ID: CLIN-0012-STA19-01
Title: Safety and Efficacy of SX600 Administered by Lumbosacral Transforaminal Epidural Injection for Radicular Pain (SALIENT)
NCT: 03952377

Statistical Analysis Plan

SAP Version 1.1 13 Jul 2022
SAP Version 1.0 06 Apr 2022

Documentation of Statistical Methods

A DOUBLE- BLINDED, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP PHASE I/II, FIRST-IN-HUMAN STUDY TO ASSESS THE SAFETY AND EFFICACY OF TWO DOSES OF SX600 ADMINISTERED BY LUMBOSACRAL TRANSFORAMINAL EPIDURAL INJECTION IN PATIENTS WITH RADICULAR PAIN SECONDARY TO LUMBAR INTERVERTEBRAL DISC HERNIATION.

Statistical Analysis Plan

VERSION: AMENDMENT FINAL 1.1
DATE OF PLAN:

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STUDY DRUG / PROTOCOL ID:
SX600 / CLIN-0012-STA01-19

PREPARED FOR:

SpineThera Australia Pty. Ltd

Sponsor: SpineThera Australia Pty. Ltd
Protocol Number: CLIN-0012-STA01-19
SAP Version and Date: Amendment Final 1.1, 13JUL2022

Approval Signatures: SpineThera Australia Pty. Ltd

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Contents

ABBREVIATIONS

AE	Adverse event
ALT	Alanine Transaminase
APPT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
ATC	Anatomic Therapeutic Class
AUC	Area Under the Curve
BP	British Pharmacopeia
BUN	Blood urea nitrogen
CK	Creatine Kinase
CRO	Clinical Research Organization
CSR	Clinical study report
DXA	Dexamethasone acetate
ECG	Electrocardiogram
EDC	Electronic Data Capture
GGT	Gamma-Glutamyl Transferase
IMP	Investigational Medicinal Product
ITT	Intent-to-treat
LDH	Lactate Dehydrogenase
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Medical Affairs
mITT	Modified Intent-to-treat
MRT	Mean Residence Time
NHMRC	National Health and Medical Research Council
NRS	Numeric Rating Scale
PP	Per protocol
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
PT	Prothrombin Time
Q1	First Quartile
Q3	Third Quartile
QoL	Quality of Life
RBC	Red Blood Cell
SAE	Serious adverse events
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SI	System of Units
SD	Standard Deviation
SOC	System Organ Class
SRC	Safety review committee
TEAE	Treatment Emergent Adverse Effects
TF-EI	Transforaminal epidural injection
TT	Thrombin Time
ULN	Upper limit of normal
WBC	White Blood Cell

1 INTRODUCTION

The statistical analysis plan (SAP) details the planned analysis required to satisfy the Clinical Study Report (CSR) of study number CLIN-0012-STA01-19: A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Phase I/II, First-in-Human Study to Assess the Safety and Efficacy of Two Doses of SX600 Administered by Lumbosacral Transforaminal Epidural Injection in Patients with Radicular Pain Secondary to Lumbar Intervertebral Disc Herniation. The content of this SAP is based on the protocol dated 17JUN2020 REV06 and on subsequent modifications made to the study due to slow enrollment of subjects.

Revision Chronology:

1.0	06APR2022	Original
1.1	12JUL2022	Amendment

Mock shells for tables, listings, and figures will be included in a separate document: Mock Shells, Protocol Number CLIN-0012-STA01-19.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objectives

- To assess the safety of two doses (12.5 mg and 25.0 mg DXA) of Dexamethasone acetate microspheres for extended-release injectable micro-suspension, SX600 (IMP) administered by transforaminal epidural injection to the lumbosacral epidural space at the L4- L5, L5-S1 level, or the S1 nerve root, compared to Placebo (0.9% Sodium Chloride Injection, BP), in the treatment of radicular pain resulting from inflammatory changes in a single affected nerve root secondary to lumbar disc herniation
- To assess the efficacy of two doses (12.5 mg and 25.0 mg DXA) of Dexamethasone acetate microspheres for extended-release injectable micro-suspension, SX600 (IMP) compared to Placebo (0.9% Sodium Chloride for Injection, BP), to alleviate the radicular pain from a single nerve root involvement secondary to lumbar disc herniation.
- To measure the systemic pharmacokinetics of two doses (12.5 mg and 25.0 mg) of Dexamethasone acetate microspheres for extended-release injectable micro-suspension, SX600 (IMP) from a single transforaminal epidural placement of 1.0 mL

2.1.2 Secondary Objectives

- To assess changes at 30-day intervals in functional outcomes following treatment
- To assess Patient Global Impression of Change
- To assess any decrease in the use of other health services
- To assess the time to loss of response in the Responders

2.2 Study Endpoints

2.2.1 Safety Endpoints

The Safety outcome will be assessed by:

- Adverse events from treatment day through study conclusion.
- Serious adverse events (SAEs) considered product or procedure-related.
- Neurological consequences of the transforaminal epidural injection (TF-EI).
- Non-laboratory adverse events following TF-EI.
- Laboratory adverse events following administration of IMP/Placebo.

Safety endpoints are as follows:

- Incidence of treatment-emergent AEs and SAEs grouped by body system.
- Changes from Baseline in clinical laboratory, urinalysis, vital signs, and ECG parameters to discharge and follow-up
- Changes from pre-dose physical exam findings to Follow-Up

2.2.2 Primary Efficacy Endpoint

- The proportion of 50% Responders at 60 days post-dosing, where a 50% Responder is defined as a patient with 50% or greater improvement from baseline in mean Worst Daily Leg Pain.

2.2.3 Secondary Efficacy Endpoints

- The proportion of patients who are 50% Responders (defined as having 50% or greater improvement in Mean Worst Daily Leg Pain score compared to baseline) at each of the other scheduled time points (14, 30, 90, 120, 150, and 180 days) post-dosing.
- Change in functional outcomes as measured by Patient's Global Impression of Change, Oswestry Disability Index and SF-36 QoL questionnaire at each visit.
- The proportion of patients who are 30% Responders (defined as having 30% or greater improvement in Mean Worst Daily Leg Pain) at each of the other scheduled time points (14, 30, 60, 90, 120, 150, and 180 days) post-dosing.
- Time to loss of response, in the subset of patients who are 50% Responders at Day 14 (50% or greater improvement in Mean Worst Daily Leg Pain).

2.2.4 Pharmacokinetic Parameters

- The maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}).
- The area under the plasma concentration versus time curve from time 0 (predose) to time infinity (AUC_{inf}).
- AUC from time 0 to time of last measurable plasma concentration (AUC_{last}).
- The percentage of the AUC that is extrapolated beyond the last measurable concentration (AUC_{ext}).
- The elimination rate constant (lz).
- The apparent systemic clearance (CL/F).
- Mean residence time (MRT).
- Apparent volume of distribution.
- Terminal phase (Vz/F), and terminal-phase half-life ($t_{½}$)

3 STUDY DESIGN

3.1 Study Design and Population

This first-in-human study is a Phase I/II, double-blind, parallel-group, randomized, placebo-controlled multi-centre trial. The study was originally designed to include 180 patients randomized 1:1:1 to receive the IMP (Dexamethasone acetate microspheres for extended-release injectable micro-suspension, SX600 at 12.5 mg or 25.0 mg) or Placebo (0.9% Sodium Chloride for Injection, BP) via transforaminal epidural injection to the lumbosacral epidural space at the L4- L5, L5-S1 level, or the S1 nerve root, as an outpatient procedure. The targeted patient total was decreased from 180 to 120 on 12 May 2021, which was documented in each sites Investigator Site File. The enrollment was stopped at 55 treated participants due to slow enrollment and the impact of Covid-19.

Patients will be screened to ensure they meet all inclusion and none of the exclusion criteria. Patients are considered enrolled in the study upon signing the Informed Consent Form by both the subjects and a study investigator (who is also a clinician). Informed Consent must be obtained prior to performing any study-related procedures. Section 21 of the protocol provides a complete list of inclusion and exclusion criteria.

Each patient will be followed for 180 days for assessment of any treatment-emergent adverse effects, status of radicular pain, functional assessments, and the use of health care services. Safety will be assessed through physical examination, vital signs, laboratory tests, and assessments of adverse events (AEs).

The study was originally expected to enroll over a period of 9 months. Each patient was expected to be in the study for 7 months. The total duration of the study was expected to be 19 months (9 months enrollment + 7 months follow-up + 3 months reporting). The 55 enrolled participants were enrolled over a two and a half year period and will be followed for the originally defined 180 days.

Systemic pharmacokinetics of dexamethasone (active moiety) were planned to be evaluated in a subset of approximately 60 patients (across IMP and placebo groups). By the time when the study is terminated by the sponsor, only 4 pharmacokinetic sub-study participants were enrolled.

3.2 Randomization and Blinding

Following the original plan in the protocol, patients who are eligible for enrollment into the study will be evaluated for randomization eligibility at Study Visits 1 and 2. The Biostatistician will prepare the randomization schedule, which will be managed by PCI Melbourne . Patients will be randomly assigned in a 1:1:1 ratio to one of two doses of SX600 (12.5 mg for the low-dose group, or 25.0 mg for the high dose group,) or Placebo (0.9% Sodium Chloride for Injection, BP or equivalent), with a planned final assignment of 60 patients/group. The list of randomized treatment assignments will be prepared by statisticians assigned to the study. The randomization number will be collected in the Electronic Data Capture (EDC) System. Refer to the Randomization Materials Specification Form for further details of randomization.

At the site, the physician who performs the TF-EI will be unblinded to the treatment assignment, but a second physician and study staff who are responsible for all subsequent patient assessments

must remain blinded to the treatment assignment. Since the reconstituted active IMP produces an opaque white suspension, it is not possible to blind the injector with a matching placebo solution for epidural administration, and hence 0.9% Sodium Chloride for Injection, BP has been chosen for the placebo comparator.

3.3 Sample Size Considerations

Limited data are available in the literature on which to base sample size/power considerations. In the study conducted by Ghahreman (Ghahremen, 2010) [(1)], the primary endpoint was the proportion of patients who achieved a 50% or greater reduction from baseline at 30 days. In the steroid arm, the observed response rate was 54%. In the control arms of this study, the response rates were 7%, 13%, 19%, and 21%. Based on these results, the assumed true response rates are 50% (active) and 20% (placebo). Using a two-sided comparison of binomial proportions at the alpha=0.05 level of significance, a sample size of 60 patients per arm will provide 94% power. If the true active arm response rate is 50% and the true placebo response rate is 25%, then the power of the study is decreased to 81%.

