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

Protocol and Protocol Amendments

Protocol Version 01	12 June 2019
Protocol Version 02	06 August 2019
Protocol Version 03	27 September 2019
Protocol Version 04	17 October 2019
Protocol Version 05	19 February 2020
Protocol Version 06	**17 June 2020**

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.

Protocol Number: **CLIN-0012-STA01-19**

Short Title: Safety and Efficacy of SX600 Administered by Lumbosacral Transforaminal Epidural Injection for Radicular Pain (SALIENT)

Investigational Product: **SX600,** Dexamethasone acetate, poly(lactic-*co*-glycolic acid), and poly(lactic acid-*co*-glycolic acid)-[*block*]-poly(ethylene glycol) microspheres for reconstitution in 0.9% Sodium Chloride for Injection, BP

Sponsor:
SpineThera Australia Pty. Ltd
C/- Prime Accounting and Business Advisory Pty Ltd
Level 19, 40 City Road,
Southbank, Victoria. 3006

Clinical Research Organization: Southern Star Research Pty. Ltd

1 Merriwa Street, Gordon NSW 2072, Australia

Lead Principal Investigator: [redacted]
Genesis Research Services
220 Denison Road, Broadmeadow NSW 2292, Australia

Authorized Signatory: [redacted]

Study Contacts: [redacted]

1 INVESTIGATOR'S ACKNOWLEDGEMENT OF RECEIPT

I have received and read the Protocol, *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*, and agree to conduct the study strictly as outlined in the protocol. I agree to maintain the confidentiality of all information received for all subjects and developed in connection with this protocol.

Printed Name of Investigator

Title of Investigator

Signature of Investigator

Date

2 SPONSOR'S SIGNATURE

Approved by:

[redacted]

SpineThera Australia Pty Ltd
Sponsor Company

Approved by:

[redacted]

SpineThera Australia Pty Ltd
Sponsor Company

3 VERSION HISTORY

Revision #	DCR#	Summary of Changes	Authors
00	0012	Initial Release	William Houghton, M.D. Jeff Missling
01	0016	Clarified doses of DXA instead of SX600; Changed blood pressure from supine to seated position; Fixed error in SF-36 definition, Clarified follow-up of SAE based upon last visit.	William Houghton, M.D. Jeff Missling
02	0037	Updates to: Title; Exclusion Criteria – system fungal and other infections, psychoses, osteoporosis; Study Schedule; Assessments – Patient Global Impression of Change, Physical Exam, Virus Serology; Summary of Known and Potential Risks – adrenal cortical suppression; Steroid contraindications – live virus vaccines; Unscheduled and Early Termination visits Safety – adverse event reporting and definitions; and general administrative changes; clarified use of extension tubing in TF-EI procedure; updated shelf life of SX600.	William Houghton, M.D. Jeff Missling
03	0044	Updated page numbers in Attachments, clarified randomisation plan, updated emergency blinding information, removal of BUN from serum chemistry, added recruitment strategy information, updated recommended extension tubing for procedure	William Houghton, M.D. Jeff Missling
04	0046	Allowed pre-dose PK blood collection at Visit 1 or Visit 2	William Hougthon, M.D. Jeff Missling
05	0054	Update to Safety contact information; clarify eligibility criteria; remove recruitment strategy information; update assessemnts; add attachments PK Collection Manual and IMP Randomisation & Shipment Process; remove references to 12-month investigational medicinal product shelf life, current data supports shelf life beyond 12 months	William Hougthon, M.D. Jeff Missling
06	0061	Update to Lead PI; elibigility criteria; study schedule and procedures; study visits; efficacy assessments	William Hougthon, M.D. Jeff Missling

4 PROCEDURES IN CASE OF EMERGENCY

24 Hour Emergency Contact

Role in Study	Contact
SpineThera Chief Medical Officer	[redacted]
Southern Star Research Medical Monitor	[redacted]

Emergency Unblinding Contact

Role in Study	Contact
Southern Star Research Unblinded Safety Officer	[redacted]

5 SYNOPSIS

SPINETHERA CLINICAL PROTOCOL SYNOPSIS

Title of Study:	**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.**
Short Title:	Safety and Efficacy of SX600 Administered by Lumbosacral Transforaminal Epidural Injection for Radicular Pain (SALIENT)
Clinical Trial Phase:	Phase I/II
Protocol No.:	**CLIN-0012-STA01-19**
Sponsor:	SpineThera Australia Pty Ltd
Investigational Medicinal Products (IMP)	IMP: SX600, a sustained-release formulation of dexamethasone acetate in PLGA and PLGA-PEG microspheres packaged as a lyophilized powder for resuspension at the time of administration in 1.2 mL of 0.9% Sodium Chloride for Injection, BP, with 1.0 mL of the re-suspended product recovered for transforaminal epidural injection. Placebo: 0.9% Sodium Chloride for Injection, BP, 1.0 mL.
Proposed Indication:	Dexamethasone acetate microspheres for extended-release injectable micro-suspension for lumbosacral transforaminal epidural injection (SX600) indicated for treatment of lumbosacral radiculopathy (radiating pain).
Purpose:	Safety and efficacy of SX600 in indicated population
Anticipated Study Period:	19 months
Objectives:	*Primary:* • 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 DXA) of dexamethasone acetate microspheres for extended-release injectable micro-suspension, SX600 (IMP) from a single transforaminal epidural placement of 1.0 mL. *Secondary:* • 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
Study Design:	This is a Phase I/II, double-blind, parallel-group, randomized, placebo-controlled multi-centre trial in 180 patients randomized 1:1:1 to receive the IMP (Dexamethasone acetate microspheres for extended-release injectable micro-suspension, containing 12.5 mg or 25.0 mg DXA) 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. Each subject 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). Systemic pharmacokinetics of dexamethasone (active moiety) will be evaluated in a subset of approximately 60 patients (across IMP and placebo groups).
Subjects & Timing	180 dosed subjects; approximately 24-28 weeks, from screening to last follow-up (FU) visit.
Inclusion Criteria:	1. Adult aged 18 to 65 years, capable of providing informed consent, capable of complying with the outcome instruments, and meeting the attendance requirements for review as defined in the study. 2. Presenting with a history of unilateral pain, radiating into a lower limb, of lancinating, burning, stabbing or electric quality, of duration of current episode being 4 weeks to 6 months prior to study enrolment, having failed conservative therapy. 3. Mean Worst Daily Leg Pain score of ≥5.0 and ≤9.0 being the *mean* NRS score (to 1 decimal place) of 5 days (as further defined in the Efficacy Assessments). 4. Demonstration of a disc herniation within 3 months by CT or MRI at the segmental levels of L4-L5, or L5-S1, [redacted]. 5. The site of the disc herniation must affect L4-5 or L5-S1, with involvement of the L4, L5, or S1 nerve roots unilaterally. 6. [redacted]

	7. [redacted] 8. Women of child-bearing potential must agree to use a medically accepted method of contraception for the duration of the study plus 30 days and register a negative pregnancy test prior to dosing. 9. Men must agree to abstain from intercourse with women or agree to use a medically accepted method of contraception and refrain from donating sperm for the duration of the study plus 30 days. 10. Willing to comply with all the study activities and procedures throughout the duration of the study.
Exclusion Criteria:	1. Documented history of allergy or intolerance to components of the IMP, relevant radiologic contrast media, or local anaesthetics. 2. Is pregnant or lactating 3. Has been taking corticosteroid medications routinely in the past 6 months *or* has received an epidural corticosteroid injection within 12 weeks of screening. 4. Has a BMI greater than 40 kg/m^2. 5. Has Diabetes Mellitus (Type 1 or Type 2) – prior confirmed HbA_{1c} or OGTT 6. [redacted] 12. Has a history of significant leg pain unrelated to disc herniation that would significantly compromise assessment of back or leg radicular pain. 13. Has radiological evidence of symptomatic disc herniation above L4-L5. 14. Has radiological evidence of clinically significant foraminal stenosis at L4-L5 or L5-S1 or of clinically significant spinal stenosis, or spondylolisthesis (Grade 2 or higher). (Note, asymptomatic foraminal stenosis at other spinal levels is not excluded). 15. Has had lumbar back surgery. 16. [redacted]

	19. [redacted] 22. Has received an implantable device for pain management. 23. [redacted]
Study Procedures:	*Screening*: **Days -28 to Day -1**: This is the screening visit to determine study eligibility, recording of all current treatments (medications, physical therapy, etc.), and signing of the Informed Consent Form. ***Day 0:*** The intervention day when TF-EI is performed, and with initial Pharmacokinetic blood sample collections in assigned subjects. *Follow-up Visits:* **Day 1 and Day 7** (telephone assessment) for assessment of adverse events and concomitant medications and therapies. **Day 14, Day 30**, **Day 60**, **Day 90**, **Day 120**, **Day 150**, **Day 180** post-dosing. The following measures will be recorded at each visit • Brief physical examination including weight, ***and*** with particular reference to neurological symptoms • Vital signs including seated blood pressure, pulse rate, respiratory rate (breaths/minute), and temperature. • Urine pregnancy test (for females of childbearing potential) • Clinical laboratory tests (haematology, coagulation, serum chemistry) • PK blood sample for dexamethasone quantitation. • Urinalysis • Concomitant medications review • Concomitant therapies review • Adverse events, including serious adverse events • Patient's Global Impression of Change • Functionality Assessment using the Oswestry Disability Index • Quality of Life Assessment using SF-36 questionnaire • Worst Daily Leg Pain electronic diary
Pharmacokinetic Assessments:	NOTE: PK parameters will be based on plasma concentrations that are dependent on the extent of systemic distribution of dexamethasone from the epidural injection. Blood samples for plasma PK will be obtained at the following time points: Pre-dose, 30, 60, 90 minutes, 2, 4, 6, 8, 12, 20, and 24 hours post-epidural injection. A blood sample for drug concentration analysis will also be collected at each follow-up visit (Days 14, 30, 60, 90, 120, 150 and 180) in all subjects.

	Blood samples in the first 24 hours at the stated times will be collected in a subset of subjects at some sites, totalling approximately 60 subjects. [redacted]: Individual pharmacokinetic parameters for SX600 will be summarized with descriptive statistics. 
Endpoints:	*Primary Efficacy* • The proportion of subjects with a 50% or greater improvement in Mean Worst Daily Leg Pain at 60 days post-dosing (Responders). *Secondary Efficacy* • The proportion of subjects who are Responders (defined as having a 50% or greater improvement in Mean Worst Daily Leg Pain) 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 subjects who have a 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. • Reduction in use of concomitant analgesics and supportive health services. • Time to loss of response, in the subset of subjects who are Responders at Day 14 (50% or greater improvement in Mean Worst Daily Leg Pain). *Safety* • 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
Analysis Populations:	Intent to Treat population: All randomized subjects. Subjects will be included in the treatment group to which they were randomized, regardless of treatment received.

