall eCOA compliance	To minimize reporting following early termination of the study for futility (pre-defined futility criteria met at interim)
			Removal of additional estimand #2	An estimate of the treatment effect using a treatment policy strategy for the intercurrent event treatment discontinuation (additional estimand #2) has limited value given the large proportion of participants discontinued due to

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				study termination by sponsor.
			Additional sentence in Section 4.1.3.2 regarding prohibited medication use after treatment discontinuation due to study termination by sponsor	To provide clarity on handling of prohibited medications following treatment discontinuation due to study termination by sponsor.
			Removal of summary of characteristics of sponsor adjudicated serious hypersensitivity reactions and potential opportunistic infections	No events reported by final reporting
			Update to analytical approach in Section 4.3.2.1.2	Improve estimation of the secondary categorical efficacy endpoints
			Removal of details of early access in Section 4.7.1	No early access performed
			Addition of Section 6.2	To include details of analytical approach for secondary categorical efficacy endpoints

1. INTRODUCTION

The purpose of this SAP is to describe the planned analysis to be included in the Clinical Study Report (CSR) for Study 214221. Details of the planned interim analyses are provided in the iDRC SAP.

Additional details with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To characterize the efficacy of GSK3858279 on pain compared to placebo in participants with DPNP	• Change from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the Numeric Rating Scale (NRS)
Secondary	
• To determine the safety and tolerability of repeated doses of GSK3858279 compared to placebo in participants with DPNP	• Occurrence of adverse events (AEs), serious adverse events (SAEs), and AEs of Special Interest (AESIs) • Occurrence of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade ≥3 hematological/clinical chemistry abnormalities
• To characterize the PK following repeated dosing of GSK3858279 in participants with DPNP	• Maximum value (Cmax), time of Cmax (tmax), trough value (Ctau), average concentration (Cavg) and area under the curve over the dosing interval (AUC(0-tau)) after the last planned dose
• To determine the efficacy of GSK3858279 compared to placebo in various dimensions of pain in participants with DPNP	• Change from baseline in the Short-Form McGill Pain Questionnaire total score over time
• To further compare the efficacy of GSK3858279 compared to placebo in pain relief in participants with DPNP	• Change from baseline in the weekly average of average daily pain intensity over time, assessed on the NRS • Occurrence of ≥30% reduction from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS • Occurrence of ≥50% reduction from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS
Tertiary or Exploratory	
• To determine the effect of GSK3858279 compared to placebo on various dimensions of pain and pain responder rate in participants with DPNP	• Change from baseline in the weekly average of worst daily pain intensity over time, assessed on the NRS • Change from baseline in the weekly average of nighttime pain intensity over time, assessed on the NRS • Occurrence of ≥30% reduction from baseline in the weekly average of average daily pain intensity over time, assessed on the NRS • Occurrence of ≥50% reduction from baseline in the weekly average of average daily pain intensity over time, assessed on the NRS
• To determine participant's impression of overall change and severity, as well as clinically meaningful within-patient change in patient	• Patient Global Impression of Change (PGIC) over time

Objectives	Endpoints
reported outcome endpoints in participants with DPNP	• Change from baseline in Patient Global Impression of Severity (PGIS) over time
• To determine the effect of GSK3858279 compared to placebo on rescue medication use in participants with DPNP	• Usage of rescue medication (occurrence, number of days, amount taken) over time
• To determine the effect of GSK3858279 compared to placebo on exploratory biomarkers in whole blood in participants with DPNP	• Change from baseline in peripheral immune cell populations, in particular CCR4-expressing cells, at Weeks 4 and 12 • Change from baseline in serum protein mediators, including but not limited to inflammatory and immune cell activation markers, may be investigated • Whole blood transcriptomics (ribonucleic acid [RNA] sequencing) and epigenetics markers may also be explored
• To determine the effect of GSK3858279 compared to placebo on pain severity and pain interference in participants with DPNP	• Change from baseline in Brief Pain Inventory Short Form (BPI-SF) pain severity and interference domains over time
Additional Safety (Tertiary)	
• To determine the safety of repeated doses of GSK3858279 compared to placebo in participants with DPNP	• Change from baseline in laboratory parameters, vital signs and ECG.
• To assess the potential for anti-GSK3858279 antibody formation (ADA and NAb) in participants with DPNP	• Occurrence of ADA and NAb and titers of ADA for samples with confirmed ADA
Additional PK/PD/TE/Biomarkers (Tertiary)	
• To characterize the PK following repeated dosing of GSK3858279 in participants with DPNP over time	• Serum PK concentrations of total GSK3858279 over time • Maximum value (Cmax), time of Cmax (tmax), trough value (Ctau), average concentration (Cavg) and area under the curve over the dosing interval (AUC(0-tau)) after the 1st, 4th and 8th dose
• To evaluate the CCL17 profile following repeat dosing of GSK3858279 in participants with DPNP over time	• Total and free CCL17 levels in serum over time • Reduction (%) from baseline in free CCL17 over time
• To explore the longitudinal dose-exposure-response relationship	• Population parameters for the model describing the relationship between dose, PK, and response (assessed on the Numeric Rating Scale [NRS]) pain over time

1.1.1. Efficacy Estimands

Estimand definitions for efficacy endpoints

Primary estimand for the primary efficacy objective	
Description	Mean change from baseline at Week 12 in the weekly average of average daily pain intensity for GSK3858279 compared to placebo in adult participants with DPNP, where persistent use of prohibited pain therapy and study treatment discontinuations due to lack of efficacy or adverse events are considered a negative outcome, in the absence of other treatment discontinuations and regardless of all other use of prohibited pain therapy and use of allowed rescue medication. Rationale: Interest lies in the treatment effect where participants discontinuing study treatment due to lack of efficacy or adverse events, or persistently taking prohibited pain therapy are reflected in the estimated effect as treatment failures, and irrespective of the use of allowed rescue medication and occasional use of prohibited pain therapy.

Primary estimand for the primary efficacy objective	
Treatment Condition	GSK3858279 (60 mg/week or 360 mg/week) compared to placebo
Endpoint	Change from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS.
Population	Adult participants with DPNP
Strategy for intercurrent events (ICEs)	ICE: study treatment discontinuation due to lack of efficacy or adverse events • Strategy: composite; study treatment discontinuation is considered a negative outcome, and post-ICE assessments will be imputed using multiple imputation based on baseline pain scores ICE: other study treatment discontinuations • Strategy: hypothetical; data collected after the ICE will not be included, and outcomes will be assumed to be similar to participants who did not experience the ICE ICE: persistent use of prohibited pain therapy • Strategy: composite; persistent use of prohibited pain therapy is considered a negative outcome, and post-ICE assessments will be imputed using multiple imputation based on baseline pain scores ICE: occasional use of prohibited pain therapy • Strategy: treatment policy; all data collected after the ICE will be included ICE: use of allowed rescue medication • Strategy: treatment policy; all data collected after the ICE will be included
Population-level summary	Difference in means between each GSK3858279 treatment arm and placebo

The following additional estimands are defined in the protocol. Since the study was terminated early for futility, only additional estimand #1 will be estimated. An estimate of the treatment effect using a treatment policy strategy for the intercurrent event treatment discontinuation (additional estimand #2) has limited value given the large proportion of participants discontinued due to study termination by sponsor.

Additional estimand #1 for the primary efficacy objective	
Description	Mean change from baseline at Week 12 in the weekly average of average daily pain intensity for GSK3858279 and placebo in adult participants with DPNP, in the absence of study treatment discontinuations, prohibited pain therapy and allowed rescue medication. Rationale: This estimand addresses the hypothetical scenario where no intercurrent events occurred, and in particular where all participants continued in the study on treatment and without taking prohibited pain therapy or rescue medication.
Treatment Condition	GSK3858279 (60 mg/week or 360 mg/week) compared to placebo
Endpoint	Change from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS, in the absence of treatment discontinuations, use of prohibited pain medications, and allowed rescue medication.
Population	Adult patients with DPNP

Additional estimand #1 for the primary efficacy objective	
Strategy for intercurrent events (ICEs)	ICE: study treatment discontinuations • Strategy: hypothetical; data collected after the ICE will not be included and outcomes will be assumed to be similar to participants who did not experience the ICE ICE: persistent use of prohibited pain therapy • Strategy: hypothetical; data collected after the ICE will not be included, and outcomes will be assumed to be similar to participants who did not experience the ICE ICE: occasional use of prohibited pain therapy • Strategy: hypothetical; assessments up to 24 hours after the ICE will not be included in the calculation of the change from baseline outcome ICE: use of allowed rescue medications • Strategy: hypothetical; assessments up to 24 hours after the ICE will not be included in the calculation of the change from baseline outcome
Population-level summary	Difference from placebo in mean change from baseline for each GSK3858279 treatment arm

Additional estimand #2 for the primary efficacy objective	
Description	Mean change from baseline at Week 12 in the weekly average of average daily pain intensity for GSK3858279 compared to placebo in adult participants with DPNP, regardless of study treatment discontinuations, use of prohibited pain therapy and use of allowed rescue medication. Rationale: Interest lies in the treatment effect irrespective of study treatment discontinuation, prohibited pain therapy and allowed rescue medication.
Treatment Condition	GSK3858279 (60 mg/week or 360 mg/week) compared to placebo
Endpoint	Change from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS
Population	Adult participants with DPNP
Strategy for intercurrent events (ICEs)	ICE: study treatment discontinuation • Strategy: treatment policy; all data collected after the ICE will be included ICE: use of prohibited pain therapy • Strategy: treatment policy; all data collected after the ICE will be included ICE: use of allowed rescue medication • Strategy: treatment policy; all data collected after the ICE will be included
Population-level summary	Difference from placebo in mean change from baseline for each GSK3858279 treatment arm

The primary and additional efficacy estimand #1 will be applied to the following continuous secondary efficacy endpoints, using the same strategies to address the same intercurrent events:

- Change from baseline in the Short-Form McGill Pain Questionnaire total score over time
- Change from baseline in the weekly average of average daily pain intensity over time, assessed on the NRS

Primary and additional estimands for the binary secondary efficacy endpoints are described below. Only primary and additional estimand #1 will be estimated due to study termination by sponsor.

