Statistical Analysis Plan

A PHASE I, DOUBLE-BLIND, PHARMACOKINETIC, SAFETY AND TOLERABILITY STUDY OF KETOPROFEN LYSINE SALT COMBINED WITH GABAPENTIN (KLS-GABA) COMPARED TO KETOPROFEN LYSINE SALT (KLS) ALONE IN HEALTHY MALE SUBJECTS (PART A) FOLLOWED BY A RANDOMISED, DOUBLE-BLIND, PLACEBO- CONTROLLED STUDY TO INVESTIGATE THE PHARMACODYNAMIC EFFECTS OF KLS, AND KLS IN COMBINATION WITH GABAPENTIN (GABA), IN HEALTHY MALE SUBJECTS USING THE INTRADERMAL (ID) CAPSAICIN MODEL (PART B)

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Statistical Analysis Plan

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Statistical Analysis Plan

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
BMI	Body Mass Index
CI	Confidence Interval
C_{max}	Peak Exposure
CRU	Clinical Research Unit
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
GABA	Gabapentin
GCP	Good Clinical Practice
ICF	informed consent form
ICH	The International Council for Harmonisation
ID	Intradermal
IMP	Investigational Medicinal Product
ITT	Intent-To-Treat
KLS	Ketoprofen Lysine Salt
LOCF	Last Observation Carried Forwards
MedDRA	Medical Dictionary For Regulatory Activities
NOCB	Next Observation Carried Backwards
PD	Pharmacodynamic
PK	Pharmacokinetic(S)
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event

INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to define the efficacy and safety analysis variables and analysis methodology to address the study objectives.

The Pharmacokinetic (PK) analysis is outside the scope of this analysis plan. That analysis will be described in a separate document.

The protocol dated 16 Jun 2021 (version V5.0) and the eCRF dated 12 Jul 2021 (version V5.0) were used in the development of this SAP.

1. STUDY OBJECTIVES AND ENDPOINTS

1.1. Study Objectives

1.1.1. Primary Objectives (Part A)

The primary objective of the Part A is:

- To determine the single dose PK of KLS-GABA (80 mg-34 mg) compared to KLS alone (80 mg) in healthy male subjects.

1.1.2. Secondary Objectives (Part A)

The secondary objective of the Part A is:

- To determine the safety and tolerability of a single oral dose of KLS-GABA (80 mg-34 mg) compared to KLS alone (80 mg) in healthy male subjects.

1.1.3. Primary Objectives (Part B)

The primary objective of the Part B is:

- To determine the pharmacodynamic (PD) effects of KLS-GABA in the ID capsaicin model in healthy male subjects.

1.1.4. Secondary Objectives (Part B)

The secondary objectives of the Part B are:

- To further investigate the safety, tolerability, and PK of single oral doses of KLS-GABA and KLS alone.
- To investigate the possible relationship between plasma levels of drug and efficacy in pain reduction.

1.2. Study Endpoints

1.2.1. Primary Endpoints (Part A)

The primary endpoints are plasma PK concentrations and parameters of ketoprofen alone when administered as KLS and ketoprofen and gabapentin when administered as KLS-GABA, including but not limited to: area under the concentration-time curve (AUC), from zero to the last quantifiable concentrations (AUC_{0-t}), AUC from zero to infinity ($AUC_{0-\infty}$), AUC from zero to 12 hours postdose (AUC_{0-12h}), AUC from zero to 24 hours postdose (AUC_{0-24h}), AUC from zero to 36 hours postdose (AUC_{0-36h}), AUC from zero to 48 hours postdose (AUC_{0-48h}), C_{max}, t_{max} and half-life ($t_{1/2}$) in healthy male subjects.

1.2.2. Secondary Endpoints (Part A)

The secondary endpoint of the study is the clinical safety data from AE reporting, 12-lead ECG, vital signs (supine blood pressure, heart rate, oral temperature), clinical laboratory evaluations (chemistry, haematology, urinalysis and coagulation) and physical examinations in healthy male subjects.

1.2.3. Primary Endpoint (Part B)

The primary endpoint of the study is:

Reduction in area of hyperalgesia post capsaicin injection from the ID capsaicin model.