	Safety population: All subjects randomized who proceed to TF-EI (includes patients with attempted but halted or failed TF-EI). In the Safety population, subjects will be included in the treatment group based on the treatment that was received. Modified Intent to Treat (mITT) population: all randomized subjects who receive IMP or placebo by TF-EI. Per Protocol population: all randomized subjects who complete the study without any major protocol violations. PK population: All subjects who received IMP or placebo and with intensive blood collections in the first 24 hours.
Rescue Therapies available:	Any one of the Group 1 and/or any one of the Group 2 rescue medications are available for increases in pain for selection and prescription by the Investigator for up to 14 days (once during the study) as addition to the medications currently used by the patient, with special consideration of safety and potential drug interactions. Group 1 (one of): Amitriptyline 5 – 50mg Nocte, *or* Pregabalin 25mg – 300mg BD, *or* Gabapentin 100mg TDS dosage, up to 600mg TDS (Acute withdrawal of gabapentin or pregabalin can result in withdrawal symptoms, with likelihood related to dose and duration of treatment. If appropriate, down-titration should take place over at least a week, starting no later than day 15 after rescue began.) and/or Group 2 (one of): Tramadol 100mg – 200mg BD, *or* Tapentadol 50 – 200mg BD [redacted]

	[redacted]
Statistical Considerations:	*Sample Size Justification* Limited data are available in the literature on which to base sample size/power considerations. In the study conducted by Ghahreman (Gharheman, 2010), the primary endpoint was the proportion of subjects 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 subjects 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%. *Primary Efficacy Analysis* The primary efficacy endpoint is the proportion of subjects with a 50% or greater improvement from baseline in Mean Worst Daily Leg Pain at 60 days. The primary endpoint will be analysed using a logistic regression model with treatment group (three levels) as a factor. The primary analysis will compare the high dose group to the placebo group using a two-sided test at the alpha=0.05 level of significance. The odds ratio of the high dose group to the placebo group with a 95% Wald confidence interval will also be reported. *Key Secondary Efficacy Analysis* If the comparison between the high dose group and the placebo group is statistically significant ($p<0.05$), then the following analyses will be conducted using a fixed sequence testing procedure to control the overall level of significance: 1. The primary analysis model will be used to compare the low dose group to the placebo group. The odds ratio of the low dose group to the placebo group with a 95% Wald confidence interval will also be reported. 2. Comparing the high dose group to the placebo group, the proportion of subjects with a 50% or greater improvement from baseline in Mean Worst Daily Leg Pain at 90 days will be analysed using the same methodology as the primary analysis. 3. The mean changes from baseline to Day 60 in the Oswestry Disability Index will be compared between the high dose group and the placebo group. 4. Comparing the low dose group to the placebo group, the proportion of subjects with a 50% or greater improvement from baseline in Mean Worst Daily Leg Pain at 90 days will be analysed using the same methodology as the primary analysis. The change from baseline to Day 60 in the Oswestry Disability Index will be analysed using an analysis of covariance (ANCOVA) model with treatment group (three levels) as a factor. All of the above analyses will be conducted using two-sided tests at the alpha=0.05 level of significance. However, once a nonsignificant result occurs, all remaining tests will be exploratory rather than confirmatory

[redacted]

Safety Analyses

Treatment-emergent AEs (TEAEs) are defined as any AE occurring during or after initiation of IMP. TEAEs will be summarized using frequency counts and percentages. Treatment-emergent AEs will also be rated according to severity and relationship to IMP. In addition, all SAEs, deaths, and AEs leading to IMP or study discontinuation will be summarized and listed separately.

Safety laboratory test parameters, vital signs, and ECG results will be tabulated and/or listed.

6 TABLE OF CONTENTS

7 LIST OF TABLES

[redacted]

8 LIST OF FIGURES

[redacted]

9 LIST OF ABBREVIATIONS

Abbreviation	Definition
AAN	Australian Approved Name
AE	Adverse Event
AKA	Artery of Adamkiewicz
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
APPT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BCC	Basal Cell Carcinoma
BD	Twice a Day
BP	British Pharmacopeia
BMI	Body Mass Index
CI	Confidence Interval
CFR	Code of Federal Regulations (USA)
CK	Creatine Kinase
CL/F	Apparent Systemic Clearance
CRF	Case Report Form
CT	Computed Tomography
CTRA	Clinical Trial Research Agreement
DSP	Dexamethasone Sodium Phosphate
DX	Dexamethasone
DXA	Dexamethasone Acetate
ECG	Electrocardiography
eCRF	Electronic Case Report Form
eCOA	Electronic clinical outcome assessment
EDC	Electronic Data Capture
EI	Epidural Injection
ERT	eResearch Technologies Inc.
FDA	Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practice
GGT	Glutamyl Transferase
GLP	Good Laboratory Practice
GRα	Glucocorticoid Receptor
GRE	Glucocorticoid Response Elements
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ITT	Intent-To-Treat
K_2EDTA	Dipotassium Ethylenediaminetetraacetic Acid
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
NASS	North American Spine Society
NHMRC	National Health and Medical Research Council

NOAEL	No Observed Adverse Effect Limit
NRS	Numeric Rating Scale
OGTT	Oral Glucose Tolerance Test
PA	Posterioranterior
PCR	Polymerase Chain Reaction
PEG	Poly(ethylene glycol)
PK	Pharmacokinetic
PLGA	Poly(lactic-*co*-glycolic acid)
PLGA-PEG	Poly(lactic-*co*-glycolic acid)-*[block]*-poly(ethylene glycol)
PT	Prothrombin Time or Preferred Term
QoL	Quality of Life
QSR	Quality System Regulations
RBC	Red Blood Cell
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCC	Squamous Cell Carcinoma
SIS	Spinal Intervention Society
SOC	System Organ Class
SOP	Standard Operating Procedure
SR	Sustained Release
SRC	Safety Review Committee
TB	Tuberculosis
TDS	Three Times A Day
TEAE	Treatment-Emergent Adverse Event
TENS	Transcutaneous Electrical Nerve Stimulation
TF-EI	Transforaminal Epidural Injection
TGA	Therapeutic Goods Administration
TT	Thrombin Time
Vz/F	Terminal Phase
WBC	White Blood Cell
WDLP	Worst Daily Leg Pain
WHO	World Health Organization
W/W	Weight/Weight

10 INTRODUCTION

SX600 (Dexamethasone acetate microspheres for extended-release injectable micro-suspension) is a sustained release formulation of dexamethasone acetate incorporated into biodegradable poly(lactic-*co*-glycolic acid) (PLGA) and poly(lactic-*co*-glycolic acid-[*block*]-poly(ethylene glycol) (PLGA-PEG) polymeric microspheres and is being developed for transforaminal epidural injection of a synthetic steroid formulation as a treatment for subjects with lumbar monoradiculopathy. This formulation is intended to provide sustained release of dexamethasone acetate. [redacted]

Low back pain has been well documented as a very common health problem globally and is the leading cause of activity limitation and work absence throughout most of the world. Low back pain causes more global disability than any other condition. The global age-standardized prevalence of low back pain in 2010 was estimated to be 9.4% (95% CI 9.0 to 9.8) (Hoy, 2014). The prevalence in Australia was 12.9% for men and 11.5% for women. In 2008-2009, around 1.8% of the total health-care expenditure in Australia ($1.2 billion) was attributed to back problems. In 2011, 'back pain and problems' were the third leading cause of disease burden in Australia, accounting for 3.6% of the total burden across all diseases and injuries (AIHW, 2016). Despite widespread clinical use of glucocorticoids for epidural injection, there are currently no steroid drugs on the U.S. or Australian market with an approved indication for epidural administration.

According to SpineThera's proprietary market research, approximately 40% of epidural steroid injections (EIs) performed in the U.S. are repeat injections within 90 days of a subject's first injection, and 33% are repeat injections within 60 days. SX600 is a sustained release formulation of dexamethasone acetate incorporated into biodegradable PLGA polymeric microspheres. This new formulation is intended to provide sustained release of the dexamethasone acetate for greater than 60 days *in vivo* after a single epidural administration, which the Sponsor hypothesizes may provide durable days of pain relief in properly selected subjects. This product may reduce the frequency of epidural steroid injections for the management of lumbar radiculopathy and finally offer physicians and subjects an approved drug for this purpose.

[redacted]

[redacted]

[redacted]

[redacted]

Current Product Name: Dexamethasone acetate microspheres for extended-release injectable micro-suspension (SX600).

This formulation is being evaluated for the indication of lumbar radiculopathy (radiating pain) caused by single intervertebral disc herniation at the L4-5 orL5-S1 levels, involving nerve roots emerging from the L4, L5, and S1 intervertebral foramina. The route of administration of the drug product is identical to that of well-established transforaminal epidural steroid injections that are performed in millions of subjects per year.

[redacted] For the Phase I/II clinical trial, two doses of SX600 will be tested.

[redacted]

Glucocorticoids work to reduce pain and inflammation by binding to the ligand-binding domain of the glucocorticoid receptor (GRα) after passively entering a cell through the membrane. The newly formed complex moves to the nucleus of the cell through the nuclear pore complex and dimerizes to engage with DNA through glucocorticoid response elements (GREs) where effects on transcription take place. Genomic mechanisms at this location include activation or repression of protein synthesis, including cytokines, chemokines, inflammatory enzymes and adhesion molecules. Thus, inflammation and immune response mechanisms are modified (Czock, 2005).

There is strong, circumstantial evidence from laboratory experiments that inflammatory processes may play a major role in the genesis of symptoms when lumbar nerve roots are affected by disc herniations. Administration of corticosteroids therefore constitutes a logical and attractive form of intervention to relieve the symptoms. The transforaminal route of administration offers the advantage that it delivers the drug, in maximum concentrations, closer, if not directly, to the site of pathology, which conventional routes of epidural administration do not guarantee. The most common approach is the transforaminal technique (Derby, 1993) and is favoured by the Spinal Intervention Society (SIS), which involves positioning a needle inside the intervertebral foramen to gain access to the nerve root (Bogduk, 2013).

[redacted]

A dose volume of 1.0 mL (SX600 in 0.9% Sodium Chloride for Injection, BP or equivalent) was selected as the ideal volume for the drug product.

[redacted]

[redacted]

least 12 months; and (5) TF-EIs substantially reduce the need for surgery (NASS Review & Recommendation Statement, 2013).

11 NON-CLINICAL STUDIES

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12 SUMMARY OF KNOWN AND POTENTIAL RISKS

No data are available on the relationship of adverse events to administration of SX600 (Dexamethasone acetate microspheres for extended-release injectable micro-suspension) because no studies have yet been conducted in human subjects. The information provided below references known information about the active moiety (dexamethasone), the active ingredient in SX600, and the transforaminal injection procedure.

Since this is a first-in-human study, no adverse events have been reported with SX600. This section will be updated as studies proceed. However, the subject should be aware of the procedural risks that include allergic reactions, haematoma, dural puncture with spinal headache or arachnoiditis, direct nerve injection and injury. Intravascular injection could lead to rare but serious neurological adverse events including spinal cord infarction, paraplegia, stroke and death. Since the lumbar levels defined in this study are below the terminal level of the spinal cord (L2), there is minimal potential risk to the spinal cord.

The subject should be warned that they might experience numbness or weakness in the lower limb following the procedure as a normal effect of the local anaesthetic injected, but this should wear off once the local anaesthetic has ceased to act. This will be monitored in the recovery facility. Because the active moiety is dexamethasone, the known side effects of this drug are well-documented. Known side effects include: anaphylactoid reactions, changes in heart rate and cardiac arrhythmias, congestive heart failure, oedema, thromboembolism, acne and skin changes, including dry scaly skin, ecchymoses and petechiae, impaired wound healing, increased sweating, rash, striae urticaria. Endocrine changes can include decreased carbohydrate and glucose tolerance, hyperglycaemia, glycosuria, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress. Fluid and electrolyte disturbances, including heart failure in susceptible subjects, fluid retention potassium loss and sodium retention have been described. Potential gastrointestinal changes including abdominal distention, elevation in serum liver enzyme levels, hepatomegaly, increased appetite, nausea, pancreatitis and peptic ulcer have been described.

Adrenocortical suppression with resultant immunosuppression is most likely to occur in patients receiving longer term, high-dose corticosteroid treatment. However, patients receiving moderate doses for short periods, or low doses over a prolonged period, may also be at risk.

Other rare musculoskeletal changes have been associated with corticosteroids, including aseptic necrosis of the femoral and humeral heads, loss of muscle mass, muscle weakness, and osteoporosis with complications in long bones and vertebral compression fractures, steroid myopathy and tendon rupture, mood swings, depression, euphoria, headache, insomnia, neuritis, neuropathy, personality changes and psychic disorders have been associated with corticosteroid use, as has decreased resistance to infection, hiccups, and weight gain.