Due to enrollment difficulties and the impact of Covid-19, the study is being terminated with a total sample size of 55 randomized patients. As a result, the originally planned efficacy analyses will not be conducted. Instead, the results of the study will be evaluated descriptively.

3.4 Safety Review Committee

A Safety Review Committee (SRC) will be assigned the responsibility of safety of the participants and will provide medical oversight and expertise to the Sponsor and sites concerning the continuation, modification, or termination of the trial. The SRC will monitor patient safety through pre-defined, periodic review of the clinical study safety data as well as relevant background knowledge about the disease, test agent/device, or participant population under investigation.

The SRC will provide safety oversight of the study per the National Health and Medical Research Council (NHMRC) Guidance on Data Safety Monitoring Boards 2018. The SRC will be composed of three to four members including a Clinical Research Organization (CRO) independent medical monitor, a biostatistician, one Investigational Site clinician and the Sponsor Chief Medical Officer. The study is double-blinded but the SRC can request unblinding to make determinations regarding study outcome.

Details of the SRC, including committee member names and responsibilities, timing of the SRC reviews, data to be reviewed, and halting criteria will be documented separately in the SRC Charter.

3.5 Interim Analysis

There are no interim analyses planned for this study.

3.6 Timing of Analyses

The final analysis will occur when the last patient completes the end-of-study visit. A topline analysis of the Worst Daily Leg Pain will be assessed at the time that the last enrolled patient completes their 90 day visit prior to full database lock. This top line analysis will include the analyses on the primary endpoint time of 60 days and a secondary endpoint time of 90 days.

4 DATA ANALYSIS CONSIDERATIONS

All analyses will be conducted based on SAS 9.4 or higher.

All data in the database will be presented in by-patient data listings.

Unless otherwise stated, all listings will be sorted by treatment group, center ID, patient number, and assessment date (and time, if available).

Unless stated otherwise, continuous data will be summarized by treatment group based on n, mean, median, standard deviation (SD), first quartile (Q1), third quartile (Q3), minimum value, and maximum value.

Unless stated otherwise, categorical data will be summarized by treatment group using n and percentage based on the number of non-missing values. The number of missing values will be presented as a separate category with no percentage, but only if one or more patients are missing data. Counts of zero will be presented without percentages.

The following levels of precision for reporting data will be applied:

- Mean, Median, Q1, and Q3: one additional decimal place to that reported for Minimum and Maximum
- SD: two additional decimal places than the Minimum and Maximum
- Percentages: reported to one decimal place

All data up to the time of study completion/withdrawal from the study will be included in the analysis, regardless of duration of treatment.

Numbering for data displays will be based on ICH E3[(2)].

4.1 Stratification and Covariates

There are no formal plans for analysis stratification.

4.2 Evaluation of Subgroups

There are no formal plans for examining subgroups.

4.3 Multiple Comparisons and Multiplicity

No formal statistical hypothesis tests will be conducted.

5 GENERAL DATA HANDLING CONVENTIONS

5.1 Assigned and Actual Treatment

As described in Section 3.2, patients will be randomized to placebo or SX600 (low-dose or high-dose). The randomized treatment assignment will be used for listings as well as selected analyses indicated for the Intent-to-Treat population.

Actual treatment groups are based on exposure data to treatment received, and will be the basis for all safety analyses.

The following three treatment groups (actual or as-randomized) are planned in this study:

- Placebo
- SX600 at 12.5 mg DXA
- SX600 at 25.0 mg DXA

5.2 Reference Dates

The following reference definitions will be applied for this study:

- Screening date is defined as the eCRF provided date on which a patient was screened for trial entry.
- Day 0 is the date on which the patient is randomized to study treatment (i.e., Randomization date), and when TF-EI is performed (i.e., Intervention date).
- Treatment date is defined as the date of dose of study drug.
- The calculation of age will use the informed consent date as its reference date.
- Efficacy data will use the treatment date as a reference date.
- Study day will be based on treatment date as a reference date.

5.3 Definitions

The following definition will be applied for this study:

50% Responder: a patient with 50% or greater improvement in Mean Worst Daily Leg Pain score compared to baseline.

Mean Worst Daily Leg Pain score is based on the Numeric Rating Scale (NRS) as described in Section 7.1.

30% Responder: a patient with 30% or greater improvement in Mean Worst Daily Leg Pain score compared to baseline.

5.4 Study Day and Duration Variables

Reference date calculations will generally be defined as the following, assuming nonmissing dates:

- Date of interest – reference date.

If either date is missing, reference date calculations will not be performed. Date imputation will be performed as identified in Section 5.7.

For instance, study day will be based on the treatment date as the reference would either have a negative value if collected before dosing, zero if collect on the day of drug dosing, or a positive value if collected after the day of drug dosing.

Duration of time is dependent on reference dates and will be calculated in a manner similar to that of the reference date calculation, assuming that dates of interest will strictly follow reference dates

(e.g. no negative values). For example, duration on study is defined as the end of study date – screening date. Patients still participating in study follow up at the time of analysis will use imputed end of study dates as described in Section 5.7.

5.5 Study Time Periods

Safety reporting will be classified by the following study periods for analysis:

Pre-therapy is defined as the period prior to a patient's treatment date.

On-therapy is defined as the period between a patient's treatment date to the end of study, including the TF-EI procedure.

5.6 Baseline and Post-Baseline Changes

Unless stated otherwise, baseline and post-baseline change values will be based on the following:

For vital signs, mean worst daily leg pain, SF-36, and Oswestry disability Index, baseline will be the value collected on the Day 0 visit. For clinical laboratory tests and 12-lead ECG, baseline will be the last nonmissing value collected prior to or on the treatment date and time. Post-baseline values will be those collected after defined baseline date.

For Mean Worst Daily Leg Pain, baseline is defined as the calculated Mean Numeric Rating Scale (NRS) score of 5 days recorded using the patient electronic diary for the 10 days preceding the Day 0 visit. The calculation method for Mean Worst Daily Leg Pain is as described in Section 7.1.

Change from baseline is defined as: value – baseline value.

Percentage change from baseline is defined as: (value – baseline value)/baseline value X 100%.

Most extreme change: The maximum most extreme change will be based on the maximum post-baseline value; the minimum most extreme change will be based on the smallest post-baseline value. This calculation will consider all assessments collected during the on-therapy period, scheduled or unscheduled.

5.7 Imputation of Partial Dates

Appendix 1 details partial date conventions that will be used for the determination of treatment-emergent adverse events, prior and concomitant medications, and procedures / therapies subsequently used after a rescue medication is taken / administered.

End of Study Date

Missing study end dates will not necessarily be imputed at the end of the study. However, in the event of an ongoing reporting need, end of study dates may be imputed as the earliest of the data cutoff date, date of death, or last date recorded on the CRF.

5.8 Multiple Assessments and Visit Windows

Nominal visits (e.g. those identified by the study CRF) will be the basis of summarization and statistical analysis. Unscheduled data may be included in summaries of most extreme and baseline values, summaries of specific abnormalities any time post-baseline, and patient data listings.

5.9 Missing Data

Missing data imputation for the primary efficacy endpoint is described in Section 0; AE and concomitant medication date imputations are described in Section 5.7. Otherwise, missing data will not be imputed.

6 STUDY PATIENT DATA

6.1 Analysis Populations

Intention-to-treat (ITT) Population: Defined as all randomized patients. Patients will be included in the treatment group to which they were randomized, regardless of treatment received.

Safety Population (SAF): Defined as all randomized patients who proceed to TF-EI (includes patients with attempted but halted or failed TF-EI). Patients will be included in the treatment group based on the treatment that was received. All safety analyses will be conducted in the Safety Population.

Modified Intention-to-treat (mITT) Population: Defined as all randomized treated patients who receive IMP or placebo by TF-EI. Patients will be reported based on randomized treatment assignment. All efficacy analyses will be conducted in the mITT Population.

Per-protocol Population (PP): Defined as all randomized patients who met all inclusion/exclusion criteria, did not have any significant protocol deviations, complied with the assigned study treatment, returned to the study site for the Primary Efficacy visit within the specified window, or discontinued study early due to lack of treatment effect or received therapy other than study specified drug during the study. Patients will be reported based on actual treatment received. The primary endpoint efficacy analysis will be repeated in the PP population. In order to minimize bias, the PP population will be defined prior to unblinding.

PK population: Defined as all patients who received IMP or placebo and with intensive blood collections in the first 24 hours (approximately 60 subjects). All PK analyses will be conducted in the PK population.

6.2 Patient Disposition

Summaries of analysis population membership and final patient status (completed or withdrawn), including reasons for withdrawal, will be produced based on all patients enrolled. Data will be presented by treatment group as well as overall for the study.

Randomization details, analysis populations, and final patient disposition status will be listed.

6.3 Protocol Deviations

Protocol deviations will be identified and classified as major or minor (violations) before the database is locked. Protocol deviations may include but are not limited to:

- Visit / Procedure / Assessment outside protocol window
- Visit / Procedure / Assessment not done
- Inclusion / Exclusion

- Informed Consent
- Study drug administration
- Study restrictions
- Other

Protocol deviations will be summarized by treatment group and overall for the study.

A listing of protocol deviations will be provided.

6.4 Demographic and Baseline Characteristics

Patient demographics will be summarized and listed for the ITT Population. These will include age, sex (Male / Female), ethnicity (Hispanic or Latino / Not Hispanic or Latino / Not reported / Unknown), race (Black or African American / American Indian or Alaska Native / Asian / Native Hawaiian or Pacific Islander / White / Other / Not reported), baseline height (cm), baseline weight (kg), and BMI (kg/m^2). Years since radicular pain associated with lumbar intervertebral disc herniation will be calculated from the start date of pain as reported on the eCRF to the date of screening and will be summarized using descriptive statistics. Leg raise (degree) assessments at Screening will be included as baseline characteristics and will be summarized. Data will be presented by treatment group as well as overall for the study.