1.2.4. Secondary Endpoints (Part B)

The secondary endpoints of the study are:

- Subjective rating of pain from the ID capsaicin model.
- Pain score of hyperalgesia from the ID capsaicin model.
- Area and pain score of brush-evoked allodynia from the ID capsaicin model.
- Area of flare (AF) from the ID capsaicin model.
- Plasma PK concentrations.
- Clinical safety data from AE reporting, 12-lead ECG, vital signs (supine blood pressure, heart rate, oral temperature), clinical laboratory evaluations (chemistry, haematology, urinalysis, and coagulation) and physical examinations in healthy male subjects.

2. STUDY DESIGN

This is a Phase I, randomised, 2-part study to determine the PK, safety, and tolerability of single oral doses of KLS-GABA compared to KLS alone in healthy male subjects (Part A), in addition to investigating the PD effects, PK/PD correlation, safety, and tolerability of three single oral dose levels of KLS GABA compared to three single oral dose levels of KLS alone, 300 mg gabapentin alone and placebo in the ID capsaicin model in healthy male subjects (Part B).

2.1. Part A

Part A is a randomised, double-blind, crossover group study to investigate a single oral dose of KLS-GABA compared to KLS alone, in healthy male subjects.

It is planned to enrol 12 subjects. Subjects will take part in 2 treatment periods, in which they will receive a single dose of KLS-GABA (80 mg-34 mg) or a single dose of KLS (80 mg) alone in each treatment period.

Subjects will be required to attend the CRU for a screening visit up to 28 days prior to first dosing in Treatment Period 1 to ensure they meet the inclusion/exclusion criteria and are in good general health.

Subjects will be admitted to the CRU on Day -1 of each treatment period for a body weight assessment and will receive a dose of KLS-GABA or KLS alone in the morning of Day 1. All subjects will undergo pre-dose safety assessments and PK blood sampling on Day 1. All subjects will remain in the CRU until Day 3 (48 hours post-dose) for the collection of safety assessments and PK blood samples at multiple time points. There will be a minimum of 7 days washout period between treatment periods.

Subjects will attend a follow-up visit 5 to 7 days post the final dose after Treatment Period 2. The duration of participation for each subject is expected to last approximately 7 weeks.

2.2. Part B

Part B is a randomised, double-blind, placebo-controlled parallel group study to investigate single oral doses of KLS alone or KLS-GABA compared to 300 mg gabapentin alone or placebo, in healthy male subjects using the ID capsaicin model.

It is planned to enrol 128 subjects randomised evenly to 8 possible treatments; subjects will receive either KLS alone, KLS-GABA, 300 mg gabapentin or placebo.

The planned treatments are:

- KLS alone (40 mg, 80 mg or 160 mg)
- KLS-GABA (40 mg-17mg, 80 mg-34 mg, or 160 mg-68 mg)
- Gabapentin* (300 mg)
- Placebo

* Product commercialised in the UK: Neurontin 300 mg hard capsules.

Subjects will be required to attend the CRU for a screening visit within 28 days prior to dosing to ensure they meet the inclusion/exclusion criteria and are in good general health.

Following initial screening, subjects will be required to attend the CRU for an additional screening visit at least 7 days prior to first dosing to assess their response to capsaicin and familiarise them in the pain measurements. Subjects will receive a single ID administration of 100 µg capsaicin into a novel site on the volar surface of the forearm. Prior to and 15 minutes after administration of capsaicin, measurements of pain, hyperalgesia, allodynia and AF will be performed according to the procedures described in Section 9. In order for the subjects to be eligible, they must be able to tolerate the injection and also demonstrate a sufficient response, defined as an area of hyperalgesia ≥ 15cm^2 15 minutes after the injection.

Subjects will be admitted to the CRU on Day -1 for collection of baseline safety assessments, pain measurements and to complete the ID capsaicin model (see Appendix 2). Subjects will receive a single 100 µg capsaicin injection into a novel site on the volar surface of the forearm.

Subjects will receive a single oral dose of KLS alone (40 mg, 80 mg or 160 mg), KLS-GABA (40 mg-17 mg, 80 mg-34 mg or 160 mg-68 mg), 300 mg gabapentin or placebo in the morning of Day 1. All subjects will undergo pre-dose safety assessments, pain measurements and PK blood sampling on Day 1. PK blood samples will also be taken prior to application of the ID capsaicin model on Day 1. All subjects will have an ID capsaicin injection on Day 1 at the t_{max} determined for KLS alone or KLS-GABA from Part A. All subjects will remain in the CRU until 12 hours post-dose for the collection of safety assessments, pain measurements and PK blood samples at multiple timepoints.