Because the IMP is a sustained release formulation of a potent corticosteroid (dexamethasone acetate) and the systemic bioavailability of this product is not yet defined in humans, the subject should be notified that any further corticosteroid administration provided as alternative treatment upon withdrawal from the study is not recommended for the duration of the study because of the risk of excessive immunosuppression, and that this must be notified to any subsequent physician referral.

Based on the pre-clinical studies conducted to date, epidural injection of SX600 at the chosen doses and in the restricted lower lumbosacral sites is expected to be well tolerated in humans. Its duration of action in producing pain relief is unknown in humans and will be determined by subject assessment out to 180 days following a single treatment.

For this study, medical imaging must demonstrate a cause of radicular pain and radiculopathy amenable to treatment with transforaminal injection of corticosteroids, such as disc herniation, and must exclude causes for which treatment by injection is not appropriate, such as tumours, cysts, and angiomas. Other causes of axial-derived pain, including clinically significant spinal and foraminal stenosis should be excluded.

This study also involves patient exposure to a very small amount of radiation. At the estimated highest radiation dose associated with TF-EI (Braun, 2018) this risk is believed to be very low.

The effects of SX600 in the unborn child and on the newborn baby are not known.

13 CONTRAINDICATIONS

13.1 Steroid Contraindications

Coexisting systemic fungal infection contraindicates the administration of corticosteroids.

Administration of live virus vaccines is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. The antibody response to other vaccines may be diminished.

13.2 Procedural Absolute Contraindications (SIS practice guidelines)

Absolute contraindications include inability or unwillingness to sign the informed consent for the procedure, history of anaphylaxis to the contrast medium, presence of an untreated or unresolved localized infection in the procedural field, and the subject is unable to cooperate during the procedure.

13.3 Procedural Relative Contraindications (SIS practice guidelines)

- Allergy to any of the drugs that are to be administered.
- Pregnancy
- Concurrent use of anticoagulants
- Anatomical derangements, congenital or surgical, that compromise the safe and successful conduct of the procedure
- Known systemic infection
- Coexisting disease producing significant respiratory or cardiovascular compromise
- Immunosuppression

Risks include but are not limited to infection, allergic reaction, haematoma, no change in pain or increased pain, dural puncture with spinal headache or arachnoiditis, and spinal cord injury. The subject should be fully informed and should understand what to expect: that they might experience numbness

or weakness in the lower limb following the procedure. This is a normal effect of the local anaesthetic that is injected, and it should wear off once the local anaesthetic has ceased to act.

[redacted]

15 JUSTIFICATION OF THE STUDY

The design and choice of the trial population for this first-in-human, clinical Phase I/II study, is based on the need to initially demonstrate the safety and efficacy of SX600 in humans. In addition, the PK and efficacy outcome measures in this study may also answer questions concerning the duration of action in a clinical setting. The study should also assist with the choice of dose for subsequent single dose studies in subjects.

This first-in-human study is a Phase I/II, double-blind, parallel-group, randomized, placebo-controlled multi-centre trial in 180 subjects randomized 1:1:1 to IMP (Dexamethasone acetate microspheres for extended-release injectable micro-suspension, SX600 at 12.5 mg or 25.0 mg DXA) 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. Only the on-site dedicated person(s) designated to prepare and administer the IMP or placebo, will be aware of treatment assignment. Each subject will be followed by a blinded, independent Investigator and site staff 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 AEs.

16 JUSTIFICATION OF THE ROUTE OF ADMINISTRATION AND DOSE

Steroids have been widely used to treat radicular pain both in cervical and lumbar radiculopathies and have been used as an off-label therapeutic modality, since no steroids are approved for epidural administration at this time. The most common approach is the transforaminal technique (Derby, 1993) and is favoured by the SIS, which involves positioning a needle inside of the intervertebral foramen to gain access to the nerve root (Bogduk, 2013). In this study, only a single transforaminal injection into foramen at the L4-5, L5-S1, or the S1 foramen will be used. Many reports, including a few randomized controlled trials, have documented the clinical utility of transforaminal epidural steroid injections. [redacted]

Dose selection:

[redacted]

The dosing proposed by SpineThera Australia falls within the normal off-label dosing of many corticosteroids, in addition to dexamethasone sodium phosphate.

17 STUDY PURPOSE

One hundred and eighty (180) subjects, aged 18 to 65 years, male and female, for the study will be sourced from those presenting to the investigative sites, where the participation in the study is offered for the management of monoradicular pain of severity (Mean Worst Daily Leg Pain of ≥5.0 and ≤9.0 being the *mean* NRS score (to 1 decimal place) of 5 days (as further defined in the Efficacy Assessments), of duration 4 weeks to 6 months that requires interventional treatment, having failed conservative therapies.

This study represents the first-in-human study and seeks to characterize the safety of SX600 (Dexamethasone acetate microspheres for extended-release injectable micro-suspension) when administered by TF-EI in a highly selected patient population in terms of specificity of the position of a single nerve root, and in the absence of axial contributions to the pain. Systemic pharmacokinetics are included to provide surrogate evidence of the duration of corticosteroid release from the microspheres as validation for the potential extended duration of action.

18 STUDY OBJECTIVES

18.1 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 DXA) of dexamethasone acetate microspheres for extended-release injectable micro-suspension, SX600 (IMP) from a single transforaminal epidural placement of 1.0 mL.

18.2 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

19 STUDY DESIGN

19.1 Duration

Following informed consent, subjects will be randomized 1:1:1 to receive SX600 (Dexamethasone acetate microspheres for extended-release injectable micro-suspension) at 12.5 mg or 25.0 mg DXA 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. Each subject 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.

The study is expected to enrol over a period of 9 months. Each subject is expected to be in the study for 7 months. The total duration of the study is expected to be 19 months (9 months enrolment + 7 months follow-up + 3 months reporting).

Subjects will be screened within 28 days (Day -28 to -1) prior to Day 0. On Day 0, following final pre-dose qualifications and pre-dose collection of blood for PK, subjects will receive a single dose of SX600 (Dexamethasone acetate microspheres for extended-release injectable micro-suspension) at 12.5 mg or 25.0 mg DXA or Placebo (0.9% Sodium Chloride for Injection, BP) via TF-EI at time zero (0).

Blood for evaluation of microsphere drug release duration will be collected for all subjects at each visit. In addition, in a subset of approximately sixty (60) subjects, blood for PK analysis will be collected at 30, 60, 90 minutes, and at 2, 4, 6, 8, 12, 20 and 24 hours. Those subjects consenting to PK assessment will remain at the investigational Site from admission to 24 hours after IMP or placebo administration.

19.2 Rationale

Safety parameters will be collected pre-dose and at intervals specified in the schedule of procedures. Safety parameters will be collected, including ECG, vital signs, clinical laboratory panels, physical exam, urinalysis, adverse events, concomitant medications, etc. at each visit, as will functionality and quality of life assessments.

This is a first-in-human study to assess the safety and efficacy of two doses (12.5 mg or 25.0 mg DXA) of dexamethasone acetate microspheres for extended-release injectable micro-suspension, SX600 (IMP) administered by transforaminal injection to the lumbosacral epidural space at the L4- L5, L5-S1 level, or the S1 nerve root, as an outpatient procedure, 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.

Subjects enrolled in the study must have a defined Mean Worst Daily Leg Pain of ≥5.0 to ≤9.0 (being the ***mean*** NRS score, to 1 decimal place, of 5 days as further defined in the Efficacy Assessments) after at least 4 weeks but less than 6 months of conservative therapy. Validation of the single herniated disc consistent with the clinical features requires an MRI or CT scan of the lesion within 3 months of planned IMP administration. The pain history must be that of unilateral pain, radiating into a lower limb, of lancinating, burning, stabbing or electric quality, of duration 4 weeks to 6 months, and in the absence of significant axial contribution to the source of the pain.

Despite widespread clinical use of glucocorticoids for epidural injection, there are currently no steroid drugs on the U.S. or Australian market with an approved indication for epidural administration. Additionally, approximately 40% of EIs performed in the U.S. are repeat injections within 90 days of a subject's first injection, and 33% are repeat injections within 60 days. This new formulation is intended to provide sustained release of the dexamethasone acetate for greater than 60 days ***in vivo*** after a single epidural administration, which the Sponsor hypothesizes may provide durable pain relief in properly selected patients. This product may reduce the frequency of epidural steroid injections for the management of lumbar radiculopathy and finally offer physicians and patients an approved drug for this purpose.

As secondary measures, functionality as measured by the Oswestry Disability Index and quality of life (SF-36 scoring) will be measured, and subjects will be followed for 180 days with 30-day visits measuring the pain response compared to baseline measures, with a Responder defined as subjects whose Mean Worst Daily Leg Pain (***mean*** NRS score, to 1 decimal place, of 5 days), is ≥50% lower than that recorded at baseline (in the week pre-treatment.) The primary efficacy endpoint will be at 8 weeks post-treatment, but all

measures will be recorded at each 30-day visit, thus providing some evidence of the duration of treatment efficacy.

19.3 Minimisation of Bias

Potential sources of bias have been considered and minimised through the study design, including:

- Eligibility of subjects will be confirmed by screening against all of the inclusion and exclusion criteria
- Investigational sites will be encouraged to enrol at least 5 subjects and enrolment at any one site will be capped at 50 subjects
- Investigational site staff who are involved in administration of IMP will not be involved in subsequent subjects' visits or assessments, in order to maintain the blind
- All investigational sites will utilize this Protocol and standardized CRFs for collection of data
- All subjects will be provided with standardised method for collection of patient-reported outcomes
- All Sponsor and Site personnel will be trained in study-specific procedures according to standardised training materials
- A Safety Review Committee, including an independent Medical Monitor will be used to assess safety
- A Statistical Analysis Plan will be developed prior to unblinding of the study.

20 STUDY ENDPOINTS

20.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with a 50% or greater improvement in Mean Worst Daily Leg Pain at 60 days post-dosing (Responders).

20.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- The proportion of subjects who are Responders (defined as having a 50% or greater improvement in Mean Worst Daily Leg Pain) 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 subjects who have a 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.
- Reduction in use of concomitant analgesics and supportive health services.
- Time to loss of response, in the subset of subjects who are Responders at Day 14 (50% or greater improvement in Mean Worst Daily Leg Pain).

20.3 Safety Endpoints

The Safety outcome will be assessed by:

- Subjects reporting AEs from treatment day through study conclusion
- The number of subjects reporting serious adverse events (SAEs) considered product or procedure-related throughout the study
- Neurological consequences of the TF-EI
- Number of subjects experiencing non-laboratory AEs following TF-EI throughout the study
- Number of subjects experiencing laboratory AEs 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

20.4 Pharmacokinetic Parameters

Individual pharmacokinetic parameters for SX600 will be summarised with descriptive statistics. Pharmacokinetic parameters will be calculated using non-compartmental analyses and PK modelling, [redacted]

[redacted]

21 SUBJECT ELIGIBILITY

One hundred and eighty subjects, male and female aged 18 to 65, will be sourced from those presenting to the investigative sites, where the participation in the study is offered for the management of monoradicular pain of severity (Mean Worst Daily Leg Pain of ≥5.0 and ≤9.0) and of duration 4 weeks to 6 months, that requires interventional treatment, having failed conservative therapies.

Subjects will be screened to ensure they meet all the inclusion and none of the exclusion criteria. Subjects 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.