The following conversions and equations will be used as applicable:

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m^2) = weight(kg)/[height$(m)^2$]

6.5 Medical History

Medical History will be coded based on the Medical Dictionary for Regulatory Affairs (MedDRA) for reporting by system organ class (SOC) and preferred term (PT) and will be summarized in descending order of overall incidence. A listing of medical history will be provided for all patients in the ITT population.

6.6 Prior and Concomitant Medication

The incidence of medication use will be summarized by WHO Drug Dictionary anatomic therapeutic class (ATC) Level 2 classification (i.e., therapeutic main group) and preferred name. A patient will be counted only once at each level of reporting. Prior medications are those which have been identified to have been discontinued prior to the treatment date (e.g., taken exclusively during the pre-therapy period). Concomitant medications are those which have been identified to have been taken at any point during the on-therapy period. This includes rescue therapies. Prior and concomitant medication use will be summarized separately and presented by treatment group.

All prior and concomitant medication data will be listed for patients in the ITT population and will include the verbatim and preferred drug name and ATC Level 2.

6.7 Concomitant Procedure / Therapy

The incidence of concomitant procedure / therapy will be summarized. A patient will be counted only once per procedure / therapy. Concomitant procedures / therapies are those which have been identified to have been taken at any point during the on-therapy period. Prior and concomitant medication use will be summarized and presented by treatment group.

All concomitant procedure / therapy data will be listed for patients in the ITT population. A listing for recovery procedures post TF-EI will be produced for the ITT population.

6.8 Study Drug Exposure and Compliance

The number and percentage of patients who attempted, halted, or failed the TF-EI procedure will be summarized in the ITT Population. For patients who complete the TF-EI procedure, the number and percentage receiving IMP per the delivery protocol will also be tabulated. The number and percentage of mis-dosed patients will also be summarized.

Listings of planned and actual treatments, and compliance with TF-EI procedure and delivery protocols of drug administration will be produced for the ITT population.

7 EFFICACY

All efficacy analysis reporting will be based on the mITT Population. Additionally, the primary efficacy analysis will be repeated in the PP Population.

7.1 Primary Efficacy Endpoint and Analyses

Efficacy assessments will be based on the categorical measure of 50% Responder, defined as a patient with 50% or greater improvement in mean Worst Daily Leg Pain (WDLP) score compared to baseline. The mean WDLP score will be derived from the E-Diary recordings entered by the subjects, [redacted]

[redacted]

[redacted]

Incomplete Mean Worst Daily Let Pain score:
All subjects with 5 or more Worst Daily Leg Pain scores recorded in the 10 days preceding the study visit will be included in the analysis. If a subject has less than 5 scores preceding a visit, the subject will not be included in the efficacy assessment for that particular visit. If that same subject has provided 5 or more scores in the 10 days preceding a later visit, the subject will be included in the efficacy assessment for the later visit.

Early Withdrawal:
If a subject withdraws from the study before their 180 day visit, the subject will be included in analyses up to the time that they either stop attending follow-up visits or their consent was withdrawn.

Rescue Medication:
[redacted] If a patient has failed rescue medication (defined as taking rescue medication for >14 days, taking rescue medication in more than one episode, or receiving treatment beyond the rescue medication regimen defined in the protocol [redacted] then the patient will be deemed a non-responder at all timepoints after exceeding the allowed rescue medication, on the day the second episode of Rescue Medication began, or after receiving the additional treatment. The patient will be included in all subsequent timepoints as a non-responder, whether withdrawn or not. [redacted]

7.1.1 Mean Worst Daily Leg Pain Score: Proportion of Patients with 50% or Greater Improvement from baseline at 60 Days Post-Dosing (Primary Endpoint)

The number and percentage of patients experiencing a 50% or greater improvement from baseline in mean Worst Daily Leg Pain score (i.e. the number and percentage of 50% Responders) will be tabulated for each treatment group. The primary analysis will descriptively compare the proportions of 50% Responders in each of the three arms. The "study success" criterion is defined as the observed percentage of 50% Responders in the high dose group being at least 10 percentage points greater than the corresponding rate in the placebo group.

Listings of Worst Daily Leg Pain will be provided for the modified intent-to-treat population.

7.2 Secondary Efficacy Endpoints and Analyses

The results for all secondary endpoints will be presented descriptively.

7.2.1 Mean Worst Daily Leg Pain Score: Proportion of Patients with 50% of Greater Improvement at 14, 30, 90, 120, 150, and 180 Days Post-Dosing

A secondary efficacy endpoint for this study is the proportion of patients with a 50% or greater improvement from baseline in mean Worst Daily Leg Pain score at 14, 30, 90, 120, 150, and 180 days post-dosing in the high dose group compared to placebo and low dose group compared to placebo. The number and percentage of patients experiencing a 50% or greater improvement from baseline in mean Worst Daily Leg Pain score will be tabulated for each treatment group and time point for the mITT population.

7.2.2 Change from Baseline in Mean Worst Daily Leg Pain Score

A graphical display of mean observed Daily Leg Pain values over time by treatment group for the mITT population will be prepared.

7.2.3 Patient's Global Impression of Change

Changes in Patient's Global Impression of Change is a secondary efficacy endpoint for this study, where PGI is assessed using the following 7-point scoring classification:

- Very Much Improved = 1
- Much Improved = 2
- Minimally Improved = 3
- No Change = 4
- Minimally Worse = 5
- Much Worse = 6
- Very Much Worse = 7

Number and percentage for each Observed Patient's Global Impression of Change values (i.e. number and percentage of patients for each rating on the PGIC 7-point scale) will be summarized at each visit for each treatment group in the mITT population. In addition, the number and percentage of patients classified as improved (values of 1, 2, and 3) and the number and percentage of patients classified as not worsened (values of 1, 2, 3, and 4) will be summarized at each visit for each of the three treatment groups for the mITT population.

Listings of Patient's Global Impression of Change values will be provided for the modified intent-to-treat population.

7.2.4 Oswestry Disability Index

Changes in Oswestry Disability Index is a secondary efficacy endpoint for this study. The Oswestry Disability Index will be calculated as:

$$Oswestry\ Disability\ Index = \frac{Total\ Score}{Total\ Possible\ Score} \times 100\%$$

For example, it all 10 questions are answered and the total score is 16, then the Oswestry Disability Index = 16/50 x 100% = 32%. If one question is missed or not applicable, the score is calculated as 16/45 x 100% = 35.5%.

Observed Oswestry Disability Index values and their change from baseline will be summarized at each visit. The number and percentage of patients for each of the five Oswestry Disability Index categorizations will be tabulated according to treatment group and timepoint in the mITT population.

Oswestry Disability Index interpretation of scores will be assessed as:

- 0% to 20%: minimal disability
- 21% to 40%: moderate disability
- 41% to 60%: severe disability
- 61% to 80%: crippling back pain
- 81% to 100%: these subjects are either bed-bound or exaggerating their symptoms

Listings of Oswestry Disability Index values will be provided for the modified intent-to-treat population.

7.2.5 SF-36 QoL Questionnaire RAND version

The SF-36 QoL RAND survey is listed in Reference, Section 11. Changes in SF-36 QoL RAND version domains are secondary efficacy endpoints for this study. Observed SF-36 QoL domain values and their change from baseline will be summarized at each visit for each treatment in the mITT population. Domains will be calculated as described in Appendix 2. The eight health concepts of SF-36 QoL are:

- Physical Functioning (PF); sum of CRF questions: 3-12
- Role Physical (RP); sum of CRF questions: 13-16
- Bodily Pain (BP); sum of CRF questions: 21-22
- General Health (GH); sum of CRF questions: 1, 33-36
- Vitality (V); sum of CRF questions: 23, 27, 29, 31
- Social Functioning (SF); sum of CRF questions: 20, 32
- Role Emotional (RE); sum of CRF questions: 17-19
- Mental Health (MH); sum of CRF questions: 24-26, 28, 30

Listings of the scored SF-36 QoL RAND version domain values will be provided for all patients. In addition, summary statistics for each of the eight domains will be provided at each visit for each treatment group.

7.2.6 Proportion of Patients with 30% of Greater Improvement at 14, 30, 60, 90, 120, 150, and 180 Days Post-Dosing

The same type of analyses as described in 7.2.1 will be conducted at each time point: 14, 30, 60, 90, 120, 150, and 180 days, but using the proportion of subjects with a 30% or greater improvement from baseline in the pain score.

7.2.7 Time to loss of response

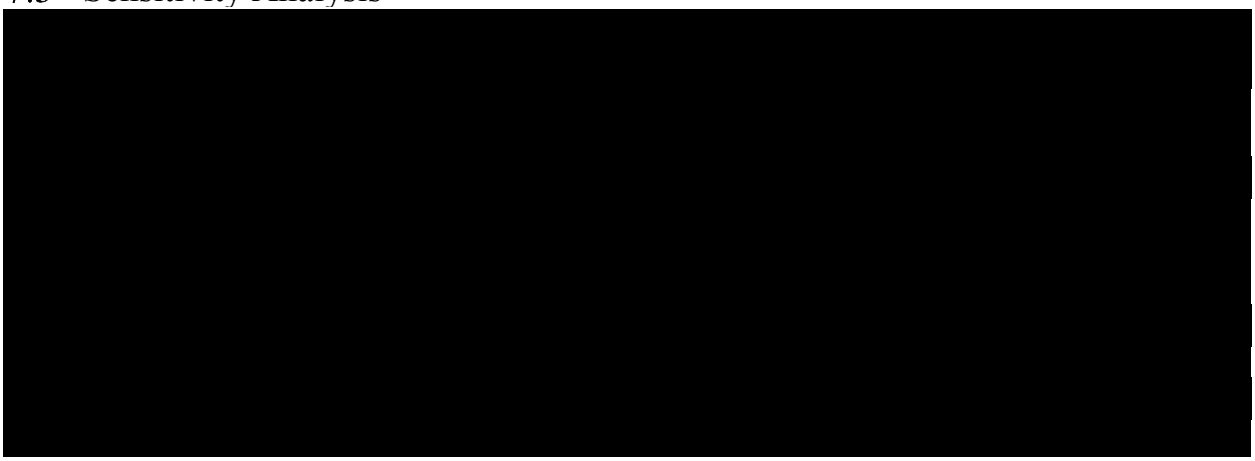
A time to loss of response analysis will be conducted for the subset of patients who have 50% or greater improvement in Mean Worst Daily Leg Pain at Day 14.