Subjects will attend a follow-up visit 5 to 7 days post-dose. The duration of participation for each subject is expected to last approximately 6 weeks.

3. CONVENTIONS

All summary tables, figures and data listings will be produced using SAS software 9.4 or above.

Summaries will be performed by treatment group, separately for Part A (crossover design) and Part B (parallel design).

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. For log-transformed data, the geometric mean, coefficient of variation (CV), median, minimum and maximum will be presented. No hypothesis testing will be conducted.

Categorical variables will be summarised by frequency counts and percentages for each category.

For AE summaries, the n and % of subjects with event, as well as the number of events, will be shown.

For all Part A endpoints, the last observation before the first dose of corresponding study treatment will be considered the baseline measurement unless otherwise specified. However, if an evaluable assessment is only available after randomisation but before the first dose of randomised treatment then this assessment will be used as baseline. For Part A, baseline for each treatment period will be defined as last observation before the first dose of study treatment (Period 1 Day -1 and Period 2 Day-1).

For Part B safety and PK endpoints, the last observation before dosing will be considered the baseline measurement unless otherwise specified. However, if an evaluable assessment is only available after randomisation but before the first dose of randomised treatment then this assessment will be used as baseline.

For Part B PD endpoints, the day -1 observation at each post-Capsaicin injection timepoint will be considered the baseline measurement for each corresponding day 1 post-Capsaicin timepoint, i.e., the baseline for day 1 15 minutes post-Capsaicin injection will be the day-1 15 minutes post-Capsaicin injection value. If a day-1 PD value at the 30-minute, 60-minute or 90-minute post-Capsaicin timepoints is missing for a subject, linear interpolation will be used to compute the missing value. If a subject's 120-minute post-Capsaicin value is missing, last observation carried forwards (LOCF) will be used instead. If a subject's 15-minute post-Capsaicin value is missing, next observation carried backwards (NOCB) will be used.

Assessments on the day of the dosing where neither time nor a nominal pre-dose indicator are captured will be considered prior to the dosing if such procedures are required by the protocol to be conducted before the dosing.

In all summaries change from baseline variables will be calculated as the post-treatment value minus the value at baseline. For Part A change from baseline will be calculated only for post-treatment evaluation during the corresponding Period (Days 1 to 3) and assigned to treatment according to treatment period (see Section X).

Data for Part A and Part B will be listed separately. All listings will be ordered by treatment sequence for Part A or by treatment for Part B and subject number and will include all available data including unscheduled data.

Unscheduled values will not be used for analysis. Assessments conducted at unscheduled visits will be listed.

There will be an interim analysis of PK for Part A and a final analysis of both parts.

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- Margins:
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4. ANALYSIS SETS AND TREATMENT GROUPS

4.1. Analysis Sets (Part A)

4.1.1. Intent-to-Treat Set (Part A)

The ITT Set will be defined as all subjects randomized. A subject's randomized treatment sequence will be used for analysis regardless of the actual treatment received. ITT Set will be used for disposition and demographic analysis.

4.1.2. Safety Set (Part A)

The Safety Set will be defined as all subjects who received a at least one dose of the IMP (KLS-GABA or KLS). The actual treatment received will be used for analysis according to treatment period. Safety Set will be used for all safety analyses and endpoints.

4.1.3. Pharmacokinetic Set (Part A)

The PK Set will be defined as all subjects who received a at least one dose of the IMP (KLS-GABA or KLS) and have evaluable PK data. The actual treatment received will be used for analysis according to treatment period. PK Set will be used for all PK analyses and endpoints.

4.2. Analysis Sets (Part B)

4.2.1. Intent-to-Treat Set (Part B)

The ITT Set will be defined as all subjects randomized. A subject's randomized treatment will be used for analysis regardless of the actual treatment received. ITT Set will be used for disposition and demographic analysis.

4.2.2. Safety Set (Part B)

The Safety Set will be defined as all subjects who received a at least one dose of the IMP (KLS, KLS-GABA, gabapentin, or Placebo). The actual treatment received will be used for analysis. Safety Set will be used for all safety analyses and endpoints.