Estimand for the binary secondary efficacy endpoint	
Treatment Condition	GSK3858279 (60 mg/week or 360 mg/week) compared to placebo
Endpoints	• Occurrence of ≥30% reduction from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS • Occurrence of ≥50% reduction from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS
Population	Adult participants with DPNP
Strategy for intercurrent events (ICEs) **(Primary estimand)**	ICE: study treatment discontinuation due to lack of efficacy or adverse event • Strategy: composite; study treatment discontinuation is considered a negative outcome, and post-ICE assessments are set to non-responder ICE: other study treatment discontinuations • Strategy: hypothetical; data collected after the ICE will not be included, and outcomes will be assumed to be similar to participants who did not experience the ICE ICE: persistent use of prohibited pain therapy • Strategy: composite; use of prohibited pain medications is considered a negative outcome, and post-ICE assessments are set to non-responder ICE: occasional use of prohibited pain therapy • Strategy: treatment policy; all data collected after the ICE will be included ICE: use of allowed rescue medication • Strategy: treatment policy; all data collected after the ICE will be included
Strategy for intercurrent events (ICEs) **(Additional estimand #1)**	ICE: study treatment discontinuations • Strategy: hypothetical; data collected after the ICE will not be included, and outcomes will be assumed to be similar to participants who did not experience the ICE ICE: use of persistent prohibited pain therapy • Strategy: hypothetical; data collected after the ICE will not be included, and outcomes will be assumed to be similar to participants who did not experience the ICE ICE: occasional use of prohibited pain therapy • Strategy: hypothetical; assessments up to 24 hours after the ICE will not be included in the calculation of the change from baseline outcome used to derive the binary endpoint ICE: use of allowed rescue medications • Strategy: hypothetical; assessments up to 24 hours after the ICE will not be included in the calculation of the change from baseline outcome used to derive the binary endpoint
Strategy for intercurrent events (ICEs) **(Additional estimand #2)**	ICE: study treatment discontinuation • Strategy: treatment policy; all data collected after the ICE will be included ICE: use of prohibited pain therapy • Strategy: treatment policy; all data collected after the ICE will be included ICE: use of allowed rescue medication • Strategy: treatment policy; all data collected after the ICE will be included
Population-level summary	Odds ratio, risk difference

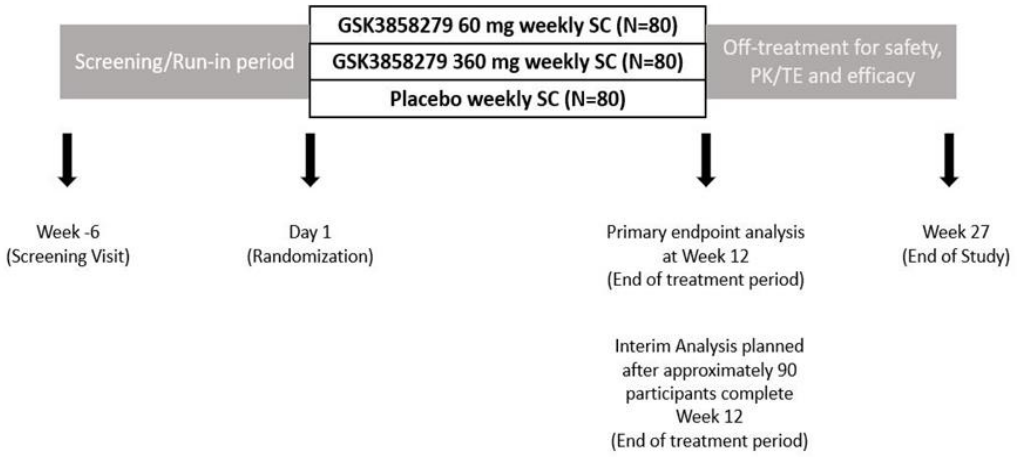
1.1.2. Safety Estimands

Primary estimand for safety objectives	
Treatment Condition	GSK3858279 (60 mg/week or 360 mg/week) compared to placebo
Endpoints	• Occurrence of Adverse Events (AEs), Serious Adverse Events (SAEs) and AEs of Special Interest (AESIs) • Occurrence of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade ≥3 hematological/clinical chemistry abnormalities
Population	Adult participants with DPNP
Strategy for intercurrent events (ICEs)	ICE: study treatment discontinuation • Strategy: treatment policy; all data collected after the ICE will be included ICE: use of prohibited pain therapy

Primary estimand for safety objectives	
	• Strategy: treatment policy; all data collected after the ICE will be included ICE: use of allowed rescue medication • Strategy: treatment policy; all data collected will be included
Population-level summary	AEs, SAEs, AESIs, NCI-CTCAEs: number and % of participants with at least one event by Preferred Term for each treatment arm

1.2. Study Design

Overview of Study Design and Key Features



Design Features	• This is a Phase 2, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy, safety, tolerability, PK and TE of GSK3858279 vs. placebo when administered with repeated weekly SC injections in approximately 240 enrolled participants with DPNP. The number of participants may be increased by approximately 15% to ensure regional requirements for recruitment are met. • Total study duration will be approximately 33 weeks. Screening will take place within 6 weeks before randomization. Treatment period is up to 12 weeks. • Participants will be followed for additional 15 weeks in the off-treatment follow-up period. There will be 2 visits during the off-treatment follow-up period in addition to end of study visit at Week 27, where bloods for PK, TE and safety will be collected. Any rescue medication use will be reported by the participant on the electronic diary (eDiary) on a daily basis.
Study intervention	• Participants will be randomized to one of 3 treatment arms. Specifically, placebo weekly, GSK3858279 60 mg weekly, or GSK3858279 360 mg weekly. • Participants will undergo a screening visit, after which they will go into a washout period of all of their DPNP pain medications (if applicable), consisting of at least 3 days or 5 half-lives, whichever is longer.
Study intervention Assignment	• Participants will be randomized to one of the 3 treatment arms. Participants will be randomized in a 1:1:1 ratio. Randomization will be stratified by participant region (Japan, China, and rest of the world) and average of daily pain score at baseline <7 or ≥7.
Interim Analysis	• An Interim Analysis for futility will be performed when approximately 30 participants per arm complete Week 12 or early withdrawal visit). Further additional interim analyses may be considered to support internal decision making and regulatory interactions. • An iDRC will be set up for reviewing the results from the interim analysis. Full details of all interim analyses are prospectively outlined in the iDRC charter and the iDRC SAP. • An external IDMC will regularly review the unblinded study safety data at scheduled intervals. Key safety data will be reviewed by the IDMC allowing ongoing external safety oversight to protect the safety of study participants as the study progresses. Details of the analyses to be reviewed by the IDMC are provided in the IDMC SAP.

2. STATISTICAL HYPOTHESES

The primary objective of this study is to estimate the mean change from baseline at Week 12 in weekly average of average daily pain intensity, assessed on the NRS, for each GSK3858279 regimen compared to placebo in adult participants with DPNP, where persistent use of prohibited pain therapy and study treatment discontinuations due to lack of efficacy or adverse events are considered a negative outcome, in the absence of other study treatment discontinuations and regardless of all other use of prohibited pain therapy and use of allowed rescue medication. A negative change from baseline is evidence of improvement in pain.

The primary efficacy analysis will be characterized using Bayesian posterior probabilities for various criteria of interest (e.g., posterior probability that the true treatment difference from placebo is less than -0.6/-0.7/-0.8), and inferences will be made by comparing these posterior probabilities to a threshold of interest e.g., 70%.

2.1. Multiplicity Adjustment

For strong control of the probability of at least one treatment arm meeting the criteria of interest under no treatment effect, a hierarchical closed testing procedure will be used with 360 mg weekly evaluated first in the hierarchy.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
Enrolled	• All participants who entered the study (who were randomized or received study intervention or underwent a post screening study procedure). • Note that screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	• Study Population
Randomized	• All participants who were randomly assigned to study intervention in the study. • The screened, enrolled and randomized populations must be nested, i.e., the enrolled population must be a subset of the screened population, the randomized population must be a subset of the enrolled population.	• Study Population (selected displays required by EudraCT)
Safety	• All participants who received at least one dose of study intervention. • Participants will be analyzed according to the study intervention they actually received for the majority of injection procedures.	• Safety
Full Analysis Set (FAS)	• All randomized participants who received at least one dose of study intervention. • Data will be reported according to the randomized study intervention.	• Study Population • Efficacy • Biomarkers • PROs

Analysis Set	Definition / Criteria	Analyses Evaluated
Pharmacokinetic (PK)	• All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • Participants will be analysed according to the study intervention they actually received.	• PK

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The study was terminated early for futility following the planned interim analysis described in Section 4.7, therefore the primary study analysis will be conducted once all randomized participants have completed their final off-treatment follow-up visit.

Participants who prematurely withdrew from study will not be replaced.

In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the actual stratum per data collected in the CRF.

Confidence/credible intervals will use 95% levels unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

It is anticipated that patient accrual will be spread thinly across centers and summaries of data by center would unlikely be informative. If this is not the case and there are appreciable numbers of participants at a particular center, an exploration of the heterogeneity of treatment effect across centers may be graphically explored providing a positive treatment effect is demonstrated in the overall study population.

The number of participants with each intercurrent event will be summarized by treatment group.