21.1 Inclusion Criteria

1. Adult aged 18 to 65 years, capable of providing informed consent, capable of complying with the outcome instruments, and meeting the attendance requirements for review as defined in the study.
2. Presenting with a history of unilateral pain, radiating into a lower limb, of lancinating, burning, stabbing or electric quality, of duration of current episode being 4 weeks to 6 months prior to study enrolment, having failed conservative therapy.
3. Mean Worst Daily Leg Pain score of ≥5.0 and ≤9.0 being the *mean* NRS score (to 1 decimal place) of 5 days (as further defined in the Efficacy Assessments).
4. Demonstration of a disc herniation within 3 months by CT or MRI at the segmental levels of L4-L5, or L5-S1, [redacted]
5. The site of the disc herniation must affect L4-5 or L5-S1, with involvement of the L4, L5, or S1 nerve roots unilaterally
6. [redacted]

[redacted]

8. Women of child-bearing potential must agree to use a medically accepted method of contraception for the duration of the study plus 30 days and register a negative pregnancy test prior to dosing.
9. Men must agree to abstain from intercourse with women or agree to use a medically accepted method of contraception and refrain from donating sperm for the duration of the study plus 30 days.
10. Willing to comply with all the study activities and procedures throughout the duration of the study.

21.2 Exclusion Criteria

Subjects who meet any of the exclusion criteria at Visit 1 will be excluded from study participation and may be replaced. Exclusion criteria must be assessed by a study investigator who is also a clinician licensed to make medical diagnoses. Subjects will not be able to participate if they have any of the following:

1. Documented history of allergy or intolerance to components of the IMP, relevant radiologic contrast media, or local anaesthetics.
2. Is pregnant or lactating.
3. Has been taking corticosteroid medications routinely in the past 6 months *or* has received an epidural corticosteroid injection within 12 weeks of screening.
4. Has a BMI greater than 40 kg/m^2.
5. Has Diabetes Mellitus (Type 1 or Type 2) - prior confirmed HbA_{1c} or OGTT
6. [redacted]

12. Has a history of significant leg pain unrelated to disc herniation that would significantly compromise assessment of back or leg radicular pain.
13. Has radiological evidence of symptomatic disc herniation above L4-L5.
14. Has radiological evidence of clinically significant foraminal stenosis at L4-L5 or L5-S1 or of clinically significant spinal stenosis, or spondylolisthesis (Grade 2 or higher). (Note, asymptomatic foraminal stenosis at other spinal levels is not excluded).
15. Has had lumbar back surgery.
16. [redacted]

19. [redacted]

22. Has received an implantable device for pain management
23. [redacted]

22 STUDY SCHEDULE AND PROCEDURES

Prior to commencing any study-related procedures it is the Principal Investigator's responsibility to ensure that the study and the Investigational Site has received Ethics approval and Regulatory Authority approval (where relevant) *and* has received written authorization to commence study-related procedures for the Sponsor *and* the Participant Informed Consent Form has been signed by the subject and a study Investigator (who is also a clinician).

Due to the nature of the investigational product and the phase of the study, the Sponsor will review all investigator CVs and the study delegation log prior to commencement of enrolment at each site. Further, diagnostic and pain assessments at Visit 1 and Visit 2 must be performed by an Investigator with Specialist Pain qualifications who has been approved by the Sponsor and delegated to perform these assessments (ie: an approved Investigator). The TF-EI at Visit 2 must be performed by an Investigator who has been approved by the Sponsor and delegated to perform this procedure. Subsequent visits can be performed by other study staff, including general practitioner investigators. Subjects who fail therapy must subsequently seen by an approved Investigator (Pain Specialist) to ensure that appropriate follow-on clinical care modalities are offered to and made available to this patient.

[redacted]

[redacted]

22.1 Consent

A subject can only consent to participation in this study after all aspects of the study have been explained to the subject, the subject has had adequate time (in their opinion) to consider the information relating to the study and that any questions they may have related to the study are answered adequately. Participation in the study is entirely voluntary and a subject may withdraw consent to participate at any time with no consequences to their standard care regimen provided by their usual treating clinician.

Sponsor and Human Research Ethics Committee approval of the Participant Informed Consent Form (including any required privacy language) is required prior to the enrolment of any subjects in this study. Any changes to the Participant Informed Consent Form language must be approved by the Sponsor and the Human Research Ethics Committee prior to being used to consent or re-consent subjects.

The Investigator must notify all subjects, including completed and withdrawn subjects, of any significant new information that becomes available during the course of the study. All previously consented subjects may be required to consider and provide reconsent.

A subject is considered enrolled in the study when the Participant Informed Consent Form has been signed by the subject and a study Investigator (who is also a clinician).

22.2 Study Visits

***Screening*: Day -28 to Day -1:**

This is the screening visit to determine study eligibility, plus baseline measure of Oswestry Disability Index, and recording of all current treatments (medications, physical therapy etc).

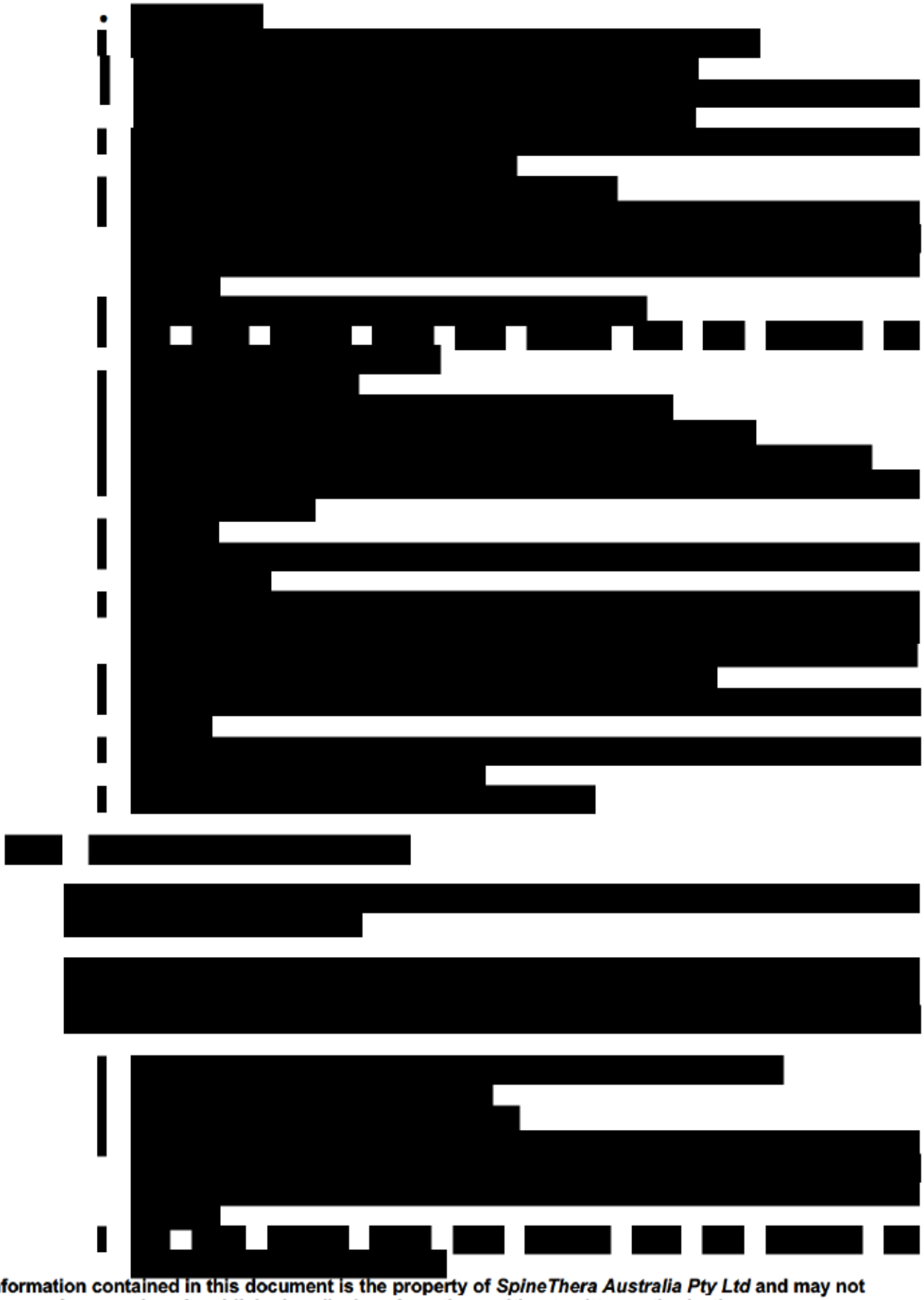
***Baseline/Treatment Day 0*:**

The intervention day when TF-EI is performed, and with 24hr Pharmacokinetic blood sample collections in the assigned subject population.

Follow-up Visits:

Post-dosing at Day 1 and Day 7, a telephone call will review subject status, and seek reporting of any AEs. At Days 14, 30, 60, 90, 120, 150, and 180 post-treatment, the subject will return to the Investigational Site for detailed assessment of both efficacy measures and safety assessments.

[redacted]



22.2.3.1 TF-EI Procedure

1. [redacted]

NOTE: If injection into an artery has been demonstrated, the procedure should be terminated, and the subject exited from the study. Physicians should not assume that simply repositioning the needle will avoid subsequent intra-arterial injection or uptake of the steroid preparation. The subject may be replaced in the study. The subject will be followed per standard of care.

8. [redacted]

[redacted]

[redacted]

22.2.3.4 Recovery Procedures Post- Epidural Injection

The patient should be transferred to the recovery area, where observations for at least 1 hour including intermittent pulse, respiration, blood pressure monitoring must be completed by a member of the study team.

Prior to discharge, a peripheral neurologic examination of the leg on the side of injection should be conducted by an approved Investigator to exclude any motor weakness, and confirmation of ability to walk and maintain secure balance should be confirmed.

Any complications attributable to, or following, the procedure should be promptly managed in an appropriate manner and recorded in the study documentation (CRF). Once the patient and the physician are satisfied that the patient has suffered no ill-effects, the patient can be discharged after a minimum of 1 hour of observation.

Discharge instructions include:

1. The patient is not to operate a motor vehicle or machinery for the remainder of the day of the procedure, because any numbness due to the local anaesthetic might interfere with their ability to use a pedal.
2. The patient should contact the physician who performed the procedure if they experience any unusual symptoms following the procedure including, but not limited to, headache, fever, chills, increased pain, or paralysis. Contact details must be provided to the patient at the time of discharge.
3. The patient should slowly resume previous activities over a period of several days.
4. Arrange for Visit 3 (14 days +/- 2 from dosing).
5. Instruction for continued daily recording each evening of Worst Daily Leg Pain in the electronic diary.
6. Remind the subject of the telephone call the next day, and again on Day 7 for safety assessment.

22.2.3.5 Procedures for Identifying Inadvertent Administration

Validation of the appropriate position of the needle tip is based on:

1. Absence of flash-back of clear fluid (CSF) or blood in the needle cavity. Further validation can be sought by aspiration of the needle.
2. Interpretation of the radiologic screening of the injection through the needle of a small volume of contrast agent while continuously screening.

[redacted]

[redacted]

22.2.3.6 Pharmacokinetic Sampling

Following IMP/placebo administration, subjects allocated to the Pharmacokinetic population, will remain in-patient for the scheduled venous blood collection over 24 hours for pharmacokinetic analysis.

After the pre-dose baseline blood sample, post-dose blood samples for the measurement of the dexamethasone concentration in systemic circulation will be collected at the following time-points post-dose: 30, 60, 90 minutes, 2, 4, 6, 8, 12, 20, and 24 hours. Subjects will be discharged from the Investigational Site following collection of the 24 hr PK sample and all 24-hour safety measures (as listed below for other subjects (Telephone call 1) have been conducted and recorded.