4.2.3. Pharmacokinetic Set (Part B)

The PK Set will be defined as all subjects who received a at least one dose of the IMP (KLS, KLS-GABA, gabapentin, or Placebo) and have evaluable PK data. The actual treatment received will be used for analysis. PK Set will be used for all PK analyses and endpoints.

4.2.4. Pharmacodynamic Set (Part B)

The PD Set will be defined as all randomised subjects who received a dose of randomised therapy and complete the ID capsaicin injection. The actual treatment received will be used for analysis. The analyses of efficacy endpoints will use the PD set.

4.3. Treatment groups

For summary statistics, subjects will be presented in different ways, as applicable:

- for Part A:
  - by planned treatment sequence of randomized subjects ("[KLS 80 mg - GABA 34 mg] – KLS 80 mg" and "KLS 80 mg – [KLS 80 mg - GABA 34 mg]"). This presentation will be used optionally for descriptive outputs (disposition, demographics, etc.), but generally will not be used for analysis of endpoints.
  - by actual treatment of subjects in each treatment period ("KLS 80 mg - GABA 34 mg" and "KLS 80 mg"). This presentation will be used for analysis of endpoints, and optionally for descriptive outputs (disposition, demographics, etc.).
- for Part B:
  - by planned treatment of subjects ("KLS 40 mg", "KLS 80 mg", "KLS 160 mg", "KLS 40 mg - GABA 17 mg", "KLS 80 mg - GABA 34 mg", "KLS 160 mg – GABA 68 mg", "Gabapentin 300 mg", "Placebo"). This presentation will be used for descriptive outputs (disposition, demographics, etc.).
  - by actual treatment of subjects ("KLS 40 mg", "KLS 80 mg", "KLS 160 mg", "KLS 40 mg - GABA 17 mg", "KLS 80 mg - GABA 34 mg", "KLS 160 mg – GABA 68 mg", "Gabapentin 300 mg", "Placebo"). This presentation will be used for analysis of safety, efficacy and PK endpoints.

5. ANALYSIS PERIODS

There will be two treatment periods within Part A. Analysis phases and treatment periods:

- SCREENING analysis phase starts with sign of Informed Consent and ends with first IMP administration;
- TREATMENT PERIOD 1 analysis phase/period starts with first IMP administration within Part A and ends with second IMP administration within Part A;
- TREATMENT PERIOD 2 analysis phase/period starts with second IMP administration within Part A and ends with the end of study.

There will be one treatment period within Part B. Analysis phases and treatment periods:

- SCREENING analysis phase starts with sign of Informed Consent and ends with first IMP administration;
- TREATMENT PERIOD analysis phase/period starts first study drug administration and ends with the end of study.

6. ANALYSIS METHODS

6.1. Participant Disposition

Disposition will be summarized descriptively using counts and percentages for All Patients separately for Part A and Part B. Subjects from Part A will be analysed by planned treatment sequence and overall. Subjects in the Part B will be analysed by planned treatment and in overall. The number and percentage of subjects entered into the study, enrolled in the study, randomized, and treated as well as number and percentage of subjects completed the study will be presented, together with number and percentage of subjects who prematurely discontinued from the study along with reasons for study discontinuation.

A listing of subject disposition status will be provided separately for Part A and Part B. The number of subjects in each analysis set will be summarized descriptively by treatment with counts and percentages separately Part A and Part B.

A listing of subject's inclusion to analysis sets will be provided separately for Part A and Part B. A subject's eligibility with inclusion/exclusion criteria completions or violations will be listed separately for Part A and Part B.

6.2. Protocol Deviations

The frequency and percentage of participants in each protocol deviation category will be summarised using the Safety Set. Participants from Part A will be analysed by planned treatment sequence and overall and by actual treatment during the study and overall. Participants in the Part B will be analysed by actual treatment and in overall.

All protocol deviations will be listed using the Safety Set.

6.3. Demographic and Baseline Characteristics

Demographic data and baseline characteristics, including age, gender, ethnicity, height, body weight and BMI will be summarised.

Demographic data will include gender, age and ethnicity. Baseline characteristics will include body weight, height and BMI.

Demographics and baseline characteristics will be summarized for all subjects overall and by treatment sequence (Part A) or treatment (Part B). Summary statistics will be generated for all continuous variables (i.e., age and weight, height and BMI) and the number and percentage of subjects within each category will be presented for all categorical variables (i.e., gender, race and ethnicity). The summary results for Part A and Part B will be based on the ITT Set.