For the cases that repeated measurement model is employed to analyse the data, an unstructured correlation matrix will be considered to account for multi-collinearity of repeated measurements data.

Vague priors will be used for the Bayesian analyses.

The randomization stratification parameters of region and baseline average NRS score (continuous) will be included as covariates in all statistical analyses of efficacy endpoints. Participants will be grouped according to the regions used in the randomization stratification (i.e., Japan, China, and Rest of World). If there are

insufficient participants in a region for the planned statistical analysis, further combining of regions will be considered.

Participant level data will be available interactively via RAPIDO Data Viewer at Statistical Analysis Complete (SAC).

4.1.2. Baseline Definition

For all endpoints the baseline value will be the last assessment prior to the first dose with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

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

For the average, worst, and night time pain intensity, the mean of the score over 7 days prior to dosing (Day -7 to Day -1) will be considered baseline. Compliance for average daily pain must be a minimum of 6 out of 7 days for inclusion. Since the diary will be completed in the evening, diary assessments on the date of the first dose of study intervention will include time post-treatment and therefore will not be included in the baseline assessment. Baseline scores will be calculated regardless of the number of available assessments.

4.1.3. Intercurrent Events

4.1.3.1. Treatment Discontinuation

As participants in this study receive study intervention weekly, the date of occurrence of treatment discontinuation will be defined as the date of the first missed dose of study intervention, i.e., date of last dose of study intervention + 7 days.

4.1.3.2. Prohibited Pain Therapy

Participants receiving prohibited pain therapy for any reason, including rescue medication (acetaminophen/paracetamol) beyond protocol allowed use, during the 12-week treatment period will be identified during periodic blinded review of the concomitant medications data using a list of dictionary codes reviewed by GSK Clinical Sciences. For participants discontinuing study treatment due to study termination, any prohibited pain therapy taken on or after the date of occurrence of treatment discontinuation, i.e., date of each participant's last dose of study intervention + 7 days, will not be considered as an intercurrent event of prohibited pain therapy.

Use of prohibited pain therapy will be categorised as "Persistent" according to the therapy specific rules defined in Table 1. Prohibited pain therapy not washed out prior to entering the study per protocol will not be considered as an intercurrent event of prohibited pain therapy. The date of the persistent pain therapy intercurrent event will be defined as the earliest date in the sequence of drug use that meets the definition of persistent prohibited pain therapy (Table 1). For example, if a participant uses opioids 2/7

days per week during weeks 1-9 and 4/7 days per week during week 10 the start date of the persistent pain therapy intercurrent event will be the first day during week 10 that the participant used an opioid. Similar logic will be applied to all prohibited pain therapy drugs, in accordance with the persistent definitions found in Table 1. To identify the excessive use of rescue medication, the date of rescue medication use will be based only on eDairy. Assessment windows to define the weeks to be used for the definitions in Table 1 are provided in Section 6.5.4.

Any use of prohibited pain therapy not classed as "Persistent" will be defined as "Occasional". The date of the other prohibited pain therapy intercurrent event will be identified based on the start and end dates on the concomitant medications form, for use when considering the hypothetical strategy for this intercurrent event. Note that restricted use of NSAIDs for non-DPNP related pain or self-limiting conditions, i.e., maximum of 3 days during each 4-week interval (avoiding the 2 weeks prior to the Week 12 visit), is permitted and will be handled with the same intercurrent event handling strategy as "Occasional" use of prohibited pain therapy and will be summarised accordingly.

Table 1 Definition of Persistent Prohibited Pain Therapy by Type

Type	Persistent Definition
Gabapentanoids	Use for at least 2 consecutive weeks for at least 4/7 days per week during Weeks 1-12
Tricyclic antidepressants	Use for at least 2 consecutive weeks for at least 4/7 days per week during Weeks 1-12
SNRIs	Use for at least 2 consecutive weeks for at least 4/7 days per week during Weeks 1-12
Anticonvulsants/antiepileptics	Use for at least 2 consecutive weeks for at least 4/7 days per week during Weeks 1-12
SSRIs (except for well-controlled depression/anxiety)	Use for at least 2 consecutive weeks for at least 4/7 days per week during Weeks 1-12
NSAIDs (except for acetylsalicylic acid used for cardiovascular prophylaxis) – excluding intraocular route.	Use for at least 2 consecutive weeks for at least 4/7 days per week during Weeks 1-12
Opioids (including tapentadol and tramadol)	Use for at least 4/7 days in any week during Weeks 1-12
Mexiletine	None – any use will be classed as "occasional"
Dextromethorphan	None – any use will be classed as "occasional"
Cannabinoids	None – any use will be classed as "occasional"
Ketamine	None – any use will be classed as "occasional"
Topical analgesics, excluding Qutenza (capsaicin) patch	Use for at least 2 consecutive weeks for at least 4/7 days per week during Weeks 1-12
Qutenza (capsaicin) 8% patch	Single application use
Acetaminophen/paracetamol (excessive use)	Use of >3g on 4 or more days per week or any dose for more than 5 days per week, for at least 2 consecutive weeks during Weeks 1-12
Total Use	Total use of any combination of prohibited medication or any dose of acetaminophen/paracetamol for more than 5 days per week, for at least 2 consecutive weeks during Weeks 1–12, provided this occurs prior to, or in the absence of, meeting the persistent definition for any single therapy above.

4.1.3.3. Allowed Use of Rescue Medication

Individual study days on which rescue medication was taken will be identified from the participant eDiary for use when considering the hypothetical strategy for this intercurrent event.

4.2. Primary Endpoint Analyses

4.2.1. Definition of endpoint/estimands

The primary efficacy endpoint is the change from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS. The weekly average pain score will be calculated for each participant using the mean of the available daily pain scores falling in the assessment windows for each week described in Section 6.5.4.

Refer to Section 1.1.1 for the primary estimand for the primary efficacy objective.

4.2.2. Main analytical approach

Raw data summary statistics for the absolute and change from baseline weekly average of average daily pain intensity will be produced. In addition, for each week, a summary of the number of daily pain scores included in the average weekly pain derivation for each participant will be produced.

The strategy for handling ICEs is described within the estimand section (Section 1.1.1). The date of the occurrence of the intercurrent event is defined in Section 4.1.3.

Statistical Model for the Primary Estimand:

The primary analysis model will be a joint model for the change from baseline in average weekly pain score (i.e., a conditional outcome model) and the time to ICE(s) (i.e., a marginal ICE model). The conditional outcome model for the change from baseline in average weekly pain score at each week during the treatment period (Week 1 to Week 12) will be a Bayesian mixed model repeated measures (MMRM), with mean model specified conditional on the occurrence of the first of those ICEs handled using a composite strategy.

From the joint model, the marginal mean treatment difference at each week will be estimated. The primary treatment difference will be the marginal treatment difference at the Week 12 timepoint. If convergence issues arise due to sparsity of change from baseline data at certain time points, those time points may be excluded from the analysis.

The fixed effects included in the conditional outcome model for the mean change from baseline are region (categorical), baseline (continuous), week (categorical), treatment (categorical), baseline*week interaction, and treatment*week interaction. An unstructured covariance matrix is assumed to model the covariance of change from baseline measurements within individual.

For the primary estimand, persistent use of prohibited pain therapy or treatment discontinuations due to lack of efficacy or adverse events are handled with a composite strategy. Change from baseline data post-ICE will be treated as missing (i.e., actual values will be disregarded), their associated mean change from baseline assumed to be zero, and their variance covariance matrix unmodified. Gibbs samplers for the missing outcomes may be multiply imputed "on the fly" in the Bayesian MCMC analysis, if desired, though doing so has no impact on the posterior distribution for the model parameters.

Other treatment discontinuations are handled with a hypothetical strategy. Change from baseline data post-ICE will be treated as missing (i.e., actual values will be disregarded), their associated mean change from baseline unmodified (consistent with a missing at random assumption), and their variance covariance matrix unmodified.

Any other missing data in the analysis model for the primary estimand (e.g., intermittent missing weekly pain assessments) will be assumed to be missing at random (MAR).

Time to ICE distributions (for composite and hypothetically handled ICEs) will be treated as independent due to a lack of data to estimate any dependence parameter. Time to first ICE handled with a composite strategy and first ICE handled with a hypothetical strategy are assumed to follow independent geometric distributions (modelling the time to the last week prior to the ICE occurrence) with the parameter defining the probability of having the ICE in the next week assumed to differ across treatment groups.

Prior Distributions:

Vague prior distributions will be used for analysis.

Specifically, for the conditional outcome model, uniform improper prior distributions will be used for each fixed effect in the regression model for the mean change from baseline. The prior for the covariance matrix will follow an inverse Wishart (IW) distribution with hyperparameters (degrees of freedom and scale parameter) set to the default value used in SAS PROC BGLIMM, i.e., the dimension of the covariance matrix plus 3. Note that the scale parameter corresponds to a multiplier of the scale matrix, which is taken to be a diagonal matrix for the IW prior used for analysis.

Each of the treatment group specific probability parameters for the time-to-ICE models will be given Beta(0.05,0.95) unit-information priors.

Estimated Quantities:

Markov-Chain-Monte-Carlo (MCMC) method will be used to estimate the posterior distributions for the change from baseline weekly average of average daily pain intensity. Posterior mean pain score, posterior mean change from baseline pain score and 95% credible intervals for the weekly average of average daily pain for each treatment arm at each week will be reported.

For each GSK3858279 treatment arm, the difference from placebo at each time point will be summarized using the posterior mean, SD and 95% equal-tail credible interval. Plots

will be created using the posterior mean and 95% credible interval to visually display the change from baseline in weekly average of average daily pain intensity at each of the study weeks for each treatment group.

Posterior mean estimates and associated inferences will be based on the *marginal* mean for each treatment group at each time point, computed using as covariate values the average baseline pain score, and the sample proportion of individuals in each regional category.