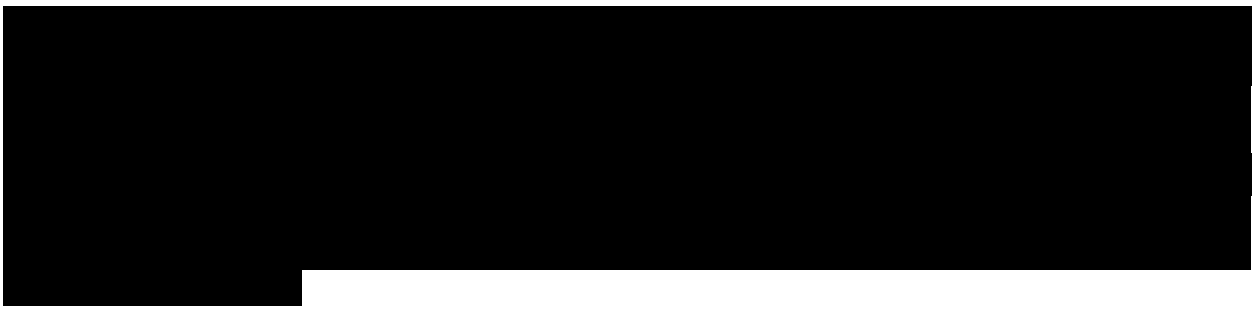
Loss of response will be defined as observing a <50% improvement from Baseline following the Day 14 visit. If a patient with a response at Day 14 does not meet the definition for loss of response at any time after Day 14, then the patient will be censored as of their last date in the study. Time to loss of response will be calculated in days as follows:

Time to loss of response (days) = [Date of first occurrence of <50% improvement from Baseline following Day 14; Or Date of Withdraw; Or Date of Last known still in the study; Or Date of concomitant medication/procedure/therapy starts after the failure of the rescue medication] – [Date of Day 14 Visit].

Time to a loss of response will be summarized based on Kaplan-Meier methods. The number and percentage of patients identified to have had a loss event and those who were censored will be displayed. The median time to loss of response and its corresponding 95% CI will also be produced. All analyses will be performed by treatment group.

7.3 Sensitivity Analysis





8 PHARMACOKINETICS/PHARMACODYNAMICS

A dexamethasone concentration over time profile for PK population will be plotted over the period from pre-dose sample collection up to 24 hours post to the IMP injection.

All dexamethasone concentrations will be provided in patient data listings for the Safety population. A separate descriptive summary of the dexamethasone concentrations by treatment group at each scheduled visit will be performed on the Safety population. A dexamethasone

concentration over time profile for the Safety population will be plotted over against all scheduled visits from Pre-dose to Day 180 where the data is available.

The analysis of PK and PD data will be described in the Clinical Study Report as there were so few PK patients enrolled.

9 SAFETY

All safety analysis reporting will be based on the Safety Population.

9.1 Adverse Events

Adverse events (AEs) will be recorded from the treatment date until the end of study. AEs will also be assessed for seriousness, severity relatedness, and expectedness. AEs will be considered treatment-emergent if their onset occurs within the on-therapy period. Any missing severity assessments will be assumed to be severe, missing relationship assessments will be assumed to be related, and missing seriousness assessments will be assumed as serious.

An overview of treatment-emergent AEs (TEAEs) will be produced, including counts and percentages of patients with any incidences of: TEAEs, TEAEs related to study treatment (i.e., either definitely, probably, or possibly related), TEAEs related to TF-EI procedure (i.e., either definitely, probably, possibly related or not related), severe or worse adverse events (i.e., either severe, life-threatening, or fatal), TEAEs leading to study withdrawal, serious adverse events (SAEs), and fatal SAEs.

Adverse events will be coded based on the Medical Dictionary for Regulatory Affairs (MedDRA) for reporting by system organ class (SOC) and preferred term (PT) in descending order of overall incidence. For these summaries, patients will be counted once within each SOC and PT.

Summaries of adverse events by SOC and PT will include the following types:

- TEAEs;
- TEAEs related to study treatment (including definitely, probably, or possibly related events, and events with missing relatedness);
- TEAEs related to TF-EI procedure (including definitely, probably, or possibly related events, and events with missing relatedness);
- Severe or worse TEAEs (including severe, life-threatening, or fatal events, and events with missing severity);
- SAEs; and
- TEAEs leading to study withdrawal;

A summary of TEAEs by SOC, PT, and maximum severity will also be prepared. Maximum severity will be based on the following scales:

- Fatal
- Life-Threatening
- Severe
- Missing

- Moderate
- Mild

A comprehensive listing of all AEs will be provided in a by-patient data listing. In addition, the following listings will be provided:

- TEAEs related to study treatment (including definitely, probably, or possibly related events, and events with missing relatedness);
- SAEs;
- TEAEs leading to study withdrawal; and
- Fatal AEs.

9.2 Clinical Laboratory Evaluations

Clinical chemistry and hematology parameters will be reported based on the International System of Units (SI). The following laboratory evaluations will be reported in data summaries:

Hematology: [redacted]

Coagulation: [redacted]

Clinical Chemistry (non-fasting serum): [redacted]

Urinalysis: [redacted]

Observed values and changes from baseline for laboratory evaluations will be summarized at each visit and for most extreme maximum and minimum changes.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively and will be used for summary statistics.

Laboratory data which is not graded will also be summarized in shift tables of baseline to each visit and most extreme change based on range categories of low (below lower limit of normal [LLN], normal, and high [above upper limit of normal [ULN]).

All laboratory parameters will be provided in patient data listings for the SAF population. Virus serology (HIV, Hepatitis A, Hepatitis B, Hepatitis C) will be provided in patient data listings for the SAF population. Pregnancy results (serum and urine) will be provided in patient data listings for the SAF population. Results from urine drug screening (cocaine, cannabinoids, opiates,

benzodiazepines, and amphetamines) will be provided in patient data listings for the SAF population.

9.3 Other Safety Evaluations

9.3.1 Vital Signs

Vital signs include: respiratory rate (breaths per minute); temperature (°C); systolic and diastolic blood pressure (mmHg); pulse rate (beats/min). Observed values and changes from baseline for vital signs will be summarized at each visit and time point, as well as for most extreme minimum, and most extreme maximum changes.

All vital signs data will be presented in data listings for all patients in the SAF.

9.3.2 Electrocardiogram (ECG)

Electrocardiogram (ECG) parameters include: HR (beats/min), PRinterval (msec), RR interval (msec), QRS interval (msec), QT interval (msec), QTcF interval (msec), QTcB interval (msec). Observed values and changes from baseline for ECG parameters will be summarized at each visit and time point, as well as for most extreme minimum, and most extreme maximum changes.

All ECG data will be presented in data listings for all patients in the SAF.

9.3.3 Physical Examinations

Physical examinations will be presented in patient data listings for all patients in the SAF.

9.3.4 MRI/CT Scans

MRI/CT scans will be presented in patient data listings for all patients in the SAF.

10 CHANGES TO THE PLANNED ANALYSIS

Due to the reduction in sample size, the efficacy analyses described in the study protocol are no longer being conducted and modified. Instead, descriptive analyses will be adopted for this study. An additional topline analysis which is not pre-specified in the protocol will be performed at the time that the last enrolled patient completes their 90 day visit with Worst Daily Leg Pain data is clean and available prior to the database lock. [redacted]

11 DOCUMENT HISTORY

Document Version, Status, Date	Summary / Reason for Changes
Version 1.0, Finale, 06APR2022	Not applicable; the first version
Version 1.1, Amendment, 13JUL2022	1. Remove "The proportion of patients who have a reduction in use of concomitant analgesics and supportive health services" from secondary efficacy endpoint as study team agreed it is no longer required. 2. Definition for baseline is updated as it is agreed baseline for the mean WDLP should be Day 0 to reflect other measurements taken on the same date. In addition, mean WDLP calculation should be based on the date of each scheduled visit. 3. Additional rule on handling character laboratory results. 4. Additional rule on handling missing / partial date on concomitant procedure / therapy to rescue medications to reflect the time point when a concomitant procedure / therapy occurred before, during, or after a rescue medication was administered. 5. Minor wording update for readability. 6. Section 8 is updated as there are 2 blood sample collection strategies hence data presentation should reflect the strategy how blood samples are collected.

12 REFERENCES

(1) Ghahreman, A., Ferch, R. & Bogduk, N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. *Pain Med* 11, 1149-1168 (2010).

(2) International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports E3. Step 4. 1995. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf.

(3) The RAND Corporation (n.d.). 36-Item Short Form Survey (SF-36) Scoring Instructions. Accessed and Retrieved from https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/survey-instrument.html on 20SEP2019.

(4) The RAND Corporation (n.d.). 36-Item Short Form Survey (SF-36) Scoring Instructions. Accessed and Retrieved from https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html on 20SEP2019.