Pharmacokinetic sampling is further outlined in Attachment 03 Pharmacokinetic (PK) Laboratory Manual (CLIN-0038).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

22.3 RANDOMISATION

Subjects will be randomly assigned in a 1:1:1 ratio to one of two doses of SX600 (12.5 mg DXA for the low-dose group, or 25.0 mg DXA for the high dose group,) or Placebo (0.9% Sodium Chloride for Injection, BP or equivalent), with a final assignment of 60 subjects/group. The list of randomized treatment assignments will be prepared by statisticians assigned to the study and will be shared with the storage and distribution subcontractor of the study. Additionally, a separate randomisation list known as a kit list will be prepared by the statisticians assigned to the study. The kit list will also be distributed to the storage and distribution subcontractor. The storage and distribution subcontractor will prepare the correctly linked kit number and randomisation number and assign the appropriate IMP to each site. The kit number will be printed on IMP labels and cartons, while the randomisation number will be written in at treatment onto the labels of the IMP. Upon delivery of IMP to sites, there will be a master allocation list with each shipment that links a kit number to a corresponding randomisation number. Each site shall assign an enrolled patient a randomisation number in numerical order. At Visit 2, the unblinded clinician will select the kit number associated with the assigned patient randomisation number and use for injection. The site will not be responsible for randomising treatment groups as each randomisation number that is assigned to each consented patient in the study will already have the treatment selected. The kit number and randomisation number will be recorded in source data.

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 subject 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.

Randomisation is further outlined in Attachment 04 IMP Randomisation and Shipment Process (CLIN-0037).

22.4 UNBLINDING

Unblinding is allowed where relevant to the acute clinical management of the subject.

The blind may be broken in situations in which the unblinded Investigator (each site must have at least one unblinded Investigator, usually the proceduralist, delegated on the study log) determines that adequate medical care cannot be provided without the knowledgeof treatment assignment, or, in situations in which a physician treating a subject cannot contact the unblided Investigator and then subsequently contacts the Southern Star Research Unblinded Safety Officer. If a code break must occur, the code break may only be undertaken by the unblinded Investigator or the Southern Star Research Unblinded Safety Officer. Contact details for the site and the Southern Star Research Unblinded Safety Officer must be made available to participants eg: using a Participant Identification Card.

Contact Information for Emergency Unblinding

[redacted]

If the blind has been broken, the unblinded Investigator must document the date and the reason the blind was broken in the source notes and CRF.

22.5 EARLY WITHDRAWAL

Subjects will be encouraged to complete the study and all assessments. A subject may withdraw consent to participate in the study at any time. A subject may be withdrawn from the study for the following reasons:

- Subject withdraws consent
- Subject is lost to follow-up
- Investigator deems early withdrawal necessary
- Other
- Study is terminated

Subjects who withdraw or are withdrawn prior to TF-EI procedure will be replaced. Subjects who withdraw or are withdrawn after IMP administration will NOT be replaced. An Early Withdrawal visit will be completed where possible. Upon withdrawal from the study and completion of the early withdrawal visit, no further study data will be collected, nor study visits occur for the subject. Subjects will be included in analyses up to the time that consent was withdrawn.

If the patient withdraws early the patient should be assessed at the time of withdrawal by an approved Investigator with Specialist Pain qualifications to ensure that appropriate follow-on clinical care modalities are offered to and made available to this patient.

Refer to Section 22.2.12 Early Termination or Subject Early Withdrawal Visit for procedures to be followed if a subject withdraws or is withdrawn from the study.

In the case of subjects who fail to appear for a follow-up assessment, efforts to contact should include at least one telephone call and one letter, which should be documented in the subjects' records. Any additional requirements of the Human Research Ethics Committee should be followed. Lost to follow-up subjects will be withdrawn.

23 ASSESSMENTS

23.1 Efficacy Assessments.

Efficacy assessment will be based on the categorical measure of a Responder, defined as the proportion of subjects at Day 60 post-dosing in each active dose group compared to placebo with a 50% or greater improvement in Mean Worst Daily Leg Pain (WDLP) score compared to baseline. This pain scoring data will be derived from the E-Diary recordings entered by the subjects using eREsearch Technologies Inc electronic Clinical Outcome Assessment SALIENT Clinical Study app (ERT LPRI 424/301). WDLP score will be collected via the app once daily between 18:00:00 and 23:59:59 using the prompt *What was your worst leg pain today?* and a visual scoring range of 0 (no leg pain) to 10 (worst imaginable leg pain).

Subjects will be trained and reminded at each study visit to enter a measure of worst daily leg pain in the evening of each day. This is to establish a learned behaviour that ensures appropriate recording of the essential time period from which the mean values are derived. Where WDLP score has not been entered into the SALIENT Clinical Study app for a given 24hour period, an email notification will be automatically sent to the study team to follow up with the subject to ensure ongoing compliance to submission of WDLP data. The mean WDLP will be calculated as defined further below.

It is important that the critical levels of Mean Worst Daily Leg Pain (NRS Score of 5.0-9.0) is *NOT communicated to the patient at any stage* so that they remain unprogrammed and objective in any daily scoring.

If, in the opinion of the Investigator, additional treatment beyond the rescue medication approach provided in this protocol is required, for example surgery, the patient will be deemed a non-responder in the efficacy analysis at timepoints after the additional treatment but will continued to be followed in the safety population. In this case, the patient shall not continue to report worst daily leg pain score in the electronic diary but shall continue to record concomitant therapy and safety measures in the paper diary.

[redacted]

23.2 Functional Outcomes

Functional outcomes following treatment will be assessed by the Oswestry Low Back Pain Disability Questionnaire (Oswestry Disability Index) which provides information as to how the pain has affected the subject's ability to manage everyday life. This test has been in use since 1980 and is considered a "gold standard" of low back pain functional outcome tools. The Questionnaire will be completed by the subject at each study visit. The Disability Index will be calculated from each completed Questionnaire by the study personnel.

Interpretation of scores is:

- 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

23.3 Patient Clinical Global Impression of Change

A Patient Clinical Global Impression of Change will be assessed using the following 7-point scoring classification:

1. Very much improved
2. Much improved
3. Slightly improved
4. No change
5. Slightly worse
6. Much worse
7. Very much worse

23.4 SF-36 Assessments

SF-36 is a set of generic, coherent, and easily administered quality-of-life measures., presented as a questionnaire that addresses eight health concepts:

- physical functioning (PF)
- role physical (RP)
- bodily pain (BP)
- general health (GH)
- vitality (V)
- social functioning (SF)
- role emotional (RE)
- mental health (MH)

The Quality of Life patient questionnaire Short Form (36) Health Survey (SF-36) will be completed by patients at each visit.

23.5 Safety Assessments

23.5.1 Adverse Events

Adverse events, including Serious Adverse Events will be collected throughout the study duration, starting at Visit 2 (Baseline/Treatment, Day 0) and ending at Visit 9 (Day 180 post-dosing) or until all ongoing adverse events are deemed resolved or stable by the Principal Investigator. Where an early withdrawal visit occurs prior to Visit 4, the Investigator must report all SAEs occurring from the time of Visit 2 (Baseline/Treatment) until 30 days after treatment with the IMP/Placebo.

Resolution of an AE is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

Adverse events will be reported by the study subjects in the subject diary and/or to the study staff at each study visit. Recording of AEs will occur on an Adverse Event eCRF which will include the reported verbatim term (diagnosis where possible), Start Date, End Date, Outcome, Severity, Causality, Action Taken with IP and procedure and Seriousness.

Any SAE or subject death that occurs from and including Visit 2 (Baseline/Treatment onwards, whether or not related to IMP/Placebo, must be reported within 24 hours via e-mail at the address noted below. A completed Serious Adverse Event Report Form with as much detail as possible must be included with the email, while ensuring that the SAE report contains the minimum criteria for reporting (participant ID, adverse event term, suspected investigational product, reason for meeting serious criteria and relationship to investigational product, name of the reporter).

Contact Information for SAE Reporting

[redacted]

Pre-existing conditions or planned treatment (such as hospitalization) for pre-existing conditions are not considered adverse events unless the nature and severity of the condition has worsened.

Details of AE definitions, collection, recording, and reporting are found in Section 26.2

23.5.2 Demographic/Medical History

Information relating to the subject's age, sex, and race, will be recorded at Screening on the appropriate CRF.
Medical history will be recorded at Screening on the appropriate CRF, and brief physical review seeking to record changes in medical history will be collected at Baseline on the day the TF-EI is performed, and at all subsequent clinic visits.

23.5.3 Physical Examination & Neurological Assessment

An abbreviated physical examination will be performed at Screening and Baseline visits, but with special attention to examination of the lower back and neurologic assessment of the lower limbs. This will particularly seek to determine motor function in the affected leg and will assess and record any sensory change that might coincide with the dermatomal representation of the affected nerve root. Examination of the lower back will seek to assess axial sources of pain that may contribute to the presenting pain and are therefore exclusionary.

If the characteristics of the pain or its intensity increases during the study, a detailed peripheral neurology examination should be performed to include motor strength and function, proprioception, sensation, reflexes, and gait and balance for the clinical assessment of a significant change in the original presenting pathology or the potential occurrence of newly-presenting co-morbidity. This can include new radiological investigation at the discretion of the Investigator, and treatment be recommended to provide "standard-of-care" management.

Careful examination of the skin in the area of potential TF-EI will be performed to identify any skin infection or inflammation that may contraindicate the procedure. Straight-leg-raising in the affected lower limb should be measured and recorded in the CRF.

The physical examination will include brief assessment of the head and neck, abdomen, chest, cardiovascular system and heart, respiratory, musculoskeletal, skin, general neurologic assessment, and any gross evidence of endocrine dysfunction. The physical assessment is mandatory at all unscheduled visits and at early termination visits per the Investigator's discretion. Body weight will also be recorded at Screening and Baseline and subsequent study visits, but subject height will be recorded at Screening Visit only.

23.5.4 Vital Signs

Blood pressure and pulse rate will be recorded at study visits and will be taken preferably using an automated recording machine programmed to take preferably 3 consecutive readings at least 2 minutes apart, with the subject seated comfortably for at least 3 minutes prior to blood pressure readings. Respiratory rate and temperature will be measured at all study visits.

23.5.5 Concomitant Medications/Therapies.

All concomitant medications and therapies in the preceding 30 days will be recorded at the Screening Visit and any changes or additions to medications or therapies for any medical reason or additions of rescue medications as listed in Section 25.8.1 must be recorded at each subsequent study visit.

The pain-relief needs of the subject should be carefully assessed at each study visit following IMP/placebo administration and prescribed medications and therapies tailored to the needs of the subject.

If, in spite of continued therapies, the subject requires additional analgesic medication for radicular pain, then a choice of rescue medication as listed in Section 25.8.1 can be added as deemed necessary and safe by the Investigator. If, in the opinion of the Investigator, additional treatment for radicular pain beyond the rescue medication provided in this protocol is required, the patient will be deemed a non-responder in the efficacy analysis at timepoints after the additional treatment but will continued to be followed in the safety population.

23.5.6 Electrocardiography (ECG)

A 12-lead ECG will be recorded in triplicate at least 2 minutes apart and assessed at the Screening Visit, and again at the final Visit 9. The assessment is optional at unscheduled visits and at early termination visits, per the Investigator's discretion.

23.5.7 Laboratory Assessments

Clinical laboratory evaluations will be performed by the local Clinical Pathology Laboratory. Specific tests to be performed are described below:

- Haematology including: [redacted]
- Coagulation [redacted]: [redacted]
- Clinical chemistry (non-fasting serum) [redacted]
- Urinalysis: [redacted].