The posterior distributions will be used to produce probability statements for each GSK3858279 treatment arm:

> Prob[True Difference (GSK3858279 treatment arm – placebo) < X] where values of X to be generated are X = 0, -0.6, -0.7, -0.8, -0.9, -1

At least 100,000 posterior samples will be generated, and random number seeds will be set so that results are fully reproducible. Technical details of the methodology and implementation are described in Section 6.1.

4.2.3. Sensitivity analyses

Since the study was terminated early for futility, no sensitivity analyses will be performed.

4.2.4. Additional estimands

Refer to Section 1.1.1 for additional estimands for the primary objective.

For the first additional estimand, in the case of the ICEs of other prohibited medication and use of allowed rescue medication, pain assessments up to 24 hours after the ICE will not be included in the derivation of the weekly average pain score used to calculate the change from baseline. If the time for the medication use on any day is unknown, pain assessments on the same day as the medication use will not be included (since the eDiary is completed at home in the evening, medication use on the same day is more likely to be prior to the pain assessment than after the pain assessment). For the ICEs of treatment discontinuation and persistent prohibited pain therapy, all data post-ICE that is set to missing due to intercurrent events under the hypothetical strategy will be assumed to be MAR. Any other missing data will also be assumed to be MAR. The MAR assumption for missing data will be implemented through the mixed model repeated measures (MMRM) model described in Section 4.2.2 and Section 6.1.6. Note that for the first additional estimand (since occurrence of an ICE does not impact the model for the mean change from baseline), a joint model is not needed and so only a Bayesian MMRM for the change from baseline will be fitted.

4.3. Secondary Endpoints Analyses

4.3.1. Definition of Endpoints/Estimands

The secondary efficacy endpoints are change from baseline in the Short-Form McGill Pain Questionnaire total score over time, change from baseline in the weekly average of average daily pain intensity over time, assessed on the NRS, as well as occurrence of ≥30%, 50% reduction from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS. Refer to Section 1.1.1 for the primary estimand for the secondary efficacy endpoints.

Additional secondary endpoints are occurrence of AEs, SAEs and AESIs, occurrence of NCI-CTCAE Version 5.0 grade ≥3 haematological/clinical chemistry abnormalities, and PK parameters (at Week 12).

4.3.2. Main analytical approach

4.3.2.1. Secondary Efficacy Endpoints

4.3.2.1.1. Continuous Secondary Efficacy Endpoints

Change from baseline in the Short-Form McGill Pain Questionnaire total score over time

- The Short-Form McGill Pain Questionnaire is a 22-item question questionnaire, where different pain variables are rated on a scale of 0-10: where 0 is no pain, and 10 is the worst possible pain. The total score will be calculated as the mean of all item ratings.
- The methods outlined in Section 4.2.2 will be used to analyse this endpoint, including the baseline Short-Form McGill Pain Questionnaire total score as an additional covariate, and including all available time points for this endpoint in the repeated measures model.
- For each GSK3858279 treatment arm, the difference from placebo at each time point will be summarized as mean, SD and 95% equal-tail credible interval of the approximate posterior distribution, and posterior probabilities described in Section 4.2.2 .
- Simple summary statistics (Mean, SD, Min, Max, Median) will also be presented for the endpoint by treatment group.

Change from baseline in the weekly average of daily pain intensity over time, assessed on the NRS

- The analysis of weekly average of daily pain intensity over time is described in Section 4.2.2.

4.3.2.1.2. Binary Secondary Efficacy Endpoints

For each responder definition (reduction of ≥30% and ≥50% from observed baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS), the marginal proportion of responders for each treatment group at each time point will be calculated based on the posterior samples from the primary analyses described in Section 4.2, using the ICE distribution and the empirical distribution of baseline covariates based on the observed covariate values of each individual in the analysis population regardless of their randomized treatment group. Technical details of the methodology and implementation are described in Section 6.2.

4.3.2.2. Additional estimands

Additional efficacy estimand #1 will also be applied to secondary continuous and binary efficacy endpoints and will use the same strategies to address the same intercurrent events. Refer to Section 1.1.1 for more details on the additional estimands.

For additional estimand #1, in the case of the ICEs of other prohibited pain therapy and use of allowed rescue medication, Short-Form McGill Pain Questionnaire assessments up to 24 hours after the ICE will not be included in the change from baseline outcome. If the time for the medication use on any day is unknown, Short-Form McGill Pain Questionnaire assessments on the day after the medication use will not be included (since the Short-Form McGill Pain Questionnaire assessments are completed at the clinic visit, it is more likely that the medication use on the day before the assessment is within 24 hours prior to the assessment rather than medication use on the same day as the assessment). Refer to Section 4.2.4 for details of ICEs handling strategies for eDairy pain assessment. For the ICEs of treatment discontinuation and persistent prohibited pain therapy, all data that is set to missing due to intercurrent events under the hypothetical strategy will be assumed to be MAR. Any other missing data will also be assumed to be MAR. The MAR assumption for missing data will be implemented through the mixed model repeated measures (MMRM) model described in Section 4.2.2.

4.3.3. Other secondary endpoints

The secondary safety endpoints are included under the safety analysis section. Specifically, the main analytical approaches for the handling AEs can be found in Section 4.5.3 and the analysis approaches for the laboratory data can be found in Section 4.5.4.1.

For information about the analysis for the secondary PK endpoints, see the PK analysis section (Section 4.6.1).

4.4. Tertiary/Exploratory Endpoints Analyses

Since the study was terminated early for futility, tertiary efficacy endpoints, patient reported outcomes, PD endpoints (CCL17 profile), D-E-R analysis and exploratory biomarkers will not be reported.

4.4.1. Immunogenicity

Immunogenicity results, including incidence of confirmed positive anti-drug antibody and titer, will be reported where data allows, according to GSK standards. Neutralising antibody will not be reported due to study termination.

A summary of adverse events by immunogenicity status will also be produced.

4.4.2. PK

For information on the PK secondary and tertiary/exploratory endpoints see Section 4.6.1.

4.5. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified. Safety data from the treatment period and the off-treatment follow-up (i.e., up to Week 27) will be summarized together.

4.5.1. Secondary Safety Endpoints Analysis

No formal statistical testing will be performed on safety data for the secondary safety endpoints.

The strategy for handling ICEs is described in the estimand section (Section 1.1.2). No imputations will be performed for the reporting of safety.

4.5.2. Extent of Exposure

Extent of exposure to GSK3858279 will be summarized using the safety analysis set for each treatment arm and overall.

The duration of exposure to study treatment in days, defined as (treatment stop date – (treatment start date) + 7), will be summarized. Last IMP dosing date will be used as treatment stop date. Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be calculated.

Participants should receive 3 injections at each visit/injection procedure; the number of injections (1, 2, 3) given at each visit will also be summarized to present the completeness of each injection procedure. The total number of injection procedures for each participant will also be summarized. In addition, the total number of planned injection procedures and total number of planned injections, as well as the total number of actual injection procedures and total number of actual injections calculated across participants will be reported over the whole treatment period for each treatment group.

4.5.3. Adverse Events

An adverse event (AE) is considered study intervention emergent if the AE onset date (and time if available) is on or after study intervention start date (and time). All AE summaries will be based on study intervention emergent events unless otherwise specified. SAE summaries will be based on all SAEs reported regardless as to whether they meet the definition of study intervention emergent or not.

Adverse events will be coded using the latest versions of the standard Medical Dictionary for Regulatory Activity (MedDRA dictionary).

A drug-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as “Yes”. A worst-case scenario approach will be taken to handle missing relatedness data, i.e., the summary table will include events with the relationship to study intervention as “Yes” or missing.

An overall summary of AEs, including counts and percentages of participants with any AE, drug-related AEs, SAEs, AEs leading to permanent discontinuation of study intervention will be produced.

Separate summaries of the number and percentage of participant with any AEs, drug-related AEs and AEs leading to permanent discontinuation of study intervention by system organ class (SOC) and preferred term (PT) will be produced. A summary of the number and percentage of participants with any AEs by maximum severity will also be produced by SOC and PT.

A summary of all common AEs, that occurred in strictly 5% of the participants or above in any treatment group will be provided by PT and ordered by overall frequency (no rounding for the percentage will be used in terms of the 5% threshold, e.g., events with 4.9% incidence rate should not be included within this table). A summary of common non-serious adverse events by SOC and PT will also be produced, including both the number and percentage of participants with the AE as well as the number of occurrences of the AE.

A summary of non-serious drug-related AEs by PT will be produced ordered by overall frequency.

The following summaries will be provided for the SAEs:

- Summary of Serious Adverse Events by System Organ Class and Preferred Term
- Summary of Serious Adverse Events by Overall Frequency
- Summary of Serious Adverse Events by System Organ Class and Preferred Term and Maximum Intensity
- Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)

A summary of AEs by immunogenicity status (participants with ADA positive, participants with ADA positive and Nab positive, and participants with ADA negative) will be produced.

All AE listings will include the treatment phase (pre-intervention, on-intervention, or post-intervention) as defined in Section 6.5.2.

4.5.3.1. Adverse Events of Special Interest

The following will be considered adverse events of special interest (AESI) for the purpose of analyses:

- Serious infections
- Opportunistic infections
- TB
- Serious hypersensitivity reactions
- Injection site reactions

Serious infections will include all serious adverse events coded to the "Infections and infestations" SOC. The additional information for serious infections collected on the serious infections targeted eCRF will be summarized including infection type and origin.

Potential opportunistic infections will be reviewed and adjudicated in a blinded fashion on an ongoing basis by the GSK3858279 Safety Review Team (SRT). Infections adjudicated as opportunistic by the SRT will be used in the summaries of this AESI. Opportunistic infections are also classified by the Investigator on a targeted eCRF. The additional information for opportunistic infections collected on the targeted eCRF will be summarized for events adjudicated as opportunistic by SRT, including infection type and origin.