13 APPENDICES

13.1 APPENDIX 1. Partial Date Conventions

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study drug start date, then not TEAE If start date >= study drug start date, then TEAE
Partial, but known components show that it cannot be on or after study drug start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Missing	If stop date is missing, assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Partial	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Missing	Assign as concomitant
Missing	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Missing	Assign as concomitant

Algorithm for Association between Concomitant Procedure / Therapy to Rescue Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < rescue medication start date, assign as prior If start date <= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If rescue medication stop date >= start date >= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If start date >= rescue medication stop date, assign as post
	Partial	If year is available and is before 2022, impute stop date as latest possible date (i.e., last day of month if day is unknown or 31st December if day and month are unknown), If year is avaulable and is 2022, stop date will be set as date of data cut-off, then: If stop date < rescue medication start date, assign as prior If start date <= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If rescue medication stop date >= start date >= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If start date >= rescue medication stop date, assign as post
	Missing	If stop date is missing and start date < rescue medication stop date, assign as concomitant If stop date is missing and start date >= rescue medication stop date, assign as post
	Ongoing	Stop date will be set as date of data cut-off. If stop date < rescue medication start date, assign as prior If start date <= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If rescue medication stop date >= start date >= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If start date >= rescue medication stop date, assign as post
Partial	Known	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < rescue medication start date, assign as prior If start date <= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If rescue medication stop date >= start date >= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If start date >= rescue medication stop date, assign as post

START DATE	STOP DATE	ACTION
	Partial	For start date: Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown). For stop date: If year is available and is before 2022, impute stop date as latest possible date (i.e., last day of month if day is unknown or 31st December if day and month are unknown), If year is avaulable and is 2022, stop date will be set as date of data cut-off, then, then: If stop date < rescue medication start date, assign as prior If start date <= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If rescue medication stop date >= start date >= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If start date >= rescue medication stop date, assign as post
	Missing	For start date: Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown). If stop date is missing and start date < rescue medication stop date, assign as concomitant If stop date is missing and start date >= rescue medication stop date, assign as post
	Ongoing	For start date: Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown). Stop date will be set as date of data cut-off If stop date < rescue medication start date, assign as prior If start date <= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If rescue medication stop date >= start date >= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If start date >= rescue medication stop date, assign as post
Missing	Known	Impute start date as the beginning of the study date. If stop date < rescue medication start date, assign as prior If start date <= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If rescue medication stop date >= start date >= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If start date >= rescue medication stop date, assign as post
	Partial	Impute start date as the beginning of the study date. Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < rescue medication start date, assign as prior If start date <= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If rescue medication stop date >= start date >= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If start date >= rescue medication stop date, assign as post
	Missing	Assign as concomitant

START DATE	STOP DATE	ACTION
	Ongoing	Impute start date as the beginning of the study date. Stop date will be set as date of data cut-off If stop date < rescue medication start date, assign as prior If start date <= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If rescue medication stop date >= start date >= rescue medication start date and stop date >= rescue medication start date, assign as concomitant If start date >= rescue medication stop date, assign as post

13.2 APPENDIX 2: SF-36 Scoring Instructions

Scoring the RAND 36-Item Health Survey is a two-step process. First, precoded numeric values are recoded per the scoring key given in Table 1. Note that all items are scored so that a high score defines a more favorable health state. In addition, each item is scored on a 0 to 100 range so that the lowest and highest possible scores are 0 and 100, respectively. Scores represent the percentage of total possible score achieved. In step 2, items in the same scale are averaged together to create the 8 scale scores. Table 2 lists the items averaged together to create each scale. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Hence, scale scores represent the average for all items in the scale that the respondent answered.

Table 1

Step 1: Recoding Items

Item numbers	Change original response category*	To recoded value of:
1,2,20,22,34,36	1 →	100
	2 →	75
	3 →	50
	4 →	25
	5 →	0
3,4,5,6,7,8,9,10,11,12	1 →	0
	2 →	50
	3 →	100
13,14,15,16,17,18,19	1 →	0
	2 →	100
21,23,26,27,30	1 →	100
	2 →	80
	3 →	60
	4 →	40
	5 →	20
	6 →	0
24,25,28,29,31	1 →	0
	2 →	20
	3 →	40

	4 →	60
	5 →	80
	6 →	100
32,33,35	1 →	0
	2 →	25
	3 →	50
	4 →	75
	5 →	100

*Precoded response choices as printed in the questionnaire.

Table 2

Step 2: Averaging Items to Form Scales

Scale	Number of Items	After recoding per Table 1, average the following items
Physical functioning	10	3 4 5 6 7 8 9 10 11 12
Role limitations due to physical health	4	13 14 15 16
Role limitations due to emotional problems	3	17 18 19
Energy/fatigue	4	23 27 29 31
Emotional well-being	5	24 25 26 28 30
Social functioning	2	20 32
Pain	2	21 22
General health	5	1 33 34 35 36

13.3 APPENDIX 3: Tables, Listings, and Figures

All tables, listings, and figures will be numbers according to the ICH-E3 Guideline. A table of contents containing the tables and listings to be produced based on the SAP text are included in a separate mock shell document appended to the SAP.

A DOUBLE- BLINDED, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP PHASE I/II, FIRST-IN-HUMAN STUDY TO ASSESS THE SAFETY AND EFFICACY OF TWO DOSES OF SX600 ADMINISTERED BY LUMBOSACRAL TRANSFORAMINAL EPIDURAL INJECTION IN PATIENTS WITH RADICULAR PAIN SECONDARY TO LUMBAR INTERVERTEBRAL DISC HERNIATION.

Statistical Analysis Plan

VERSION: DRAFT 0.3
DATE OF PLAN:

06-April-2022

STUDY DRUG / PROTOCOL ID:
SX600 / CLIN-0012-STA01-19

PREPARED FOR:

SpineThera Australia Pty. Ltd

Sponsor: SpineThera Australia Pty. Ltd
Protocol Number: CLIN-0012-STA01-19
SAP Version and Date: Final 1.0, 06APR2022

Approval Signatures: SpineThera Australia Pty. Ltd

[redacted] _____ _____
Date

Chief Medical Officer & Secretary/Director SpineThera Australia Pty Ltd

[redacted] _____ _____
Date

President, CSD Biostatistics, Inc., Statistical consultant to SpineThera

Approval Signatures: Southern Star Research

[redacted] _____ _____
Date

Associate Director, Statistics
Southern Star Research

Sponsor: SpineThera Australia Pty. Ltd
Protocol Number: CLIN-0012-STA01-19
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ABBREVIATIONS

AE	Adverse event
ALT	Alanine Transaminase
APPT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
ATC	Anatomic Therapeutic Class
AUC	Area Under the Curve
BP	British Pharmacopeia
BUN	Blood urea nitrogen
CK	Creatine Kinase
CRO	Clinical Research Organization
CSR	Clinical study report
DXA	Dexamethasone acetate
ECG	Electrocardiogram
EDC	Electronic Data Capture
GGT	Gamma-Glutamyl Transferase
IMP	Investigational Medicinal Product
ITT	Intent-to-treat
LDH	Lactate Dehydrogenase
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Medical Affairs
mITT	Modified Intent-to-treat
MRT	Mean Residence Time
NHMRC	National Health and Medical Research Council
NRS	Numeric Rating Scale
PP	Per protocol
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
PT	Prothrombin Time
Q1	First Quartile
Q3	Third Quartile
QoL	Quality of Life
RBC	Red Blood Cell
SAE	Serious adverse events
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SI	System of Units
SD	Standard Deviation
SOC	System Organ Class
SRC	Safety review committee
TEAE	Treatment Emergent Adverse Effects
TF-EI	Transforaminal epidural injection
TT	Thrombin Time
ULN	Upper limit of normal
WBC	White Blood Cell

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1 INTRODUCTION

The statistical analysis plan (SAP) details the planned analysis required to satisfy the Clinical Study Report (CSR) of study number CLIN-0012-STA01-19: A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Phase I/II, First-in-Human Study to Assess the Safety and Efficacy of Two Doses of SX600 Administered by Lumbosacral Transforaminal Epidural Injection in Patients with Radicular Pain Secondary to Lumbar Intervertebral Disc Herniation. The content of this SAP is based on the protocol dated 17JUN2020 REV06 and on subsequent modifications made to the study due to slow enrollment of subjects.

Revision Chronology:

1.0	06APR2022	Original

Mock shells for tables, listings, and figures will be included in a separate document: Mock Shells, Protocol Number CLIN-0012-STA01-19.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objectives

- To assess the safety of two doses (12.5 mg and 25.0 mg DXA) of Dexamethasone acetate microspheres for extended-release injectable micro-suspension, SX600 (IMP) administered by transforaminal epidural injection to the lumbosacral epidural space at the L4- L5, L5-S1 level, or the S1 nerve root, compared to Placebo (0.9% Sodium Chloride for Injection, BP), in the treatment of radicular pain resulting from inflammatory changes in a single affected nerve root secondary to lumbar disc herniation
- To assess the efficacy of two doses (12.5 mg and 25.0 mg DXA) of Dexamethasone acetate microspheres for extended-release injectable micro-suspension, SX600 (IMP) compared to Placebo (0.9% Sodium Chloride for Injection, BP), to alleviate the radicular pain from a single nerve root involvement secondary to lumbar disc herniation.
- To measure the systemic pharmacokinetics of two doses (12.5 mg and 25.0 mg) of Dexamethasone acetate microspheres for extended-release injectable micro-suspension, SX600 (IMP) from a single transforaminal epidural placement of 1.0 mL

2.1.2 Secondary Objectives

- To assess changes at 30-day intervals in functional outcomes following treatment
- To assess Patient Global Impression of Change
- To assess any decrease in the use of other health services
- To assess the time to loss of response in the Responders

2.2 Study Endpoints

2.2.1 Safety Endpoints

The Safety outcome will be assessed by:

- Adverse events from treatment day through study conclusion.

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- Serious adverse events (SAEs) considered product or procedure-related.
- Neurological consequences of the transforaminal epidural injection (TF-EI).
- Non-laboratory adverse events following TF-EI.
- Laboratory adverse events following administration of IMP/Placebo.

Safety endpoints are as follows:

- Incidence of treatment-emergent AEs and SAEs grouped by body system.
- Changes from Baseline in clinical laboratory, urinalysis, vital signs, and ECG parameters to discharge and follow-up
- Changes from pre-dose physical exam findings to Follow-Up

2.2.2 Primary Efficacy Endpoint

- The proportion of 50% Responders at 60 days post-dosing, where a 50% Responder is defined as a patient with 50% or greater improvement from baseline in mean Worst Daily Leg Pain.

2.2.3 Secondary Efficacy Endpoints

- The proportion of patients who are 50% Responders (defined as having 50% or greater improvement in Mean Worst Daily Leg Pain score compared to baseline) at each of the other scheduled time points (14, 30, 90, 120, 150, and 180 days) post-dosing.
- Change in functional outcomes as measured by Patient's Global Impression of Change, Oswestry Disability Index and SF-36 QoL questionnaire at each visit.
- The proportion of patients who are 30% Responders (defined as having 30% or greater improvement in Mean Worst Daily Leg Pain) at each of the other scheduled time points (14, 30, 60, 90, 120, 150, and 180 days) post-dosing.
- The proportion of patients who have a reduction in use of concomitant analgesics and supportive health services.
- Time to loss of response, in the subset of patients who are 50% Responders at Day 14 (50% or greater improvement in Mean Worst Daily Leg Pain).