6.4. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) of latest version (version will be clarified in the output footnotes), listed and summarized with descriptive statistics by System Organ Class (SOC) and Preferred Term (PT) separately for Part A (by treatment sequence based on ITT Set) and for Part B (by treatment based on ITT Set).

6.5. Prior and Concomitant Medication

Medications will be coded with the latest version of the WHO drug dictionary, listed and presented by ATC Class 2 and Preferred Term. Each medication will be classified as prior or concomitant.

Prior medication will be defined as any medication that was stopped prior to the start of taking the study drug/ taken during the 30-day period before signing the ICF. Prior medications will be summarised based on ITT Set by treatment sequence and overall for Part A and based on Safety Set by treatment and overall for Part B.

Concomitant medication will be defined as any ongoing medication used at the time of the start of taking the study drug /all medications taken after the study drug administration. Concomitant medications will be summarised based on Safety Set by treatment according to treatment period and overall. If the medication was ongoing during both treatment periods in Part A then it will be considered as concomitant for both treatments.

6.6. Safety Parameters

Unless specified in any of the furthers sections, analysis of Safety parameters will be based on Safety Set.

6.6.1. Adverse Events (AE)

All verbatim AE terms will be coded using MedDRA of latest version (version will be clarified in the output footnotes) and summarized by system organ class (SOC) and preferred term (PT).

A TEAE will be defined as any AE that has an onset on or after taking study drug, or any pre-existing condition that has worsened on or after taking study drug. For Part A each TEAE will be attributed to treatment period and treatment according to onset date.

The frequency and incidence of TEAEs will be summarised by SOC and PT by treatment according to treatment period and overall. Summaries will also include, but not limited to, relationship to study drug and maximum severity. The summary will be sorted by SOC and PT by frequency from the highest to the lowest. All AE data will be listed.

For each of the summaries produced at the participant level, multiple occurrences of the same event within a participant will be counted once in the summaries by SOC and PT; multiple occurrences of the same event within a participant will be counted once in the maximum severity category and/or maximum drug relationship category. If severity or relationship is found to be missing, the most severe occurrence will be imputed for that particular summary.

These summaries will also present the number of events that occurred, so multiple occurrences of the same event within a participant will all be accounted for in the maximum intensity category and maximum relationship category they were classed as.

6.6.2. 12-lead electrocardiogram (ECG)

Descriptive statistics will be calculated for absolute value and change from baseline (pre-dose) of each parameter by visit and by treatment according to treatment period and overall. Where multiple values are recorded at a timepoint for a subject, the mean of the values will be used in the summary statistics.

6.6.3. Vital signs

Vital signs will include systolic blood pressure, diastolic blood pressure, body temperature and heart rate. Descriptive statistics will be calculated for absolute value and change from baseline (pre-dose) of each parameter by visit, by timepoint and by treatment according to treatment period. Frequency tabulations of the abnormalities will be provided for each parameter by visit, by timepoint (including only timepoints with PI Interpretation) and by treatment according to treatment period and overall.

6.6.4. Clinical laboratory

Clinical Laboratory evaluation results (haematology and blood chemistry) will be summarised. Descriptive statistics will be calculated for absolute value and change from baseline (pre-dose) of each parameter by visit and by treatment according to treatment period. Categorical parameters (if applicable) will be summarised by counts and percentages of participants within each category by treatment group and visit. All presentations will be based on the International System of Units. The frequency of laboratory abnormalities will be tabulated.

Urinalysis data will be listed only. Clinical Laboratory listings will flag values that are outside normal reference ranges or markedly abnormal findings.

6.6.5. Physical Examination

Physical examination data will be summarised separately for Part A (by treatment sequence based on ITT Set) and for Part B (by treatment based on Safety Set).

6.7. Pharmacokinetic Analysis

The PK analysis is outside the scope of this analysis plan. That analysis will be described in a separate document.

6.8. Pharmacodynamic Analysis

PD analysis will be conducted for Part B only and will be based on Pharmacodynamic Set.

6.8.1. Descriptive PD analysis

Descriptive statistics will be calculated for absolute value and change from baseline (with baseline defined as the day -1 observation at each post-Capsaicin injection timepoint) for Scores (VAS or NRS) and Area measured (cm^2) by visit and by treatment according to treatment period.