TB events will be identified based on a pre-defined list of preferred terms determined by the GSK3858279 SRT.

Potential hypersensitivity reactions will be reviewed and adjudicated in a blinded fashion on an ongoing basis by the GSK3858279 SRT. Events adjudicated as serious hypersensitivity reactions by the SRT will be used in the summaries of this AESI. Serious hypersensitivity reactions are also classified by the Investigator on the eCRF including symptoms/management data. The symptoms/management data for serious hypersensitivity reactions collected on the targeted eCRF and adjudicated as hypersensitivity reactions by SRT will be summarized.

Injection site reactions (ISRs) will be identified based on a pre-defined list of preferred terms determined by the GSK3858279 SRT. Injection site reactions are also identified by the Investigator on the eCRF and symptoms of the ISRs are recorded. The symptoms data for the injection site reactions collected on the target eCRF for ISRs identified based on the pre-defined list of preferred terms will be summarized.

A summary of event characteristics of injection site reactions, serious infections and TB will be provided, including the number of participants with any event, number of events, number of participants with any event that is serious, number of participants with any event that is related to study intervention, number of occurrences (one, two, three or more), maximum severity, maximum severity for events related to study intervention,

outcomes and the action taken for the event. The percentage will be calculated with total number of participants as the denominator. The worst-case approach will be applied at participant level for the maximum severity, i.e., a participant will only be counted once as the worst case from all the events experienced by the participant. For action taken to an event, a participant will be counted once under each action, e.g., if a participant has an event leading to both study intervention discontinuation and dose reduction, the participant will be counted once under both actions.

4.5.4. Additional Safety Assessments

4.5.4.1. Laboratory Data

Laboratory data will be presented in tabular and/or graphical format and summarized descriptively according to GSK standards.

Summaries of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE Version 5.0. These summaries will display the number and percentage of participants with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0.

In addition, summaries of worst-case changes from baseline with respect to normal range will be generated for all lab tests. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst-case post-baseline. If a participant has a decrease to low and an increase to high during the same time interval, then the participant is counted in both the “Decrease to Low” categories and the “Increase to High” categories.

Separate summary tables for haematology, and chemistry laboratory tests will be produced. Liver function laboratory tests will be included with chemistry lab tests.

4.5.4.2. Vital Signs

Vital signs data will be presented in tabular format and summarized descriptively according to GSK standards.

Summaries of grade increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be provided separately. These summaries will display the number and percentage of participants with any grade increase, increase to Grade 2 and increase to Grade 3 for worst case post-baseline only. The grade definitions for SBP and DBP are presented within Table 2.

Table 2 Grade Definition for SBP and DBP

Grade	SBP	DBP
0	<120	<80
1	120-139	80-89
2	140-159	90-99

Grade	SBP	DBP
3	≥160	≥100

4.5.4.3. ECG

The QTc data analysis will use the collected values based on Fridericia formula.

The QTc values based on Fridericia formula will be rounded to the integer and the values will be categorised into the following CTCAE grade and ranges: Grade 0 (≤450 msec), Grade 1 (>450 and ≤480 msec), Grade 2 (>480 and ≤500 msec), and Grade 3 (>500 msec). Summaries of grade increase will be provided. These summaries will display the number and percentage of participants with any grade increase, increase to grade 2 and increase to grade 2 for the worst-case post-baseline only. Missing baseline grade will be assumed as grade 0.

The changes in QTc values will be categorised into the clinical concern ranges which are specific to changes in QTc: 31-60 and > 60 msec. A summary of change in QTc value will display the number and percentage of participants with a change within each range for the worst-case post-baseline only. Participants with missing baseline value will be excluded from this summary.

For time points where multiple measurements are taken, please refer to Section 6.5.5.

4.5.4.4. Pregnancies

While pregnancy itself is not considered to be an AE or an SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If the participant becomes pregnant whilst on the study, the information will be included in the narratives and no separate table or listing will be produced.

4.6. Other Analyses

4.6.1. Pharmacokinetic Analysis

The serum pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified. Missing serum concentration data will be considered Missing at Random and no imputations for missing data will be carried out. All calculations will be based on actual sampling times.

Observed GSK3858279 concentration-time data (tertiary endpoint) will be summarized (Geometric Mean, 95% CI, SD, Min, Max, Median) by treatment group. Individual and mean/median concentration-time profiles of GSK3858279 (stratified by treatment group) will be plotted.

Pharmacokinetic parameters (secondary endpoints (Cmax, Tmax, Ctau, Cavg and AUC(0-tau) after last dose (Week 12) will be derived using a model-based approach. Tertiary endpoints (Cmax, Tmax, Ctau, Cavg and AUC(0-tau) after 1st, 4th, and 8th dose) and accumulation ratios (AR)) will not be provided due to study termination.

4.6.2. Subgroup Analysis

Subgroup analyses will not be performed due to study termination by sponsor.

4.6.3. Analyses to Support Regional Submission

Analyses to support regional submission will not be performed due to study termination by sponsor.

4.7. Interim Analyses

An interim analysis for overall study futility will be performed when ~30 participants per arm qualify for a Week 12 efficacy assessment (either by attending the Week 12 visit or through data imputation strategy). Interim NRS pain data will be used to build a predictive distribution of end-of-study Week 12 NRS pain, to enable decisions on study futility.

The objective of the interim analysis is to assess futility based on the difference from placebo in efficacy endpoints at Week 12. Thus, resulting in either continuing the study with no change to the planned randomization or study arms, or stopping the study for futility.

Additional administrative interim analyses may occur in order to inform internal decision making and/or to inform regulatory interactions. No change to the study is planned as a result of these additional interim analyses.

Full details of all interim analyses will be prospectively outlined in the iDRC Charter and the iDRC SAP. In addition, the iDRC charter outlines how the internal data review committee will ensure data integrity and appropriate quality control of data prior to making decisions and an outline of the committee membership.

In addition to the planned interim analyses, an external IDMC will regularly review the unblinded study safety data at scheduled intervals. Key safety data will be reviewed by the IDMC allowing ongoing external safety oversight to protect the safety of study participants as the study progresses. Full details are provided in the IDMC charter and the IDMC SAP.

4.8. Changes to Protocol Defined Analyses

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
Primary study analysis and reporting conducted when the planned target sample size of ~240 randomized participants have completed week 12; end of study analysis when the target sample size of ~240 has completed the study (including the off-treatment follow-up)	The primary study analysis will be conducted once all randomized participants have completed their final off-treatment follow-up visit.	Study was terminated early for futility following the interim analysis.

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
Additional estimand #2 defined for primary and secondary endpoints	Analysis removed.	An estimate of the treatment effect using a treatment policy strategy for the intercurrent event treatment discontinuation (additional estimand #2) has limited value given the large proportion of participants discontinued due to study termination by sponsor.
D-E-R model will be fitted using total GSK3858279 and longitudinal NRS response data from all treatment arms and all time points	D-E-R model will not be fitted.	Study was terminated early for futility following the interim analysis.

5. SAMPLE SIZE DETERMINATION

Approximately 240 participants will first be stratified based on region (Japan, China or the rest of the world) and an average of the average daily pain score at baseline (<7 or ≥7) and then randomized in a 1:1:1 ratio to GSK3858279 60 mg SC weekly, GSK3858279 360 mg SC weekly and placebo SC weekly within each stratum. The recruitment may continue beyond this by approximately 15% to ensure regional requirements are met. The probability of achieving various criteria of interest given various sample sizes was assessed, conditional on different true values for the treatment difference. Calculations are based on simple pairwise comparisons between a GSK3858279 treatment arm and placebo (with vague priors). The results are summarized in Table 3 and are not conditional on the planned interim analysis. Based on these results, a sample size of 80 participants per arm is considered sufficient for a comparison between a GSK3858279 treatment arm and placebo.

For these calculations, the population standard deviation for the change from baseline is assumed to be 2.2 for each treatment arm. [Rauck, 2013] reported a standard deviation of 2.2 for change in NRS Pain through Week 16. Similarly, [Campbell, 2012] reported a standard deviation of 2.1 for change in NRS Pain at Week 16. The same standard deviation (i.e., 2.1) was reported in an unpublished clinical trial by Laurenza and his team [Laurenza, 2014].

Table 3 Probability of Meeting Various Criteria of Interest Conditional on True Treatment Differences, and not Conditional on Interim Analysis Results

			Probability of meeting criterion given true treatment difference (Δ)					
Criterion of Interest	N per arm	Assumed SD	Δ = -1.2	Δ = -1	Δ = -0.8	Δ = -0.6	Δ = 0	Observed difference vs. placebo required
Posterior probability (true difference from placebo < -0.6) > 70%	70	2.2	86%	71%	51%	30%	2%	-0.795
		2.7	79%	64%	47%	30%	3%	-0.839
	80	2.2	89%	73%	52%	30%	1%	-0.782
		2.7	81%	66%	48%	30%	3%	-0.823
	90	2.2	90%	76%	53%	30%	<1%	-0.772
		2.7	83%	68%	49%	30%	2%	-0.811
	100	2.2	92%	78%	55%	30%	<1%	-0.763
		2.7	85%	70%	50%	30%	2%	-0.800
Posterior probability (true difference from placebo < -0.7) > 70%	70	2.2	79%	61%	40%	21%	<1%	-0.895
		2.7	72%	55%	38%	23%	2%	-0.939
	80	2.2	82%	63%	41%	21%	<1%	-0.882
		2.7	74%	57%	39%	22%	2%	-0.924
	90	2.2	84%	65%	41%	20%	<1%	-0.872
		2.7	76%	59%	39%	22%	1%	-0.911
	100	2.2	86%	67%	42%	20%	<1%	-0.863
		2.7	78%	60%	40%	21%	1%	-0.900
Posterior probability (true difference from placebo < -0.8) > 70%	70	2.2	71%	51%	30%	14%	<1%	-0.995
		2.7	64%	47%	30%	17%	1%	-1.040
	80	2.2	73%	52%	30%	14%	<1%	-0.982
		2.7	66%	48%	30%	16%	<1%	-1.024
	90	2.2	76%	53%	30%	13%	<1%	-0.972
		2.7	68%	49%	30%	15%	<1%	-1.011
	100	2.2	78%	55%	30%	12%	<1%	-0.963
		2.7	70%	50%	30%	15%	<1%	-1.000

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Details of Bayesian MMRM

6.1.1. Parameterization

6.1.1.1. Definitions

Last Visit Complete (LVC) is defined as the last visit with a non-missing value of CFB prior to any values being set to missing as a part of the intercurrent event handling strategy. For modeling intercurrent event times, when no intercurrent events have occurred for an individual and LVC=$\boldsymbol{k}$, we will infer that the time-to-last visit before ICE must be at least $\boldsymbol{k}$ (for fitting marginal ICE models). This is analogous to right-censorship of time-to-event data.