2.2.4 Pharmacokinetic Parameters

- The maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}).
- The area under the plasma concentration versus time curve from time 0 (predose) to time infinity (AUC_{inf}).
- AUC from time 0 to time of last measurable plasma concentration (AUC_{last}).
- The percentage of the AUC that is extrapolated beyond the last measurable concentration (AUC_{ext}).
- The elimination rate constant (lz).
- The apparent systemic clearance (CL/F).
- Mean residence time (MRT).
- Apparent volume of distribution.
- Terminal phase (Vz/F), and terminal-phase half-life (t½)

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3 STUDY DESIGN

3.1 Study Design and Population

This first-in-human study is a Phase I/II, double-blind, parallel-group, randomized, placebo-controlled multi-centre trial. The study was originally designed to include 180 patients randomized 1:1:1 to receive the IMP (Dexamethasone acetate microspheres for extended-release injectable micro-suspension, SX600 at 12.5 mg or 25.0 mg) or Placebo (0.9% Sodium Chloride for Injection, BP) via transforaminal epidural injection to the lumbosacral epidural space at the L4- L5, L5-S1 level, or the S1 nerve root, as an outpatient procedure. The targeted patient total was decreased from 180 to 120 on 12 May 2021, which was documented in each sites Investigator Site File. The enrollment was stopped at 55 treated participants due to slow enrollment and the impact of Covid-19.

Patients will be screened to ensure they meet all inclusion and none of the exclusion criteria. Patients are considered enrolled in the study upon signing the Informed Consent Form by both the subjects and a study investigator (who is also a clinician). Informed Consent must be obtained prior to performing any study-related procedures. Section 21 of the protocol provides a complete list of inclusion and exclusion criteria.

Each patient will be followed for 180 days for assessment of any treatment-emergent adverse effects, status of radicular pain, functional assessments, and the use of health care services. Safety will be assessed through physical examination, vital signs, laboratory tests, and assessments of adverse events (AEs).

The study was originally expected to enroll over a period of 9 months. Each patient was expected to be in the study for 7 months. The total duration of the study was expected to be 19 months (9 months enrollment + 7 months follow-up + 3 months reporting). The 55 enrolled participants were enrolled over a two and a half year period and will be followed for the originally defined 180 days.

Systemic pharmacokinetics of dexamethasone (active moiety) were planned to be evaluated in a subset of approximately 60 patients (across IMP and placebo groups). By the time when the study is terminated by the sponsor, only 4 pharmacokinetic sub-study participants were enrolled.

3.2 Randomization and Blinding

Following the original plan in the protocol, patients who are eligible for enrollment into the study will be evaluated for randomization eligibility at Study Visits 1 and 2. The Biostatistician will prepare the randomization schedule, which will be managed by PCI Melbourne . Patients will be randomly assigned in a 1:1:1 ratio to one of two doses of SX600 (12.5 mg for the low-dose group, or 25.0 mg for the high dose group,) or Placebo (0.9% Sodium Chloride for Injection, BP or equivalent), with a planned final assignment of 60 patients/group. The list of randomized treatment assignments will be prepared by statisticians assigned to the study. The randomization number will be collected in the Electronic Data Capture (EDC) System. Refer to the Randomization Materials Specification Form for further details of randomization.

At the site, the physician who performs the TF-EI will be unblinded to the treatment assignment, but a second physician and study staff who are responsible for all subsequent patient assessments

must remain blinded to the treatment assignment. Since the reconstituted active IMP produces an opaque white suspension, it is not possible to blind the injector with a matching placebo solution for epidural administration, and hence 0.9% Sodium Chloride for Injection, BP has been chosen for the placebo comparator.

3.3 Sample Size Considerations

Limited data are available in the literature on which to base sample size/power considerations. In the study conducted by Ghahreman (Ghahremen, 2010) [(1)], the primary endpoint was the proportion of patients who achieved a 50% or greater reduction from baseline at 30 days. In the steroid arm, the observed response rate was 54%. In the control arms of this study, the response rates were 7%, 13%, 19%, and 21%. Based on these results, the assumed true response rates are 50% (active) and 20% (placebo). Using a two-sided comparison of binomial proportions at the alpha=0.05 level of significance, a sample size of 60 patients per arm will provide 94% power. If the true active arm response rate is 50% and the true placebo response rate is 25%, then the power of the study is decreased to 81%.

Due to enrollment difficulties and the impact of Covid-19, the study is being terminated with a total sample size of 55 randomized patients. As a result, the originally planned efficacy analyses will not be conducted. Instead, the results of the study will be evaluated descriptively.

3.4 Safety Review Committee

A Safety Review Committee (SRC) will be assigned the responsibility of safety of the participants and will provide medical oversight and expertise to the Sponsor and sites concerning the continuation, modification, or termination of the trial. The SRC will monitor patient safety through pre-defined, periodic review of the clinical study safety data as well as relevant background knowledge about the disease, test agent/device, or participant population under investigation.

The SRC will provide safety oversight of the study per the National Health and Medical Research Council (NHMRC) Guidance on Data Safety Monitoring Boards 2018. The SRC will be composed of three to four members including a Clinical Research Organization (CRO) independent medical monitor, a biostatistician, one Investigational Site clinician and the Sponsor Chief Medical Officer. The study is double-blinded but the SRC can request unblinding to make determinations regarding study outcome.

Details of the SRC, including committee member names and responsibilities, timing of the SRC reviews, data to be reviewed, and halting criteria will be documented separately in the SRC Charter.

3.5 Interim Analysis

There are no interim analyses planned for this study.

3.6 Timing of Analyses

The final analysis will occur when the last patient completes the end-of-study visit. A topline analysis of the Worst Daily Leg Pain will be assessed at the time that the last enrolled patient completes their 90 day visit prior to full database lock. This top line analysis will include the analyses on the primary endpoint time of 60 days and a secondary endpoint time of 90 days.

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4 DATA ANALYSIS CONSIDERATIONS

All analyses will be conducted based on SAS 9.4 or higher.

All data in the database will be presented in by-patient data listings.

Unless otherwise stated, all listings will be sorted by treatment group, center ID, patient number, and assessment date (and time, if available).

Unless stated otherwise, continuous data will be summarized by treatment group based on n, mean, median, standard deviation (SD), first quartile (Q1), third quartile (Q3), minimum value, and maximum value.

Unless stated otherwise, categorical data will be summarized by treatment group using n and percentage based on the number of non-missing values. The number of missing values will be presented as a separate category with no percentage, but only if one or more patients are missing data. Counts of zero will be presented without percentages.

The following levels of precision for reporting data will be applied:

- Mean, Median, Q1, and Q3: one additional decimal place to that reported for Minimum and Maximum
- SD: two additional decimal places than the Minimum and Maximum
- Percentages: reported to one decimal place

All data up to the time of study completion/withdrawal from the study will be included in the analysis, regardless of duration of treatment.

Numbering for data displays will be based on ICH E3[(2)].

4.1 Stratification and Covariates

There are no formal plans for analysis stratification.

4.2 Evaluation of Subgroups

There are no formal plans for examining subgroups.

4.3 Multiple Comparisons and Multiplicity

No formal statistical hypothesis tests will be conducted.

5 GENERAL DATA HANDLING CONVENTIONS

5.1 Assigned and Actual Treatment

As described in Section 3.2, patients will be randomized to placebo or SX600 (low-dose or high-dose). The randomized treatment assignment will be used for listings as well as selected analyses indicated for the Intent-to-Treat population.

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Actual treatment groups are based on exposure data to treatment received, and will be the basis for all safety analyses.

The following three treatment groups (actual or as-randomized) are planned in this study:

- Placebo
- SX600 12.5 mg
- SX600 25.0 mg

5.2 Reference Dates

The following reference definitions will be applied for this study:

- Screening date is defined as the eCRF provided date on which a patient was screened for trial entry.
- Day 0 is the date on which the patient is randomized to study treatment (i.e., Randomization date), and when TF-EI is performed (i.e., Intervention date).
- Treatment date is defined as the date of dose of study drug.
- The calculation of age will use the informed consent date as its reference date.
- Efficacy data will use the treatment date as a reference date.
- Study day will be based on treatment date as a reference date.

5.3 Definitions

The following definition will be applied for this study:

50% Responder: a patient with 50% or greater improvement in Mean Worst Daily Leg Pain score compared to baseline.

Mean Worst Daily Leg Pain score is based on the Numeric Rating Scale (NRS) as described in Section 7.1.

30% Responder: a patient with 30% or greater improvement in Mean Worst Daily Leg Pain score compared to baseline.

5.4 Study Day and Duration Variables

Reference date calculations will generally be defined as the following, assuming nonmissing dates:

- Date of interest – reference date.

If either date is missing, reference date calculations will not be performed. Date imputation will be performed as identified in Section 5.7.

For instance, study day will be based on the treatment date as the reference would either have a negative value if collected before dosing, zero if collect on the day of drug dosing, or a positive value if collected after the day of drug dosing.

Duration of time is dependent on reference dates and will be calculated in a manner similar to that of the reference date calculation, assuming that dates of interest will strictly follow reference dates

(e.g. no negative values). For example, duration on study is defined as the end of study date – screening date. Patients still participating in study follow up at the time of analysis will use imputed end of study dates as described in Section 5.8.

5.5 Study Time Periods

Safety reporting will be classified by the following study periods for analysis:

Pre-therapy is defined as the period prior to a patient's treatment date.

On-therapy is defined as the period between a patient's treatment date to the end of study, including the TF-EI procedure.

5.6 Baseline and Post-Baseline Changes

Unless stated otherwise, baseline and post-baseline change values will be based on the following:

Baseline will be based on the last nonmissing value collected prior to or on the treatment date and time. Post-baseline values will be those collected after the treatment date.

For Mean Worst Daily Leg Pain, baseline is defined as the calculated Mean Numeric Rating Scale (NRS) score of 5 days recorded using the patient electronic diary for the 10 days preceding the Day 0 visit. The calculation method for Mean Worst Daily Leg Pain is as described in Section 7.1.

Change from baseline is defined as: value – baseline value.

Percentage change from baseline is defined as: (value – baseline value)/baseline value X 100%.

Most extreme change: The maximum most extreme change will be based on the maximum post-baseline value; the minimum most extreme change will be based on the smallest post-baseline value. This calculation will consider all assessments collected during the on-therapy period, scheduled or unscheduled.