The list of PD parameters includes:

- area of hyperalgesia (Primary Endpoint);
- measurement of pain score;
- pain score of hyperalgesia;
- area of allodynia;

- pain score of allodynia;
- area of flare.

6.8.2. PD Figures

Corresponding figures will be produced for each PD parameter (see Section 6.8.1):

- individual PD figures by timepoint separately for each patient.
- PD figures by treatment group (individual and combined – see below) and timepoint with the overall mean (± Standard Error) across patients.

6.8.3. PD Modelling

Two separate sets models will be fit to the data. Individual models will be fit per treatment group ("KLS 40 mg", "KLS 80 mg", "KLS 160 mg", "KLS 40 mg - GABA 17 mg", "KLS 80 mg - GABA 34 mg", "KLS 160 mg – GABA 68 mg", "Gabapentin 300 mg", "Placebo") to assess means and change from baseline in score and area for each PD parameter (see Section 6.8.1). Combined models will be fit using combined treatments (i.e. different doses of the same treatment combined –"KLS alone", "KLS-GABA", "Gabapentin", "Placebo") to assess differences in means and change from baseline in score and area for each PD parameter (see Section 6.8.1).

Individual models (by treatment):

The MMRM model will contain terms for the actual treatment group (and timepoint and will contain baseline Score / Area as a covariate and subject as a random effect.

An unstructured covariance matrix will be assumed. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: toeplitz with heterogeneity, autogressive with heterogeneity, toeplitz, and autoregressive.

Least squares (LS) means will be reported by timepoint along with corresponding 95% confidence intervals (CIs).

The model will be fit separately for each treatment group, for the following dependent variables:

- Score / Area for each PD parameter
- Change in score / Area for each PD parameter

Combined models (treatment as a term; comparing against placebo):

The MMRM model will contain terms for actual combined treatment group and timepoint and will contain baseline Score / Area as a covariate and subject as a random effect.

An unstructured covariance matrix will be assumed. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: toeplitz with heterogeneity, autogressive with heterogeneity, toeplitz, and autoregressive.

LS means will be reported by timepoint for each treatment group; the difference in LS means between each dose arm and placebo will be presented along with corresponding 95% CIs.

The modelling will be conducted separately for the following dependent variables:

- Score / Area for each PD parameter
- Change in score / Area for each PD parameter

6.8.4. Pharmacokinetic/Pharmacodynamic Statistical Analysis

The relationship between the PK parameters and PD parameters will be investigated by estimating the Pearson and Spearman correlation coefficients by treatment. This analysis will be conducted for Part B only based on PK population.

7. HANDLING OF MISSING OR INCOMPLETE DATA

Unrecorded values, other than PD baseline values, will be treated as missing. Efforts will be made to prevent this from occurring. For complete missing visits, the missing data will be treated as missing at random and will not be imputed in the statistical analysis except for partial dates.

As mentioned in Section 3, any missing PD baseline values at the 30-minute, 60-minute and 90-minute post-Capsaicin timepoints will be imputed using Linear Interpolation. Missing PD baseline values at the 15-minute and 120-minute post-Capsaicin timepoints will be imputed using NOCB and LOCF, respectively. If there are any missing PD baseline values, the imputed values will be clearly flagged in the listings. Separate summary statistics tables will be created for the PD data with non-imputed values and the PD data with imputed values.

7.1. Prior and Concomitant Medication Dates

Partial dates for any prior and concomitant medications recorded in the eCRF will be imputed using the following convention:

- If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month.
- If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.

The recorded partial date will be displayed in listings. No imputation will be performed for completely missing start and end dates.

7.2. AE Start and End Dates

The eCRF allows for the possibility of partial dates (i.e. only month and year) to be recorded for AE start and end dates; that is the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time of onset and the duration of the event:

- Missing Start Day: First of the month will be used unless this is before the start date of first study treatment; in this case the study treatment start date will be used and hence the event is considered treatment emergent.
- Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study completion; in this case the study stop date will be used.

Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

8. CHANGES FROM THE PROTOCOL-PLANNED ANALYSES

Primary endpoint of Part B has been changed to “Reduction in area of hyperalgesia” from “Analgesia/reduction in pain”.

9. TABLE AND LISTING SHELLS

TFL Shells will be provided as a separate document. The TFLs listed and the corresponding numbering may be subject to alteration.