23.5.8 Virus Serology

HIV (antibodies to human immunodeficiency virus type 1 (HIV-1)), Hepatitis A (hepatitis A virus antibodies (HAV)), Hepatitis B(hepatitis B surface antigen (HBsAg)) and Hepatitis C (hepatitis C virus antibodies (HCV))testing will be performed at Visit 1, D-28 – D-1 Screening, on a blood sample sent to the local Clinical Pathology Laboratory. HIV testing will be performed as per local standards. It is recommended that an antibody or antibody/antigen test be used for screening. If antibody or antibody/antigen testing results in an indeterminate test, HIV PCR may be used to further evaluate the HIV status of the subject.

23.5.8.1 Pregnancy Screen

Pregnancy testing will be performed in all female subjects of child-bearing potential at Visit 1, D-28 – D-1, Screening (serum) Serum pregnancy testing will be performed at the local Pathology Laboratory. At Visit

2 and all subsequent visits, urine pregnancy test will be performed. Urine pregnancy test in females of childbearing potential will be performed in the research clinic, or Local Pathology. Any pregnancy in a subject or partner of a subject must be reported within 24 hours per Section 26.3.

23.5.9 Urine Drug Screening

Urine drug screen (cocaine, cannabinoids, opiates, benzodiazepines, and amphetamines) will be tested at Visit 1 Screening visit Treatment on a sample sent to the local Clinical Pathology Laboratory, and at Visit 2 Baseline using a urine dip test at the study site. Subjects with a positive screen test results for any of the above substances will be excluded from the study (with the exception of positive testing for amphetamines for prescribed ADHD therapy or benzodiazepines for the pre-study prescribed treatment as sedative-hypnotics or for anxiety). Positive drug tests cannot be repeated.

23.5.10 Pharmacokinetic Assessments

In this study, systemic blood levels reflect a surrogate measure of drug concentration released locally from the drug depot in the transforaminal site.

Every study subject will have an aliquot of blood collected at each clinic visit to assess drug release duration from the microspheres. At the completion of the study, a reduced sample of placebo subject samples will be analysed, and if a timepoint is reached where no dexamethasone is measured in any of the active dose group subjects, then further analysis may be discontinued.

Blood to assess microsphere drug release duration will be collected for all subjects at each visit. In addition, approximately sixty (60) subjects from a subset of sites will be assigned to a "PK Population".

Plasma PK: PK parameters based on plasma concentration will be dependent on the extent of systemic absorption of dexamethasone from the epidural depot.

Blood samples for plasma PK will be obtained at the following time points:

Collection time	Window
30 minutes post TF-EI	±5 minutes
60 minutes post TF-EI	±10 minutes
90 minutes post TF-EI	±10 minutes
2 hours post TF-EI	±20 minutes
4 hours post TF-EI	±20 minutes
6 hours post TF-EI	±20 minutes
8 hours post TF-EI	±20 minutes
12 hours post TF-EI	±20 minutes
20 hours post TF-EI	±20 minutes
24 hours post TF-EI	±20 minutes

A blood sample for drug concentration analysis will be collected pre-dosing and at each follow-up visit (pre-dose,14, 30, 60, 90, 120, 150 and 180-days post-dosing) in all subjects.

The following PK parameters will be determined:
Individual pharmacokinetic parameters for SX600 will be summarized with descriptive statistics. [redacted]

[redacted]

23.5.11 TF-EI Imaging

Available imaging of transforaminal contrast spread during TF-EI will be collected as source and may be used for efficacy and safety analysis where relevant.

24 DEVIATION HANDLING

Deviations will be defined by NHMRC Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods 2018.

All deviations will be recorded on the Deviation page of the eCRF. Additionally, Serious Breaches will be reported on the NHMRC Serious Breach Report Form (Sponsor) and Suspected Breaches will be reported on the NHMRC Suspected Breach Report Form (Third Party).

Table 5. Deviation Definitions.

Deviation	Any breach, divergence or departure from the requirements of Good Clinical Practice or the clinical trial protocol.
Serious Breach	A breach of Good Clinical Practice or the protocol that is likely to affect to a significant degree: a) The safety or rights of a trial participant, or b) The reliability and robustness of the data generated in the clinical trial.
Suspected Breach	A report that is judged by the reporter as a possible serious breach but has yet to be formally confirmed as a serious breach by the sponsor

Table 6. Deviation Reporting Requirements and Timeframes.

Sponsor	
Serious Breach	Report to **HREC** within **7 calendar days** of confirming a serious breach has occurred and provide follow-up reports when required
	Notify trial **site**'s Principal Investigator within **7 calendar days** of confirming a serious breach has occurred
	Report to **HREC** within **7 calendar days** of the decision, where a Sponsor determines a third-party report, provided to it by the HREC, meets the definition of a serious breach
	Report to **HREC** by letter or e-mail, including a justification for this decision, within **7 calendar days** of confirming a serious breach has not occurred where the Sponsor determines a third-party report, provided to it by the HREC, does not meet the definition of a serious breach
	Notify the **TGA** and **HREC** if the serious breach leads to the closure of the site
	Report to the **TGA** any serious breach that involves a defective product that may have wider implications for the supply chain for that marketed product
Investigator	
Serious Breach or Suspected Breach	Report to Sponsor within **72 hours** of awareness
Serious Breach (that have been confirmed by the Sponsor as occurring at the site)	Report to the **Institution** within **72 hours** of being notified of the serious breach

25 INVESTIGATIONAL DRUG INFORMATION AND MANAGEMENT

25.1 Investigational Drug Regimen

In SX600, the dexamethasone acetate (DXA) is dispersed in a biodegradable polymer matrix and formed into solid microspheres to slowly release the drug and potentially provide durable pain relief in subjects. [redacted]

A dose volume of 1.0 mL (SX600 in 0.9% Sodium Chloride Injection, BP) was selected as the ideal volume for the IMP. [redacted] Two doses of SX600 will be tested in the Phase I/II clinical trial, 12.5 mg and 25.0 mg dexamethasone acetate reconstituted in 0.9% Sodium Chloride for Injection, BP, and delivered in 1.0 mL to the subjects.

[redacted]

[redacted]

The Placebo product for the clinical trial will be 0.9% Sodium Chloride for Injection, BP.

25.2 Dose Rationale

SX600 (Dexamethasone acetate microspheres for extended-release injectable micro-suspension) is a microsphere formulation of dexamethasone acetate, a corticosteroid, to be administered by transforaminal epidural injection. The route of administration of the IMP is identical to that of well-established transforaminal epidural steroid injections that are performed off-label in millions of subjects per year. Dosing in this study will involve a single administration of a 1 ml dose delivered to the transforaminal epidural space adjacent to an affected nerve root.

Based on the NOAEL doses identified in the nonclinical studies conducted in beagle dogs and rats, and the toxicokinetic profile [redacted] it has been calculated that human doses of 12.5 mg and 25.0 mg DXA as single doses are safe and will fulfil the expectation of prolonged release.

25.3 Investigational Drug Packaging and Labelling

All IMP used in this study will be prepared, packaged, and labelled in accordance with the Standard Operating procedures (SOPs) of the Sponsor or its qualified subcontractors, Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonization (ICH) guidelines for GCP, guidelines for Quality System Regulations (QSR), and applicable regulations.

[redacted]

[redacted]quivalent

- Carton containing a 2 mL vial of 25.0 mg DXA dose of IMP

25.4 Investigational Drug Storage

[redacted]

25.5 Investigational Drug Preparation

[redacted]

[redacted]

25.6 Investigational Drug Administration

A detailed description of the Transforaminal procedure has been presented in Section 22.2.3.1.

25.7 Investigational Drug Accountability

It is the responsibility of the Principal Investigator to ensure IMP/Placebo accountability, reconciliation and record maintenance at the investigational site. All discrepancies in IMP/Placebo accountability must be accompanied by a written account from the Investigator.

In accordance with all applicable regulatory requirements, the Investigator and/or designated site staff must maintain IMP/Placebo accountability records throughout the course of the study. Details IMP/Placebo received at site will be documented. Details of IMP/Placebo supplied and/or administered to subjects will be documented by investigational site staff who are listed on the Delegation of Authority log as 'unblinded' to treatment assignment.

An unblinded study Monitor will verify all accountability records during periodic monitoring visits. Unused and used IMP/Placebo must be stored on site until such accountability has taken place and authorization is received from the Sponsor or Sponsor's designee that the study drug may be returned for destruction.

25.8 Treatment of Subjects

25.8.1 Rescue Medication

All subjects entering this study are required to keep all analgesic medication and other therapy usage [such as physiotherapy, acupuncture, or TENS] stable or decreased during the study, and only use the rescue pain medication as needed and specified by the protocol.

If pain control is unsatisfactory, the Investigator has a range of Rescue medications that can be added to the maintenance therapy that the subject takes as concomitant medications.

Any one of the Group 1 and/or any one of the Group 2 rescue medications are available for increases in pain for selection and prescription by the Investigator for up to 14 days (once during the study) as addition

to the medications currently used by the patient, with special consideration of safety and potential drug interactions.

Group 1 (one of):

Amitriptyline	5 – 50mg Nocte, *or*
Pregabalin	25mg – 300mg BD, *or*
Gabapentin	100mg TDS dosage, up to 600mg TDS

(Acute withdrawal of gabapentin or pregabalin can result in withdrawal symptoms, with likelihood of withdrawal related to dose and duration of treatment. If appropriate, down-titration should take place over at least one week, starting no later than day 15 after rescue began.)

and/or Group 2 (one of):

Tramadol	100mg – 200mg BD, *or*
Tapentadol	50 – 200mg BD

[redacted]

25.9 Treatment Compliance

Treatment compliance with the IMP is not an issue, because this involves a single administrative procedure via the transforaminal epidural injection on Day 0 of the study. However, compliance with protocol requirements for concomitant medications and supportive therapies will be aided using a paper diary provided to each subject at study commencement that will seek to record changes in maintenance treatments (doses up or down, or missed), or the recording of any additional medication.

26 SAFETY

It is the responsibility of the Sponsor and Investigational site to follow local regulatory requirements and guidelines with respect to safety.

26.1 Adverse Event Definitions

Adverse events will be defined by the NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (November 2016).

Table 7. Adverse Event Definitions.

Seriousness	
Adverse event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and that does not necessarily have a causal relationship with this treatment.
Adverse reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Safety Critical Adverse Events	Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations that should be reported to the sponsor according to the reporting requirements specified in the protocol.
Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)	Any adverse event/adverse reaction that results in death, is life-threatening*, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
Significant Safety Issue (SSI)	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
Urgent Safety Measure (USM)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.
Severity	
Mild	event requires minimal or no treatment and does not interfere with the participant's daily activities
Moderate	event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe	event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
Life-threatening	event in which the subject was at risk of death *at the time of the event**
Fatal	event that resulted in death
Causality **relatedness to IMP/Placebo *or* relatedness to TF-EI procedure**	
Definitely related	There is a reasonable possibility that the IMP/Placebo or the TF-EI procedure caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the IMP/Placebo or the TF-EI procedure and the adverse event.
Probably related	
Possibly related	

Not related	There is not a reasonable possibility that the IMP/Placebo or the TF-EI procedure caused the adverse event
Expectedness	
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction that is both serious and unexpected.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the Reference Safety Information (RSI)

*Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgement should be exercised in deciding whether an adverse event/ reaction should be classified as serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must be assessed for seriousness, severity, relatedness, expectedness and timing by a study Investigator (who is also a clinician). All changes to an AE must be documented. AEs characterized as intermittent require documentation of onset and duration of each episode.

26.2 Reporting Procedures

Adverse events will be reported according to local regulatory requirements. It is the responsibility of the Investigator to meet any additional AE reporting requirements stipulated by the HREC responsible for oversight of the study.

Table 8. Adverse event reporting requirements and timeframes.