5.7 Imputation of Partial Dates

Appendix 1 details partial date conventions that will be used for the determination of treatment-emergent adverse events, and prior and concomitant medications.

End of Study Date

Missing study end dates will not necessarily be imputed at the end of the study. However, in the event of an ongoing reporting need, end of study dates may be imputed as the earliest of the data cutoff date, date of death, or last date recorded on the CRF.

5.8 Multiple Assessments and Visit Windows

Nominal visits (e.g. those identified by the study CRF) will be the basis of summarization and statistical analysis. Unscheduled data may be included in summaries of most extreme and baseline values, summaries of specific abnormalities any time post-baseline, and patient data listings.

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5.9 Missing Data

Missing data imputation for the primary efficacy endpoint is described in Section 0; AE and concomitant medication date imputations are described in Section 5.7. Otherwise, missing data will not be imputed.

6 STUDY PATIENT DATA

6.1 Analysis Populations

Intention-to-treat (ITT) Population: Defined as all randomized patients. Patients will be included in the treatment group to which they were randomized, regardless of treatment received.

Safety Population (SAF): Defined as all randomized patients who proceed to TF-EI (includes patients with attempted but halted or failed TF-EI). Patients will be included in the treatment group based on the treatment that was received. All safety analyses will be conducted in the Safety Population.

Modified Intention-to-treat (mITT) Population: Defined as all randomized treated patients who receive IMP or placebo by TF-EI. Patients will be reported based on randomized treatment assignment. All efficacy analyses will be conducted in the mITT Population.

Per-protocol Population (PP): Defined as all randomized patients who met all inclusion/exclusion criteria, did not have any significant protocol deviations, complied with the assigned study treatment, returned to the study site for the Primary Efficacy visit within the specified window, or discontinued study early due to lack of treatment effect or received therapy other than study specified drug during the study. Patients will be reported based on actual treatment received. The primary endpoint efficacy analysis will be repeated in the PP population. In order to minimize bias, the PP population will be defined prior to unblinding.

PK population: Defined as all patients who received IMP or placebo and with intensive blood collections in the first 24 hours (approximately 60 subjects). All PK analyses will be conducted in the PK population.

6.2 Patient Disposition

Summaries of analysis population membership and final patient status (completed or withdrawn), including reasons for withdrawal, will be produced based on all patients enrolled. Data will be presented by treatment group as well as overall for the study.

Randomization details, analysis populations, and final patient disposition status will be listed.

6.3 Protocol Deviations

Protocol deviations will be identified and classified as major or minor (violations) before the database is locked. Protocol deviations may include but are not limited to:

- Visit / Procedure / Assessment outside protocol window
- Visit / Procedure / Assessment not done
- Inclusion / Exclusion

- Informed Consent
- Study drug administration
- Study restrictions
- Other

Protocol deviations will be summarized by treatment group and overall for the study.

A listing of protocol deviations will be provided.

6.4 Demographic and Baseline Characteristics

Patient demographics will be summarized and listed for the ITT Population. These will include age, sex (Male / Female), ethnicity (Hispanic or Latino / Not Hispanic or Latino / Not reported / Unknown), race (Black or African American / American Indian or Alaska Native / Asian / Native Hawaiian or Pacific Islander / White / Other / Not reported), baseline height (cm), baseline weight (kg), and BMI (kg/m^2). Years since radicular pain associated with lumbar intervertebral disc herniation will be calculated from the start date of pain as reported on the eCRF to the date of screening and will be summarized using descriptive statistics. Leg raise (degree) assessments at Screening will be included as baseline characteristics and will be summarized. Data will be presented by treatment group as well as overall for the study.

The following conversions and equations will be used as applicable:

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m^2) = weight(kg)/[height$(m)^2$]

6.5 Medical History

Medical History will be coded based on the Medical Dictionary for Regulatory Affairs (MedDRA) for reporting by system organ class (SOC) and preferred term (PT) and will be summarized in descending order of overall incidence. A listing of medical history will be provided for all patients in the ITT population.

6.6 Prior and Concomitant Medication

The incidence of medication use will be summarized by WHO Drug Dictionary anatomic therapeutic class (ATC) Level 2 classification (i.e., therapeutic main group) and preferred name. A patient will be counted only once at each level of reporting. Prior medications are those which have been identified to have been discontinued prior to the treatment date (e.g., taken exclusively during the pre-therapy period). Concomitant medications are those which have been identified to have been taken at any point during the on-therapy period. This includes rescue therapies. Prior and concomitant medication use will be summarized separately and presented by treatment group.

All prior and concomitant medication data will be listed for patients in the ITT population and will include the verbatim and preferred drug name and ATC Level 2.

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6.7 Concomitant Procedure / Therapy

The incidence of concomitant procedure / therapy will be summarized. A patient will be counted only once per procedure / therapy. Concomitant procedures / therapies are those which have been identified to have been taken at any point during the on-therapy period. Prior and concomitant medication use will be summarized and presented by treatment group.

All concomitant procedure / therapy data will be listed for patients in the ITT population. A listing for recovery procedures post TF-EI will be produced for the ITT population.

6.8 Study Drug Exposure and Compliance

The number and percentage of patients who attempted, halted, or failed the TF-EI procedure will be summarized in the ITT Population. For patients who complete the TF-EI procedure, the number and percentage receiving IMP per the delivery protocol will also be tabulated. The number and percentage of mis-dosed patients will also be summarized.

Listings of planned and actual treatments, and compliance with TF-EI procedure and delivery protocols of drug administration will be produced for the ITT population.

7 EFFICACY

All efficacy analysis reporting will be based on the mITT Population. Additionally, the primary efficacy analysis will be repeated in the PP Population.

7.1 Primary Efficacy Endpoint and Analyses

Efficacy assessments will be based on the categorical measure of 50% Responder, defined as a patient with 50% or greater improvement in mean Worst Daily Leg Pain (WDLP) score compared to baseline. The mean WDLP score will be derived from the E-Diary recordings entered by the subjects, [redacted]

concomitant medications / procedures beyond rescue medications are observed. The same derivation rule will be applied on those secondary endpoints where are appropriate.

Incomplete Mean Worst Daily Let Pain score:
All subjects with 5 or more Worst Daily Leg Pain scores recorded in the 10 days preceding the study visit will be included in the analysis. If a subject has less than 5 scores preceding a visit, the subject will not be included in the efficacy assessment for that particular visit. If that same subject has provided 5 or more scores in the 10 days preceding a later visit, the subject will be included in the efficacy assessment for the later visit.

Early Withdrawal:
If a subject withdraws from the study before their 180 day visit, the subject will be included in analyses up to the time that they either stop attending follow-up visits or their consent was withdrawn.

Rescue Medication:
[redacted] If a patient has failed rescue medication (defined as taking rescue medication for >14 days, taking rescue medication in more than one episode, or receiving treatment beyond the rescue medication regimen defined in the protocol [redacted] then the patient will be deemed a non-responder at all timepoints after exceeding the allowed rescue medication, [redacted]

7.1.1 Mean Worst Daily Leg Pain Score: Proportion of Patients with 50% or Greater Improvement from baseline at 60 Days Post-Dosing (Primary Endpoint)

The number and percentage of patients experiencing a 50% or greater improvement from baseline in mean Worst Daily Leg Pain score (i.e. the number and percentage of 50% Responders) will be tabulated for each treatment group. The primary analysis will descriptively compare the proportions of 50% Responders in each of the three arms. The "study success" criterion is defined as the observed percentage of 50% Responders in the high dose group being at least 10 percentage points greater than the corresponding rate in the placebo group.

Listings of Worst Daily Leg Pain will be provided for the modified intent-to-treat population.

7.2 Secondary Efficacy Endpoints and Analyses

The results for all secondary endpoints will be presented descriptively.

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7.2.1 Mean Worst Daily Leg Pain Score: Proportion of Patients with 50% of Greater Improvement at 14, 30, 90, 120, 150, and 180 Days Post-Dosing

A secondary efficacy endpoint for this study is the proportion of patients with a 50% or greater improvement from baseline in mean Worst Daily Leg Pain score at 14, 30, 90, 120, 150, and 180 days post-dosing in the high dose group compared to placebo and low dose group compared to placebo. The number and percentage of patients experiencing a 50% or greater improvement from baseline in mean Worst Daily Leg Pain score will be tabulated for each treatment group and time point for the mITT population.

7.2.2 Change from Baseline in Mean Worst Daily Leg Pain Score

A graphical display of average patients observed Daily Leg Pain values over time by treatment group for the mITT population will be prepared.

7.2.3 Patient's Global Impression of Change

Changes in Patient's Global Impression of Change is a secondary efficacy endpoint for this study, where PGI is assessed using the following 7-point scoring classification:

- Very Much Improved = 1
- Much Improved = 2
- Minimally Improved = 3
- No Change = 4
- Minimally Worse = 5
- Much Worse = 6
- Very Much Worse = 7

Number and percentage for each Observed Patient's Global Impression of Change values will be summarized at each visit for each treatment group in the mITT population. In addition, the number and percentage of patients classified as improved (values of 1, 2, and 3) and the number and percentage of patients classified as not worsened (values of 1, 2, 3, and 4) will be summarized at each visit for each of the three treatment groups for the mITT population.

Listings of Patient's Global Impression of Change values will be provided for the modified intent-to-treat population.

7.2.4 Oswestry Disability Index

Changes in Oswestry Disability Index is a secondary efficacy endpoint for this study. The Oswestry Disability Index will be calculated as:

$$Oswestry\ Disability\ Index = \frac{Total\ Score}{Total\ Possible\ Score} \times 100\%$$

For example, it all 10 questions are answered and the total score is 16, then the Oswestry Disability Index = 16/50 x 100% = 32%. If one question is missed or not applicable, the score is calculated as 16/45 x 100% = 35.5%.

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Observed Oswestry Disability Index values and their change from baseline will be summarized at each visit. The number and percentage of Oswestry Disability Index categorization will be tabulated for each treatment group and time point in the mITT population.

Oswestry Disability Index interpretation of scores will be assessed as:

- 0% to 20%: minimal disability
- 21% to 40%: moderate disability
- 41% to 60%: severe disability
- 61% to 80%: crippling back pain
- 81% to 100%: these subjects are either bed-bound or exaggerating their symptoms

Listings of Oswestry Disability Index values will be provided for the modified intent-to-treat population.