Time to withdrawal (TTW) is relevant for analysis of additional estimand #2. For additional estimand #2, time to withdrawal for an individual will be defined as the later of the time of (1) documented study withdrawal or (2) the time of their last non-missing outcome value.

6.1.1.2. Random Variable and Covariate Notation

Denote time-to-last visit prior to a composite handled intercurrent event as C_i, and time-to-last visit prior to a hypothetical handled intercurrent event as H_i. $\boldsymbol{Y}_i = (Y_{i1}, \ldots, Y_{iT})$ represents the change from baseline (CFB) outcome vector from Week 1 to Week T, and

$$\boldsymbol{X}_i = \begin{bmatrix} \boldsymbol{x}'_{i1} \\ \vdots \\ \boldsymbol{x}'_{iT} \end{bmatrix}$$

denotes the $T \times q$ covariate matrix with rows defined by the $q \times 1$ covariate vectors $\boldsymbol{x}_{it}$ corresponding to week $t = 1, \ldots, T$. The dimension q will be described in Section 6.1.1.3.1.

6.1.1.3. Outcome and Intercurrent Event Model

For now, we will omit any index for treatment. The outcome model is assumed to obey the following structure:

$$f(\boldsymbol{Y}_i, C_i, H_i|\boldsymbol{\xi}) = f(\boldsymbol{Y}_i|C_i, H_i, \boldsymbol{\beta}, \boldsymbol{\Sigma}) f(C_i|\pi_c) f(H_i|\pi_h).$$

where $\boldsymbol{\xi} = \{\boldsymbol{\beta}, \boldsymbol{\Sigma}, \pi_c, \pi_h\}$ represents the collection of all model parameters.

6.1.1.3.1. Conditional Outcome Model

The first component of the joint distribution, denoted by $f(\boldsymbol{Y}_i|C_i, H_i, \boldsymbol{\beta}, \boldsymbol{\Sigma})$, corresponds to an MMRM written as

$$\boldsymbol{Y}_i = \boldsymbol{W}(C_i)\boldsymbol{X}_i\boldsymbol{\beta} + \boldsymbol{\epsilon}_i,$$

where $\boldsymbol{W}(C_i)$ is the diagonal matrix given by

$$\boldsymbol{W}(C_i) = \begin{bmatrix} (C_i \geq 1) & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & (C_i \geq T) \end{bmatrix},$$

where $\boldsymbol{\epsilon}_i \sim MVN(\boldsymbol{0}, \boldsymbol{\Sigma})$.

The element in row t and column t of $\boldsymbol{W}(C_i)$ will be equal to 1 if only if $(C_i \geq t)$ – that is, if and only if the time-to-last visit prior to a composite handled intercurrent event is at least t. Otherwise, the corresponding element will be zero and the t^{th} row of $\boldsymbol{W}(C_i)\boldsymbol{X}_i$ will be a zero vector so that conditional on C_i the expected value $E[Y_{it}|\boldsymbol{x}_{it}, C_i] = 0$.

For the model in question, the number of elements in $\boldsymbol{\beta}$ is equal to $q = (G + 1) \times T + p$, where G is the number of investigational treatment groups, T is the number of time points, and p is the number of additional covariate effects (e.g., effects associated with a time × baseline value interaction and geographic region).

6.1.1.3.2. Marginal Intercurrent Event Model

In practice we either cannot, or it is unlikely that we will observe both C_i and H_i. Thus, it will not be practical to assume a marginal joint distribution where they are dependent. Moreover, due to sparsity of intercurrent events, fitting a complex regression model for either C_i or H_i is not practical.

Here, we posit a simple treatment-group specific model for C_i. An analogous model will be fit for H_i but specification of that model is omitted to avoid redundancy. Specifically, we assume

$$C_i \sim \text{Geometric}(\pi_{cg}),$$

for individual i in treatment group g. The PMF for C_i has the form

$$P(C_i = k) = (1 - \pi_{cg})^k \pi_{cg},$$

for $k \geq 0$.

6.1.1.3.3. Lower Bounds for Intercurrent Event Times Based on Observed Data

We consider the scenario where C_i and H_i are effectively independent competing risks. Thus, for an individual ongoing in the study, we might observe $C_i = c$ in which case we infer $H_i \geq c$ in addition to $H_i \geq k$ (equal to is included due to discreteness). Similarly, if we observe $H_i = h$, we can infer $C_i \geq h$ in addition to $C_i \geq k$. If neither intercurrent event has occurred by the time an individual has completed their last outcome assessment (i.e., week k), then we can just infer $C_i \geq k$ and $H_i \geq k$. These points will be relevant because in the MCMC model fitting scheme the values of C_i and H_i that are not observed will be sampled subject to the appropriate lower bound as described above. It is unlikely that time-to-last visit prior to an intercurrent event will be observed *after* LVC (*i.e.* last visit with a non-missing value of CFB prior to any values being set to missing as a part of the intercurrent event handling strategy), however it is reasonable to assume the same follow-up for all intercurrent events and so if $h > k$, it is reasonable to use h as the lower bound for C_i (and analogously for H_i).

6.1.2. Mathematical Representation of the Primary Estimand

Let $Y_{i,t}(0)$ and $Y_{i,t}(g)$ correspond to the week t change from baseline outcome values for an individual if treated with placebo (0) and investigational treatment g, respectively. Define the covariate vector $\boldsymbol{x}_{it} = (w_{it}\ z_{it1} \cdots z_{itG}\ s_i)$ where

- w_{it} is a $1 \times T$ vector with a value of 1 for element t and a value of zero otherwise,
- z_{itg} is a $1 \times T$ vector with a value of 1 for element t if individual i receives investigational treatment g and a value of zero otherwise, and
- s_i is a $1 \times p$ vector of covariate effects (e.g., including baseline value by time interactions, and region of origin).

Let $\boldsymbol{\alpha}_w, \boldsymbol{\gamma}_g$ and $\boldsymbol{\psi}_s$ be the corresponding regression parameters in the linear model. Thus $\boldsymbol{\beta} = (\boldsymbol{\alpha}_w', \boldsymbol{\gamma}_1', \ldots, \boldsymbol{\gamma}_G', \boldsymbol{\psi}_s')'$. The population summary of interest is defined mathematically as

$$E[Y_{it}(g) - Y_{it}(0)] = E\left[E\left[Y_{i,t}(g) - Y_{i,t}(0)\middle| C_i(g), C_i(0), X_i\right]\right].$$

Taking expectations, we obtain

$$P(C(g) \geq t)\left(\alpha_{wt} + \gamma_{gt} + E[s_{it}]\boldsymbol{\psi}_s\right) - P(C(0) \geq t)(\alpha_{wt} + E[s_{it}]\boldsymbol{\psi}_s).$$

Note that $P(C(g) \geq t) = \left(1 - \pi_{cg}\right)^{t+1}$ for the assumed geometric distribution.

6.1.3. Data Preprocessing

Outcome values for any visit occurring after $\min(C_i, H_i)$ will be set to missing prior to analysis. All missing data will be imputed "on the fly" in the Bayesian analysis consistent with the intercurrent event handling strategy as described above.

6.1.4. Prior Distributions

- ICE geometric distribution parameters: $\pi_g \sim \text{Beta}(a_0 = 0.05, b_0 = 0.95)$
- Linear model regression parameters: $p(\boldsymbol{\beta}) \propto 1$.
- Linear model covariance matrix: $\boldsymbol{\Sigma} \sim \text{Inverse} - \text{Wishart}\left(T + 3, I_{T \times T} \cdot (T + 3)\right)$

6.1.5. Gibbs Sampler

A Gibbs sampler can be used to fit this model. Initialize parameter values by random draws from an appropriate distribution to obtain $\boldsymbol{\xi}^{(0)}$. Proceeds as follows at iteration $b = 1, \ldots, B$:

- Sample $D_{miss}^{(b+1)} | D_{obs}, \boldsymbol{\xi}^{(b)}$ where $D_{miss}^{(b+1)}$ are the missing intercurrent event and outcome data and D_{obs} are the observed intercurrent even and outcome data.

  Let $D^{(b+1)} = \{(C_i, H_i, Y_i, X_i) : i = 1, \ldots, N\}$ be the data at iteration $b + 1$. Subsequently we will include the super script in references to data (e.g., write $C_i^{(b+1)}$) but it should be understood that only a subset of the data change from iteration to iteration of the MCMC sampler.