Sponsor	
Significant Safety Issue (SSI) Including SSIs that arise from overseas reports relating to a clinical trial in Australia	Notify **TGA, HREC and all Investigators** without undue delay and no later than **15 calendar days** of the sponsor instigating or being made aware of the issue
Urgent Safety Measure (USM)	Notify **TGA** within **24 hours**. Notify the HREC and all Investigators within **72 hours** of the Sponsor instigating or being made aware of the issue
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Report to the **TGA** Fatal or life threatening Australian SUSARs, immediately, but no later than **7 calendar days** after being made aware of the case, with any follow-up information within a further **8 calendar days** For all other Australian SUSARs, no later than **15 calendar days** after being made aware of the case
Notification of amendment, temporary halt or early termination of trial for safety reasons	Notify **TGA, HREC and all Investigators** without undue delay and no later than **15 calendar days** of the sponsor instigating or being made aware of the issue
Action with respect to safety that has been taken by another country's regulatory agency (relevant to an ongoing clinical trial in Australia	Report to the **TGA** without undue delay and no later than **72 hours** of the trial Sponsor becoming aware of the action

Other single case adverse events (AEs)	Report to the **TGA** at their request
Annual Safety Reports	Report to the **TGA** at their request
Investigator	
Adverse Events (AEs) and Adverse Reactions (ARs)	Report to the **Sponsor** as soon as practicable
Serious Adverse Events (SAEs)	Report to the **Sponsor as soon as possible** and without unjustified delay and **within 24 hours** of the event
Urgent Safety Measure (USM) instigated at the site	Report to the **Sponsor** within **24 hours**
Significant Safety Issues (SSIs) and SUSARs arising from the local site	Report to the **Institution and the Sponsor** without undue delay and no later than **72 hours** of the Principal Investigator becoming aware of the event
Annual Safety Reports	Report to the **HREC** as per the HREC requirements

Any SAE or subject death that occurs from and including Visit 2 (Baseline/Treatment onwards, whether or not related to IMP/Placebo, must be reported within 24 hours via e-mail at the address noted below. A completed Serious Adverse Event Report Form with as much detail as possible must be included with the email while ensuring that the SAE report contains the minimum criteria for reporting (participant ID, adverse event term, suspected investigational product, reason for meeting serious criteria and relationship to investigational product, name of the reporter) The Investigator must report all SAEs occurring from the time of Visit 2 (Baseline/Treatment) until 30 days after last study visit.

Contact Information for SAE Reporting

[redacted]

Other supporting documentation of the event may be requested by the Sponsor or additional information may be received by the Sponsor (e.g., evolution of the SAE, other signs or symptoms, final diagnosis, final outcome, hospital discharge summary, or autopsy report).and should be provided as soon as possible to ensure compliance of reporting with local regulatory requirements. The same procedures and timelines as for initial reporting, listed above, should be followed for any follow-up information. If necessary, the study site will be visited to collect additional information.
Follow-up information is required on all SAEs until one of the following criteria is satisfied:

- The final outcome of the case is known.
- The event is resolved, or the medical condition of the subject has stabilized.
- No further information is available.
- Sponsor assessment has been finalized.

The SpineThera Chief Medical Officer will be notified of the SAE by Southern Star Research. The Sponsor is responsible for reporting of safety information to the Regulatory Authority. The Safety Review Committee will provide safety oversight per Section 26.4.

At any time after completion of the study, if the Investigator becomes aware of an SAE that is suspected to be related to study product, the Investigator will report the event to the Sponsor.

The Investigator has a responsibility to ensure the conduct of the trial, including the monitoring of safety and reporting of adverse events, complies with the study protocol. Initial safety reports should be followed by detailed written reports including comments on potential confounding factors, results of investigations, treatment required and outcome. The Sponsor and Principal Investigator should review the adverse outcome in the context of known information on the medicine and make a determination as to whether the event was drug-related (i.e. an adverse reaction).

The Sponsor will review all adverse events for completeness and accuracy and request clarification and/or additional information from the Investigator where necessary. The Sponsor will utilize MedDRA, the Medical Dictionary for Regulatory Activities, to assign a MedDRA term for each adverse event based on the information provided by the investigator.

26.3 Pregnancy

Pregnancy in a subject or partner of a subject must be reported within 24 hours via e-mail at the address noted below. A completed Pregnancy Report Form with as much detail as possible must be included with the email. It is the responsibility of the Investigator to follow-up any pregnancy, including pregnancies of partners of subjects, until outcome (e.g. birth or spontaneous abortion) and report any incidents of congenital abnormality/birth defect as an SAE, dependent on local privacy laws. The outcome of the pregnancy should also be reported. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by emailing a completed SAE Report Form to the Sponsor within 24 hours of knowledge of the event. Subjects will remain in the study and undertake all study-related procedures, unless the subject chooses to withdraw from the study.

Contact Information for Pregnancy Reporting

[redacted]

26.4 Safety Oversight: Safety Review Committee

A Safety Review Committee (SRC) assigned the responsibility of safety of the participants will provide medical oversight and expertise to the Sponsor and sites concerning the continuation, modification, or termination of the trial. The SRC will monitor subject 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 the safety oversight of the study per the NHMRC Guidance on Data Safety Monitoring Boards 2018. The SRC will be composed of three to four members including a 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.

The SRC will be charged with reviewing the protocols with respect to ethical and safety standards and making recommendations if necessary. During the study, the SRC will meet via teleconference or web-based meetings at least every 3 months to review safety issues and to monitor Investigational Site performance in execution of the protocol. Prior to each meeting, a safety report on all subjects will be generated.

The SRC will either recommend continued enrolment of the remaining subjects or discontinuation of enrolment/termination of the study. Though the timing of the SRC review will be expedited, enrolment may continue while awaiting the SRC review. In addition, a computerized system will be used to acquire any data regarding halting criteria throughout the study.

If any of the halting rules are met, the study will not proceed with the remaining enrolment without a review by and recommendation from the SRC to proceed. Upon completion of this review and receipt of the advice of the SRC, SpineThera will determine if study entry or study dosing should be interrupted or if study entry and study dosing may continue according to the protocol, documenting reason(s) for decision taken

27 STUDY SUSPENSION OR EARLY TERMINATION

Suspension is a temporary pause in study activities. Early termination is the closure of the study prior to the defined endpoint. Suspension or early termination can occur either at an Investigational Site or across the entire study and may be at the direction of the Sponsor, the HREC or the Regulatory Authority.

Reasons for suspension or early termination of the study may include, but are not limited to, the following:

- Incidence or severity of adverse events represent a significant medical risk. Severity of adverse events will be determined per Table 9: Adverse Event Definitions Specifically, but not limited to:
    - three or more subjects experience the same serious adverse event as evaluated by a licensed clinician.
    - three or more subjects who received one treatment dose experience a severe, treatment-related laboratory abnormality in the same laboratory parameter.
    - an overall pattern of symptomatic, clinical, or laboratory events that the Safety Review Committee consider to be associated with IMP and that may collectively represent a serious potential concern for safety.
- An issue relating to IMP manufacturing or distribution.
- Failure to obtain Human Research Ethics approval or HREC annual report acknowledgement for the study.
- Failure of the Investigator/Investigational Site to comply with the protocol, the Clinical Trial Research Agreement or applicable regulatory guidelines in conducting the study.
- Failure of the Investigator/Investigational Site to accurately and completely collect and record study related data as per GCP.

In the case of study suspension, it is the responsibility of the Sponsor to notify all Investigators and the Human Research Ethics Committee, including the reason for suspension. It is the responsibility of the Investigator to ensure enrolment and treatment (IMP/Placebo administration) of subjects ceases immediately and until the suspension is lifted by the Sponsor and acknowledged by the Human Research Ethics Committee. Enrolled *and* treated subjects will continue to be managed per protocol.

In the case of termination, it is the Sponsor's responsibility to notify all Investigators, the Regulatory Authority and Human Research Ethics Committee immediately, including the reason for termination. It is the Investigator's responsibility to inform the subjects and ensure appropriate care and follow-up is provided.

28 ETHICS

28.1 Statement of Compliance

The study will be conducted according to ICH Harmonised Guideline Integrated Addendum to ICH E6(R1): Guideline For Good Clinical Practice ICH E6(R2) – annotated with TGA comments, and in accordance with the national and local laws, regulations, standards, and requirements of the country/ies in which the study is conducted.

The study will follow and comply with:

- The principles of Good Clinical Practice
- 21 CFR Part 11
- 21 CFR Part 50 (informed consent)
- 21 CFR Part 54 (financial disclosure by clinical investigators)
- Local Ethics Committee and Regulatory Authority requirements
- The Clinical Trial Research Agreement (CTRA)
- This subject eligibility and study procedures as outlined in this protocol

This study will only commence once Ethics Committee approval and Regulatory Authority acknowledgement has been received, where relevant. The Protocol and any subsequent amendments must be approved by the Sponsor and the Ethics Committee prior to any study-related procedures being undertaken at an investigational site. The CIP and any subsequent amendments must be acknowledged by the site Principal Investigator prior to any study-related procedures being undertaken at the Investigational Site.

The investigators shall make written commitments to comply with GCP and this protocol.

The study will be publicly registered prior to first enrolment.

29 STUDY ADMINISTRATION

29.1 Study Monitoring

It is the responsibility of the Sponsor to ensure monitoring of this clinical study. Site monitoring will be conducted by trained Sponsor personnel or delegates to ensure the study is conducted in accordance with the GCP, the Protocol, Clinical Trial Research Agreements and local laws and regulatory requirements, as specified in the study Monitoring Plan.

It is the responsibility of the Investigator to allow monitors access to the clinical trial records including regulatory files, IMP accountability records, laboratory records and Participant Informed Consent Forms, *and* subjects' medical records including clinic and hospital records, in accordance with the Participant Informed Consent Form. The Principal Investigator must also make every effort to be available to meet with the Sponsor and/or study monitors during monitoring visits to discuss any problems and actions to be taken and document visit findings and discussions. Further, it is the Principal Investigators responsibility to comply with Sponsor requests relating to GCP or protocol compliance issues identified as the result of monitoring.

29.2 Source Documents

It is the responsibility of the Principal Investigator to ensure source documents listed below are appropriately prepared and maintained at the Investigational Site, including security and limited access to personal or sensitive information of subjects.

- Regulatory Authority notification or approval
- Ethics Committee approval documentation including Ethics Committee composition and certification.
- All correspondence between the Ethics Committee, Regulatory Authorities, the Institution, Sponsor or delegate, Monitor and the investigator relating to the clinical study
- Subjects' records including, but not limited to:
    - Signed and dated Participant Informed Consent Form for all subjects, including revisions or updates
    - Subject identification log
    - Adverse events
    - Concomitant medications and therapies
    - Medical history
    - Procedure-related information
    - Efficacy Information
- Deviations from the protocol with rationale
- Fully executed Clinical Trial Research Agreement, Form of Indemnity, Insurance Certificates and Financial Disclosures
- All approved versions of the Protocol and Investigator Brochure including completed Acknowledgment of Receipt

- Participant Informed Consent Form master, Patient Reported Outcomes master and other information given to the subject.
- Current signed and dated curriculum vitae of all Investigational Site staff undertaking study-related procedures
- Documentation of delegated tasks for all Investigational site staff undertaking study-related procedures
- Study training records for all Investigational Site staff.
- IMP shipping records, accountability records and environmental monitoring logs
- Equipment maintenance records, where applicable
- Any other document that local or international Regulatory Agencies may require to be maintained

It is the responsibility of the Sponsor to ensure the documents listed below are appropriately prepared and maintained:

- Regulatory Authority notification or approval
- Ethics Committee approval documentation including Ethics Committee composition and certification.
- All correspondence relating to the clinical study
- fully executed Clinical Trial Research Agreements, Form of Indemnity, Insurance Certificates and Financial Disclosures
- All approved versions of the Protocol and Investigator Brochure including completed Acknowledgments of Receipt
- Participant Informed Consent Form master, Patient Reported Outcomes master and other information given to the subject.
- List of Investigator and Investigational Sites/Institutions
- Current signed and dated curriculum vitae of all Investigational Site staff undertaking study-related procedures
- Documentation of delegated tasks for all Investigational site staff undertaking study-related procedures
- Study training records for all Sponsor/delegate staff.
- List of study Monitors, all Monitoring Visit Reports and follow-up letters
- IMP shipping records, accountability records
- All approved versions of study management reports and plans including the Monitoring Plan, Statistical Analysis Plans, Document Management Plan, Safety Management Plan etc.
- Case Report Forms
- Clinical Study Report
- Any other document that local or international Regulatory Agencies may require to be maintained

Records will be retained by the Sponsor and the Investigational Sites for a minimum of 15 years after product approval or the date on which the study is terminated.