7.2.5 SF-36 QoL Questionnaire RAND version

The SF-36 QoL RAND survey is listed in Reference, Section 11. Changes in SF-36 QoL RAND version domains are secondary efficacy endpoints for this study. Observed SF-36 QoL domain values and their change from baseline will be summarized at each visit for each treatment in the mITT population. Domains will be calculated as described in Appendix 2. The eight health concepts of SF-36 QoL are:

- Physical Functioning (PF); sum of CRF questions: 3-12
- Role Physical (RP); sum of CRF questions: 13-16
- Bodily Pain (BP); sum of CRF questions: 21-22
- General Health (GH); sum of CRF questions: 1, 33-36
- Vitality (V); sum of CRF questions: 23, 27, 29, 31
- Social Functioning (SF); sum of CRF questions: 20, 32
- Role Emotional (RE); sum of CRF questions: 17-19
- Mental Health (MH); sum of CRF questions: 24-26, 28, 30

Listings of the scored SF-36 QoL RAND version domain values will be provided for all patients. In addition, summary statistics for each of the eight domains will be provided at each visit for each treatment group.

7.2.6 Proportion of Patients with 30% of Greater Improvement at 14, 30, 60, 90, 120, 150, and 180 Days Post-Dosing

The same type of analyses as described in 7.2.1 will be conducted at each time point: 14, 30, 60, 90, 120, 150, and 180 days, but using the proportion of subjects with a 30% or greater improvement from baseline in the pain score.

7.2.7 Proportion of Patients with Reduction in use of concomitant analgesics and supportive health services

The number and percentage of patients experiencing a reduction in use of concomitant analgesics and supportive health services will be tabulated for each treatment group at each visit for the mITT population.

Listings of concomitant analgesics and supportive health services will be provided for the mITT population.

7.2.8 Time to loss of response

A time to loss of response analysis will be conducted for the subset of patients who have 50% or greater improvement in Mean Worst Daily Leg Pain at Day 14.

Loss of response will be defined as observing a <50% improvement from Baseline following the Day 14 visit. If a patient with a response at Day 14 does not meet the definition for loss of response at any time after Day 14, then the patient will be censored as of their last date in the study. Time to loss of response will be calculated in days as follows:

Time to loss of response (days) = [Date of first occurrence of <50% improvement from Baseline following Day 14; Or Date of Withdraw; Or Date of Last known still in the study; Or Date of concomitant medication/procedure/therapy starts after the failure of the rescue medication] – [Date of Day 14 Visit].

Time to a loss of response will be summarized based on Kaplan-Meier methods. The number and percentage of patients identified to have had a loss event and those who were censored will be displayed. The median time to loss of response and its corresponding 95% CI will also be produced. All analyses will be performed by treatment group.

7.3 Sensitivity Analysis

[redacted]

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[redacted].

8 PHARMACOKINETICS/PHARMACODYNAMICS

A time to concentration profile will be plotted for those patients who are involved with the PK and PD data.

The analysis of PK and PD data will be described in the Clinical Study Report as there were so few PK patients enrolled.

9 SAFETY

All safety analysis reporting will be based on the Safety Population.

9.1 Adverse Events

Adverse events (AEs) will be recorded from the treatment date until the end of study. AEs will also be assessed for seriousness, severity relatedness, and expectedness. AEs will be considered treatment-emergent if their onset occurs within the on-therapy period. Any missing severity assessments will be assumed to be severe, missing relationship assessments will be assumed to be related, and missing seriousness assessments will be assumed as serious.

An overview of treatment-emergent AEs (TEAEs) will be produced, including counts and percentages of patients with any incidences of: TEAEs, TEAEs related to study treatment (i.e., either definitely, probably, or possibly related), TEAEs related to TF-EI procedure (i.e., either definitely, probably, possibly related or not related), severe or worse adverse events (i.e., either severe, life-threatening, or fatal), TEAEs leading to study withdrawal, serious adverse events (SAEs), and fatal SAEs.

Adverse events will be coded based on the Medical Dictionary for Regulatory Affairs (MedDRA) for reporting by system organ class (SOC) and preferred term (PT) in descending order of overall incidence. For these summaries, patients will be counted once within each SOC and PT.

Summaries of adverse events by SOC and PT will include the following types:

- TEAEs;
- TEAEs related to study treatment (including definitely, probably, or possibly related events, and events with missing relatedness);
- TEAEs related to TF-EI procedure (including definitely, probably, or possibly related events, and events with missing relatedness);
- Severe or worse TEAEs (including severe, life-threatening, or fatal events, and events with missing severity);
- SAEs; and
- TEAEs leading to study withdrawal;

A summary of TEAEs by SOC, PT, and maximum severity will also be prepared. Maximum severity will be based on the following scales:

- Fatal
- Life-Threatening
- Severe
- Missing
- Moderate
- Mild

A comprehensive listing of all AEs will be provided in a by-patient data listing. In addition, the following listings will be provided:

- TEAEs related to study treatment (including definitely, probably, or possibly related events, and events with missing relatedness);
- SAEs;
- TEAEs leading to study withdrawal; and
- Fatal AEs.

9.2 Clinical Laboratory Evaluations

Clinical chemistry and hematology parameters will be reported based on the International System of Units (SI). The following laboratory evaluations will be reported in data summaries:

Hematolog [redacted]

Coagulatio [redacted]

Clinical Chemistry (non-fasting serum): [redacted]

Urinalysis: [redacted]

Observed values and changes from baseline for laboratory evaluations will be summarized at each visit and for most extreme maximum and minimum changes.

Laboratory data which is not graded will also be summarized in shift tables of baseline to each visit and most extreme change based on range categories of low (below lower limit of normal [LLN], normal, and high [above upper limit of normal [ULN]).

All laboratory parameters will be provided in patient data listings for the SAF population. Virus serology (HIV, Hepatitis A, Hepatitis B, Hepatitis C) will be provided in patient data listings for the SAF population. Pregnancy results (serum and urine) will be provided in patient data listings for the SAF population. Results from urine drug screening (cocaine, cannabinoids, opiates,

benzodiazepines, and amphetamines) will be provided in patient data listings for the SAF population.

9.3 Other Safety Evaluations

9.3.1 Vital Signs

Vital signs include: respiratory rate (breaths per minute); temperature (°C); systolic and diastolic blood pressure (mmHg); pulse rate (beats/min). Observed values and changes from baseline for vital signs will be summarized at each visit and time point, as well as for most extreme minimum, and most extreme maximum changes.

All vital signs data will be presented in data listings for all patients in the SAF.

9.3.2 Electrocardiogram (ECG)

Electrocardiogram (ECG) parameters include: HR (beats/min), PRinterval (msec), RR interval (msec), QRS interval (msec), QT interval (msec), QTcF interval (msec), QTcB interval (msec). Observed values and changes from baseline for ECG parameters will be summarized at each visit and time point, as well as for most extreme minimum, and most extreme maximum changes.

All ECG data will be presented in data listings for all patients in the SAF.

9.3.3 Physical Examinations

Physical examinations will be presented in patient data listings for all patients in the SAF.

9.3.4 MRI/CT Scans

MRI/CT scans will be presented in patient data listings for all patients in the SAF.

10 CHANGES TO THE PLANNED ANALYSIS

Due to the reduction in sample size, the efficacy analyses described in the study protocol are no longer being conducted and modified. Instead, descriptive analyses will be adopted for this study. An additional topline analysis which is not pre-specified in the protocol will be performed at the time that the last enrolled patient completes their 90 day visit with Worst Daily Leg Pain data [redacted]

11 REFERENCES

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12 APPENDICES

12.1 APPENDIX 1. Partial Date Conventions

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study drug start date, then not TEAE If start date >= study drug start date, then TEAE
Partial, but known components show that it cannot be on or after study drug start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE

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Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Missing	If stop date is missing, assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Partial	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Missing	Assign as concomitant
Missing	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Missing	Assign as concomitant

Sponsor: SpineThera Australia Pty. Ltd
Protocol Number: CLIN-0012-STA01-19
SAP Version and Date: Final 1.0, 06APR2022

12.2 APPENDIX 2: SF-36 Scoring Instructions

Scoring the RAND 36-Item Health Survey is a two-step process. First, precoded numeric values are recoded per the scoring key given in Table 1. Note that all items are scored so that a high score defines a more favorable health state. In addition, each item is scored on a 0 to 100 range so that the lowest and highest possible scores are 0 and 100, respectively. Scores represent the percentage of total possible score achieved. In step 2, items in the same scale are averaged together to create the 8 scale scores. Table 2 lists the items averaged together to create each scale. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Hence, scale scores represent the average for all items in the scale that the respondent answered.

Table 1

Step 1: Recoding Items

Item numbers	Change original response category*	To recoded value of:
1,2,20,22,34,36	1 →	100
	2 →	75
	3 →	50
	4 →	25
	5 →	0
3,4,5,6,7,8,9,10,11,12	1 →	0
	2 →	50
	3 →	100
13,14,15,16,17,18,19	1 →	0
	2 →	100
21,23,26,27,30	1 →	100
	2 →	80
	3 →	60
	4 →	40
	5 →	20
	6 →	0
24,25,28,29,31	1 →	0
	2 →	20
	3 →	40

	4 →	60
	5 →	80
	6 →	100
32,33,35	1 →	0
	2 →	25
	3 →	50
	4 →	75
	5 →	100

*Precoded response choices as printed in the questionnaire.

Table 2

Step 2: Averaging Items to Form Scales

Scale	Number of Items	After recoding per Table 1, average the following items
Physical functioning	10	3 4 5 6 7 8 9 10 11 12
Role limitations due to physical health	4	13 14 15 16
Role limitations due to emotional problems	3	17 18 19
Energy/fatigue	4	23 27 29 31
Emotional well-being	5	24 25 26 28 30
Social functioning	2	20 32
Pain	2	21 22
General health	5	1 33 34 35 36

12.3 APPENDIX 3: Tables, Listings, and Figures

All tables, listings, and figures will be numbers according to the ICH-E3 Guideline. A table of contents containing the tables and listings to be produced based on the SAP text are included in a separate mock shell document appended to the SAP.