- Sample $\pi_{cg}^{(b+1)} \sim \text{Beta}\left(n_g + a_0, \sum_{i=1}^{N} C_i^{(b+1)} + b_0\right)$ and $\pi_{hg}^{(b+1)} \sim \text{Beta}\left(n_g + a_0, \sum_{i=1}^{N} H_i^{(b+1)} + b_0\right)$. Note that given $D^{(b+1)}$, these full conditionals do not depend on the outcome data.
- Let $\boldsymbol{\beta}$ be the vector of all regression parameters and let $\widetilde{\boldsymbol{X}}_i^{(b+1)} = \boldsymbol{W}\left(C_i^{(b+1)}\right)\boldsymbol{X}_i$. Sample $\boldsymbol{\beta}^{(b+1)} \sim \text{MVN}(\mathbf{A}, \mathbf{B})$ where

$$\mathbf{A} = \left(\sum_{i=1}^{N} \widetilde{\boldsymbol{X}}_i^{(b+1),T} \boldsymbol{\Sigma}^{(b)^{-1}} \widetilde{\boldsymbol{X}}_i^{(b+1)}\right)^{-1} \left(\sum_{i=1}^{N} \widetilde{\boldsymbol{X}}_i^{(b+1),T} \boldsymbol{\Sigma}^{(b)^{-1}} \boldsymbol{Y}_i^{(b+1)}\right).$$

$$\mathbf{B} = \left(\sum_{i=1}^{N} \widetilde{\boldsymbol{X}}_i^{(b+1),T} \boldsymbol{\Sigma}^{(b)^{-1}} \widetilde{\boldsymbol{X}}_i^{(b+1)}\right)^{-1}$$

- Define $\boldsymbol{R}_i^{(b+1)} = \boldsymbol{Y}_i^{(b+1)} - \widetilde{\boldsymbol{X}}_i^{(b+1)} \beta^{(b+1)}$.

  Sample $\boldsymbol{\Sigma}^{(b+1)} \sim \text{iWishart}\left(N + (T+3), \sum_{i=1}^{N} \boldsymbol{R}_i^{(b+1)} \boldsymbol{R}_i^{(b+1),T} + I_{T\times T} \cdot (T+3)\right)$.

6.1.5.1. Additional Details on Step 1

Without loss of generality consider the case where C_i is missing but where we can therefore infer that $C_i \geq \max(h, k)$.

Let $\boldsymbol{Y}_i = \left(Y_{i1}, \ldots, Y_{ik}, Y_{i,k+1}, \ldots, Y_T\right) = \left(\boldsymbol{Y}_{i,miss}, \boldsymbol{Y}_{i,obs}\right)$. We thus need to sample from the distribution $\left(C_i, \boldsymbol{Y}_{i,miss} \middle| H_i, \boldsymbol{Y}_{i,obs}, \boldsymbol{X}_i, \boldsymbol{\xi}^{(b)}\right)$ which can be factored as $\left(C_i \middle| H_i, \boldsymbol{Y}_{i,obs}, \boldsymbol{X}_i, \boldsymbol{\xi}^{(b)}\right)\left(\boldsymbol{Y}_{i,miss} \middle| C_i, H_i, \boldsymbol{Y}_{i,obs}, \boldsymbol{X}_i, \boldsymbol{\xi}^{(b)}\right)$.

- Consider sampling $\left(C_i \middle| H_i, \boldsymbol{Y}_{i,obs}, \boldsymbol{X}_i, \boldsymbol{\xi}^{(b)}\right)$. By virtue of observing $LVC = k$ and potentially $H_i = h$, it follows that $C_i \geq \max(h, k)$. Thus $\widetilde{\boldsymbol{X}}_{i,obs} = \boldsymbol{X}_{i,obs}$ and the density for $\boldsymbol{Y}_{i,obs}$ does not depend on C_i. It follows that $\left(C_i \middle| H_i, \boldsymbol{Y}_{i,obs}, \boldsymbol{X}_i, \boldsymbol{\xi}^{(b)}\right) = \left(C_i \middle| \pi_c^{(b)}\right)$ thus remains a geometric distribution (with truncated domain satisfying $C_i \geq \max(h, k)$).
- Given that $\boldsymbol{Y}_i | X_i, C_i^{(b+1)}, \boldsymbol{\xi}^{(b)} \sim \text{MVN}\left(\widetilde{\boldsymbol{X}}_i^{(b+1)} \beta^{(b)}, \boldsymbol{\Sigma}^{(b)}\right)$, it is straightforward to sample $\boldsymbol{Y}_{i,miss}$ from its full conditional given $\boldsymbol{Y}_{i,miss} | \boldsymbol{Y}_{i,obs}, X_i, C_i^b, \boldsymbol{\xi}^{(b)}$.

6.1.6. Additional Estimand #1

All ICEs are handled with a hypothetical strategy. In this case we are modeling time to the last visit prior to any ICE based on ICEs of treatment discontinuation and persistent prohibited pain therapy. All outcome values occurring after the earliest of the qualifying ICEs should be set to missing. Compared to the primary estimand, the model associated with this estimand is given by

$$\boldsymbol{Y}_i = \boldsymbol{X}_i \boldsymbol{\beta} + \boldsymbol{\epsilon}_i,$$

i.e., the traditional Bayesian MMRM. As a result of this ICE handling strategy, additional estimand #1 is given by

$$\left(\alpha_{wt} + \gamma_{gt} + E[s_i]\boldsymbol{\psi}_s\right) - \left(\alpha_{wt} + E[s_i]\boldsymbol{\psi}_s\right) = \gamma_{gt},$$

which is characterized already by the model fit for the primary estimand.

6.2. Appendix 2 Details of Responder Analysis

An individual will be considered a responder at week *t* if their observed outcome value is reduced by at least $(\Delta \times 100)\%$ (e.g., $\Delta = 0.3, 0.5$) at week *t* compared to their observed baseline value. For an individual with observed baseline value b_0 and week *t* value b_t, to be a responder at time *t* their observed outcome value must satisfy

$$b_t \leq (1-\Delta)b_0 \Leftrightarrow b_t - b_0 \leq (1-\Delta)b_0 - b_0 \Leftrightarrow y_t \leq -\Delta b_0$$

Thus, the individuals' observed week *t* change from baseline outcome value y_t must be no more than $-\Delta b_0$.

The random variable corresponding to whether an individual *i* in treatment group *g* will be a responder at time *t* is given by $R_{it}(g) = 1\{Y_{it}(g) \leq -\Delta B_{i0}\}$. The marginal risk difference between investigational treatment *g* and placebo at time *t* is defined mathematically as

$$E[R_t(g) - R_t(0)], \tag{6.1}$$

and the marginal odds ratio between investigational treatment *g* and placebo at time *t* is defined mathematically as

$$E\left[\frac{R_t(g)/(1-R_t(g))}{R_t(0)/(1-R_t(0))}\right]. \tag{6.2}$$

For the purpose of illustration, we will only go through the derivation of marginal risk difference here. To compute Equation (6.1) (i.e. represent this expectation as a function of model parameters), we evaluate an equivalent double expectation given as

$$E[E[R_t(g) - R_t(0) \mid C(g), C(0), S]],$$

where the inner expectation is taken with respect to $Y_t(g)$ and $Y_t(0)$ conditional on the counterfactual times of the ICEs being handled with the composite strategy $C(g)$ and $C(0)$ and the baseline covariates S. The outer expectation is then taken with respect to the random quantities conditioned on in the inner expectation (i.e., $C(g), C(0)$and S).

For the inner expectation,

$$E[R_t(g)|C(g), C(0), S] = 1\{C(g) \geq t\} \times \Phi(-\Delta B_0|Z = g, S) + 1\{C(g) < t\} \times 0$$

and $E[R_t(0) \mid C(g), C(0), S] = 1\{C(0) \geq t\} \times \Phi(-\Delta B_0 \mid Z = 0, S) + 1\{C(0) < t\} \times 0,$

where $\Phi(\cdot)$ is the normal CDF function and random baseline value B_0 should be understood to be contained in S. Thus, Equation (6.1) is equal to the expected value of

$$1\{C(g) \geq t\} \times \Phi(-\Delta B_0 \,|Z = g, S) - 1\{C(0) \geq t\} \times \Phi(-\Delta B_0 \,|Z = 0, S). \quad (6.3)$$

For that expectation, we again can break the calculation down by first conditioning on S and taking the expectation of Equation (6.3) given S, and then finally taking expectations with respect to S. Taking expectations conditional on S yields

$$P(C(g) \geq t) \times \Phi(-\Delta B_0 \,|\, Z = g, S) - P(C(0) \geq t) \times \Phi(-\Delta B_0 \,|\, Z = 0, S) \quad (6.4)$$

since we have assumed the ICE distribution does not depend on covariates other than treatment group. The final calculation requires us to take the expectation of Equation (6.4) with respect to S.

In general, to avoid having to model the covariate distribution, we simply use the empirical distribution of S based on the observed covariate values $\{s_i : i = 1, \ldots, N\}$, where N is the number of individuals in the analysis population with observed baseline covariate values (regardless of their randomized treatment group). Thus, for example, we assume

$$E_S[\Phi(-\Delta B_0 \,|\, Z = g, S)] = \frac{1}{N} \sum_{i=1}^{N} \Phi(-\Delta b_{i0} \,|\, Z = g, s_i\,).$$

The population averaged (i.e., marginal) treatment effect is then given by Equation (6.5).

$$P(C(g) \geq t) \times \frac{1}{N} \sum_{i=1}^{N} \Phi(-\Delta b_{i0} | Z = g, s_i\,) - P(C(0) \geq t) \times \frac{1}{N} \sum_{i=1}^{N} \Phi(-\Delta b_{i0} | Z = 0, s_i\,) \quad (6.5)$$

6.3. Appendix 3 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Full Analysis Set. A summary of the number of participants in each of the participant level analysis sets will be provided.

In this multicenter global study, enrollment will be presented by country and site.

6.3.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized. For those who have neither completed nor withdrawn, they will be categorised as on study intervention or in follow up.

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

The number of participants with each intercurrent event will be summarized by treatment group.

6.3.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, height/weight at screening and race will be summarized with descriptive statistics. In addition, the following age categories will be summarized separately based on the Enrolled Analysis Set: 18-64, and ≥65-75. If the summary of demographics meets the criteria for de-identification, as described in the relevant procedural document, a de-identified version should be produced.

Two summaries of baseline disease characteristics will be provided: one for the efficacy parameters and another for the disease characteristics. The baseline efficacy parameter characteristics summary will include baseline average pain intensity, worst pain intensity, night-time pain intensity and baseline short-form McGill pain questionnaire score. The baseline disease characteristics summary will include time since diagnosis.

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

Disease treatment failure history will be summarized based on the targeted eCRF, including what DPNP treatments were previously taken by a participant and the reason for treatment failure.

Substance use, including smoking history, tobacco use, alcohol and drug history will be summarized.

6.3.3. Protocol Deviations

Important protocol deviations will be summarized.

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

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

6.3.4. Prior and Concomitant Medications

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

Concomitant medications will be summarised by study period (on-intervention/post-intervention, as defined in Section 6.5.2).

6.4. Appendix 4 Electronic Clinical Outcome Assessment (eCOA) Compliance

Overall eCOA compliance (across eCOAs for primary and secondary endpoints during treatment period for all participants) for the study will be reported, calculated as:

$$\frac{\text{Total number of complete eCOAs}}{\text{Expected number of complete eCOAs per participant} \times \text{total number of participants}}$$

Participants who discontinued study treatment due to study termination by the sponsor are expected to be compliant with their eCOAs up to the date of occurrence of treatment discontinuation, i.e., date of each participant's last dose of study intervention + 7 days. Other participants are expected to be compliant with their eCOAs up to the study completion/withdrawal date for site based assessments and up to but not including the study completion/withdrawal date for eDiary assessments.

An eCOA is considered complete if there is no missing data within the assessment. The overall study eCOA compliance will be reported for each treatment group.

6.5. Appendix 5 Data Derivations Rule

6.5.1. Criteria for Potential Clinical Importance

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 will be used to assign grades to the relevant laboratory parameters, blood pressure and QTc.

In addition, the following criteria in Table 4 will be used to flag potential clinical importance:

Table 4 Definitions of PCI Ranges

Parameters	Unit	PCI Range
Heart rate	bpm	<60 (L); >100 (H)
QRS interval	Msec	<75 (L); >110 (H)

6.5.2. Study Period

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

Pre-intervention is defined as time prior to the first dose of study intervention.

On-intervention is defined as time from first dose up to and including last dose date plus 6 days. If time of assessment or study intervention is not collected, the following assessments on the first dose date will be assumed to be taken prior to the first dose and therefore considered pre-intervention: ECG, Lab and vital signs; in addition, first dose date is considered on-intervention for AEs and concomitant medications where no start time is recorded.

Post-intervention is defined as any time post on-intervention window, i.e., ≥ last dose date + 7 days.

6.5.3. Study Day and Reference Dates

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

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

The study day is calculated as below:

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

6.5.4. Assessment Window

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

Data recorded at an early withdrawal visit will be re-assigned in the ADaM data sets to the closest nominal visit at which collection of data was scheduled, unless information already exists at that visit. Early withdrawal data re-assigned to a scheduled visit will be included in analyses, tables and figures by scheduled visit. Early withdrawal visit data

that is not re-assigned to a scheduled visit will not be included in analyses, tables and figures by scheduled visit.

For the purposes of deriving the weekly pain assessments, study weeks during the treatment period will be defined based on the visit date as shown in Table 5 below. If there are more than 7 days in the assessment window, the average pain score will be derived over all available days in the assessment window, hence the number of daily pain scores included in the weekly average may exceed 7. In the case of missed visits, the nominal visit date will be used. Study weeks during the follow up period will also be defined based on the nominal visit.

Table 5 Assessment Windows for Calculation of Weekly Pain Scores from eDiary

Study week	Assessment window		Additional Rules
	First date included	Last date included	
Baseline	Date of first dose of study treatment – 7 days	Date of first dose of study treatment – 1 day	
Week 1	Date of first dose of study treatment	Week 1 visit date – 1 day	If visit date is missing, or for study weeks during the follow-up period (i.e. weeks 13 – 27) use nominal visit dates as follows:- Week 1 – Day 8 Week 2 – Day 15 Week 3 – Day 22 Week 4 – Day 29 Week 5 – Day 36 Week 6 – Day 43 Week 7 – Day 50 Week 8 – Day 57 Week 9 – Day 64 Week 10 – Day 71 Week 11 – Day 78 Week 12 – Day 85 Week 13 – Day 92 Week 14 – Day 99 Week 15 – Day 106 Week 16 – Day 113 Week 17 – Day 120 Week 18 – Day 127 Week 19 – Day 134 Week 20 – Day 141 Week 21 – Day 148 Week 22 – Day 155 Week 23 – Day 162 Week 24 – Day 169 Week 25 – Day 176 Week 26 – Day 183 Week 27 – Day 190
Week 2	Week 1 visit date	Week 2 visit date – 1 day	
Week 3	Week 2 visit date	Week 3 visit date – 1 day	
Week 4	Week 3 visit date	Week 4 visit date – 1 day	
Week 5	Week 4 visit date	Week 5 visit date – 1 day	
Week 6	Week 5 visit date	Week 6 visit date – 1 day	
Week 7	Week 6 visit date	Week 7 visit date – 1 day	
Week 8	Week 7 visit date	Week 8 visit date – 1 day	
Week 9	Week 8 visit date	Week 9 visit date – 1 day	
Week 10	Week 9 visit date	Week 10 visit date – 1 day	
Week 11	Week 10 visit date	Week 11 visit date – 1 day	
Week 12	Week 11 visit date	Week 12 visit date – 1 day	
Week 13	Week 12 visit date	Week 13 visit date – 1 day	
Week 14	Week 13 visit date	Week 14 visit date – 1 day	
Week 15	Week 14 visit date	Week 15 visit date – 1 day	
Week 16	Week 15 visit date	Week 16 visit date – 1 day	
Week 17	Week 16 visit date	Week 17 visit date – 1 day	
Week 18	Week 17 visit date	Week 18 visit date – 1 day	
Week 19	Week 18 visit date	Week 19 visit date – 1 day	
Week 20	Week 19 visit date	Week 20 visit date – 1 day	
Week 21	Week 20 visit date	Week 21 visit date – 1 day	
Week 22	Week 21 visit date	Week 22 visit date – 1 day	
Week 23	Week 22 visit date	Week 23 visit date – 1 day	
Week 24	Week 23 visit date	Week 24 visit date – 1 day	
Week 25	Week 24 visit date	Week 25 visit date – 1 day	
Week 26	Week 25 visit date	Week 26 visit date – 1 day	
Week 27	Week 26 visit date	Week 27 visit date – 1 day	

Study weeks for the assessment of rescue and prohibited medication use will be defined based on study day as shown in the table below.

Table 6 Assessment Windows for Rescue and Prohibited Medication

Study week	Assessment window
Baseline	Day -7 to -1
Week 1	Day 1 to 7
Week 2	Day 8 to 14
Week 3	Day 15 to 21
Week 4	Day 22 to 28
Week 5	Day 29 to 35
Week 6	Day 36 to 42
Week 7	Day 43 to 49
Week 8	Day 50 to 56
Week 9	Day 57 to 63
Week 10	Day 64 to 70
Week 11	Day 71 to 77
Week 12	Day 78 to 84
Week 13	Day 85 to 91
Week 14	Day 92 to 98
Week 15	Day 99 to 105
Week 16	Day 106 to 112
Week 17	Day 113 to 119
Week 18	Day 120 to 126
Week 19	Day 127 to 133
Week 20	Day 134 to 140
Week 21	Day 141 to 147
Week 22	Day 148 to 154
Week 23	Day 155 to 161
Week 24	Day 162 to 168
Week 25	Day 169 to 175
Week 26	Day 176 to 182
Week 27	Day 183 to 189

6.5.5. Multiple measurements at One Analysis Time Point

Mean of the measurements will be calculated where required 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.

6.5.6. Handling of Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>
• Partial dates will be displayed as captured in participant listing displays.
• However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.
• Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.
</td></tr>
<tr><td>Adverse Events</td><td>
• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
• If month and year of start date = month and year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = 1st of month.
– Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:
• If year of start date = year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
– Else set start date = study intervention start date.
Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>
• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
• If month and year of start date = month and year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
– Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail	
		• *If year of start date = year of study intervention start date, then* – *If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.* – *Else set start date = study. intervention start date.* *Else set start date = January 1.*
	Missing end day	*A '28/29/30/31' will be used for the day (dependent on the month and year).*
	Missing end day and month	*A '31' will be used for the day and 'Dec' will be used for the month.*
	Completely missing start/end date	*No imputation*

6.5.7. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

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None

7. REFERENCES

Campbell CM, Kipnes MS, Stouch BC. Randomized Control Trial of Topical Clonidine for Treatment of Painful Diabetic Neuropathy. Pain. 2012;153(9):1815-23.

Laurenza A. An Evaluation of the Efficacy and Safety of E2007 in Patients with Painful Diabetic Neuropathy. Updated 11 July 2014. Accessed 27 August 2024 https://classic.clinicaltrials.gov/ct2/show/NCT00505284

Rauck R, Makumi CW, Schwartz S, et al. A Randomized, Controlled Trial of Gabapentin Enacarbil in Subjects with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy. Pain Pract. 2013;13(6):485-96.