The Principal Investigator, Investigational Site and Institution will allow access to all source documents for monitoring, Ethics Committee review, assessment, audits or regulatory inspections from commencement of the study and at least through to the end of the minimum retention period.

29.3 Data Collection and Management

Data will be collected using an electronic data management system which is 21 CFR Part 11 compliant.

Data generated within this clinical study will be handled according to the relevant SOPs and/or the Data Management Plan of the Sponsor and/or their delegate(s). An electronic CRF (eCRF) will be created by the data management group for recording of the required data. Automated and manual checks will be run against the data to ensure completeness and consistency.

Data collection and entry into the eCRF will be completed by authorised study site personnel designated by the Investigator, following appropriate training. The Investigator must verify that all data recorded in the eCRFs are accurate and correct and he/she will be required to sign off on the final clinical data.

Data in the eCRFs shall be derived from source documents. Source documents are documents used by the Investigator or study site that relate to the subject's medical record, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study.

Adverse events will be coded using the MedDRA and medications will be coded using the WHO Drug Dictionary.

eCRFs will be completed for subjects who have signed the ICF, are eligible for this study and have been randomized in the study.

30 CONFIDENTIALITY

All subject data will be treated as confidential as per local laws and guidelines. Subjects will be identified to the Sponsor in a key-coded form only. As the Investigational Site will maintain a master subject log, all data will be potentially re-identifiable. Source documents requested by the Sponsor (for example, medical records related to a SAE) will have personal and sensitive information redacted by the Investigational Site prior to transfer to the Sponsor. Subjects will not be identified by name in any publications arising from this study.

31 STATISTICAL CONSIDERATIONS

31.1 Introduction

Data will be summarized descriptively by treatment arm and overall. The descriptive summary for categorical variables will include counts and percentages. The descriptive summary for continuous variables will include number of subjects, means, medians, standard deviations and minimum and maximum values.

All collected data will be listed for all subjects.

Unless otherwise specified, all statistical tests will be conducted at the two-sided 0.05 alpha level with 95% confidence intervals. A comprehensive statistical analysis plan (SAP) will be prepared prior to database lock and unblinding. Further analytical details will be provided in the SAP.

31.2 Sample Size Justification

Limited data are available in the literature on which to base sample size/power considerations. In the study conducted by Ghahreman (Gharheman, 2010), the primary endpoint was the proportion of subjects 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 subjects 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%.

31.3 Data Analysis Populations

The Intent-to-Treat (ITT) population includes all randomized subjects. In the ITT population, subjects will be included in the treatment group to which they were randomized, regardless of treatment received. A safety

analysis will be conducted in the ITT population, which includes patients in which a TF-EI procedure was attempted but abandoned prior to drug delivery and patients who received IMP or placebo, thereby differentiating the effects of the procedure.

The Safety population includes all randomized subjects who proceed to TF-EI (including patients with attempted but halted or failed TF-EI). In the Safety population, subjects will be included in the treatment group based on the treatment that was received. All safety analyses will be conducted in the Safety population.

The modified Intent to Treat population includes all randomized subjects who receive IMP or placebo by TF-EI. This population forms the basis of the primary efficacy and safety analyses. In the mITT population, subjects will be included in the treatment group to which they were randomized, regardless of treatment received. All efficacy analyses will be conducted in the mITT population. The planned enrolment for the study is 180 subjects in the mITT population.

The Per-Protocol (PP) efficacy analysis population includes all randomized subjects who met all inclusion/exclusion criteria; did not have any significant protocol deviations; complied with the assigned study treatment; and either 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 due to receiving therapy other than study specified drug during the study. Supportive efficacy analyses will be conducted in the PP population.

PK population: All subjects 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.

In order to minimize bias, the PP population will be defined prior to unblinding.

31.4 Study Disposition

The number and percent of subjects in each analysis population will be summarized. The number of subjects who complete the study, discontinue prematurely, and their reason for study discontinuation will be tabulated.

31.5 Baseline Characteristics and Demographics

Summary descriptive statistics for baseline and demographic characteristics will be provided for all subjects. Demographic data will include age, race, sex, body weight and height. Other baseline and background characteristics will also be summarized.

31.6 Efficacy Analyses

31.6.1 Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of subjects with a 50% or greater improvement from baseline in Mean Worst Daily Leg Pain at 60 days. The primary endpoint will be analysed using a logistic regression model with treatment group (three levels) as a factor. The primary analysis will compare the high dose group to the placebo group using a two-sided test at the alpha=0.05 level of significance. The odds ratio of the high dose group to the placebo group with a 95% Wald confidence interval will also be reported.

31.6.2 Key Secondary Efficacy Analysis

If the comparison between the high dose group and the placebo group is statistically significant ($p<0.05$), then the following analyses will be conducted using a fixed sequence testing procedure to control the overall level of significance:

1. The primary analysis model will be used to compare the low dose group to the placebo group. The odds ratio of the low dose group to the placebo group with a 95% Wald confidence interval will also be reported.
2. Comparing the high dose group to the placebo group, the proportion of subjects with a 50% or greater improvement from baseline in Mean Worst Daily Leg Pain at 90 days will be analysed using the same methodology as the primary analysis.
3. The mean changes from baseline to Day 60 in the Oswestry Disability Index will be compared between the high dose group and the placebo group.
4. Comparing the low dose group to the placebo group, the proportion of subjects with a 50% or greater improvement from baseline in Mean Worst Daily Leg Pain at 90 days will be analysed using the same methodology as the primary analysis.

The change from baseline to Day 60 in the Oswestry Disability Index will be analysed using an analysis of covariance (ANCOVA) model with treatment group (three levels) as a factor.

All of the above analyses will be conducted using two-sided tests at the alpha=0.05 level of significance. However, once a nonsignificant result occurs, all remaining tests will be exploratory rather than confirmatory.

[redacted]

31.7 Safety Analyses

Adverse events will be coded using the MedDRA.

Treatment-emergent AEs (TEAEs) are defined as any AE occurring during or after initiation of IMP. TEAEs will be summarized using frequency counts and percentages. Treatment-emergent AEs will also be rated for severity and relationship to IMP. In addition, all SAEs, deaths, and AEs leading to IMP or study discontinuation will be summarized and listed separately.

Safety laboratory test parameters, vital signs, and ECG results will be tabulated and/or listed.

31.8 PK Analyses

Individual pharmacokinetic parameters for SX600 will be summarized with descriptive statistics. Individual measures will be calculated using non-compartmental analyses and PK modelling.

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33 ATTACHMENTS

Attachment #	Title	# of Pages
01	Major antipsychotic or major antidepressant drugs	01
02	TF-EI Procedure & IMP/Placebo Preparation (CLIN-0022)	14
03	Pharmacokinetic (PK) Laboratory Manual (CLIN-0038)	12
04	IMP Randomisation and Shipment Process (CLIN-0037)	10

A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group 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.

Protocol Number: **CLIN-0012-STA01-19**

Short Title: Safety and Efficacy of SX600 Administered by Lumbosacral Transforaminal Epidural Injection for Radicular Pain (SALIENT)

Investigational Product: **SX600,** Dexamethasone acetate, poly(lactic-*co*-glycolic acid), and poly(lactic acid-*co*-glycolic acid)-[*block*]-poly(ethylene glycol) microspheres for reconstitution in 0.9% Sodium Chloride for Injection, BP

Sponsor:

SpineThera Australia Pty. Ltd
C/- Prime Accounting and Business Advisory Pty Ltd
Level 19, 40 City Road,
Southbank, Victoria. 3006

Clinical Research Organization:

Neuroscience Trials Australia
Florey Institute of Neuroscience and Mental Health
245 Burgundy Street, Heidelberg VIC 3081, Australia

Lead Principal Investigator:

[redacted]
Monash Clinical Research and Metro Pain Clinic
Monash House, 271 Clayton Rd, Clayton VIC, Australia

Authorized Signatory:

[redacted]

Study Contacts:

[redacted]

1 INVESTIGATOR'S AKNOWLEDGEMENT OF RECEIPT

I have received and read the Protocol, *A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group 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*, and agree to conduct the study strictly as outlined in the protocol. I agree to maintain the confidentiality of all information received for all subjects and developed in connection with this protocol.

Printed Name of Investigator

Title of Investigator

Signature of Investigator

Date

2 SPONSOR'S SIGNATURE

Approved by:

[redacted]

SpineThera Australia Pty Ltd
Sponsor Company

Approved by:

[redacted]

SpineThera Australia Pty Ltd
Sponsor Company

3 VERSION HISTORY

Revision #	DCR#	Summary of Changes	Authors
00	0012	Initial Release	William Houghton, M.D. Jeff Missling

4 PROCEDURES IN CASE OF EMERGENCY

24 Hour Emergency Contact

Role in Study	Contact
SpineThera Chief Medical Officer	[redacted]
Neuroscience Trials Australia Medical Monitor	[redacted]

5 SYNOPSIS

SPINETHERA CLINICAL PROTOCOL SYNOPSIS

Title of Study:	**A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group 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.**
Short Title:	Safety and Efficacy of SX600 Administered by Lumbosacral Transforaminal Epidural Injection for Radicular Pain (SALIENT)
Clinical Trial Phase:	Phase I/II
Protocol No.:	**CLIN-0012-STA01-19**
Sponsor:	SpineThera Australia Pty Ltd
Investigational Medicinal Products (IMP)	IMP: SX600, a sustained-release formulation of dexamethasone acetate in PLGA and PLGA-PEG microspheres packaged as a lyophilized powder for resuspension at the time of administration in 1.2 mL of 0.9% Sodium Chloride for Injection, BP, with 1.0 mL of the re-suspended product recovered for transforaminal epidural injection. Placebo: 0.9% Sodium Chloride for Injection, BP, 1.0 mL.
Proposed Indication:	Dexamethasone acetate microspheres for extended-release injectable micro-suspension for lumbosacral transforaminal epidural injection (SX600) indicated for treatment of lumbosacral radiculopathy (radiating pain).
Purpose:	Safety and efficacy of SX600 in indicated population
Anticipated Study Period:	19 months
Objectives:	*Primary:* • To assess the safety of two doses (12.5 mg and 25.0 mg) 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) 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.

	Secondary: • 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
Study Design:	This is a Phase I/II, double-blind, parallel-group, randomized, placebo-controlled multi-centre trial in 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. Each subject 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). Systemic pharmacokinetics of dexamethasone (active moiety) will be evaluated in a subset of approximately 60 patients (across IMP and placebo groups).
Subjects & Timing	180 dosed subjects; approximately 24-28 weeks, from screening to last follow-up (FU) visit.
Inclusion Criteria:	1. Adult aged 18 to 65 years, capable of providing informed consent, capable of complying with the outcome instruments, and meeting the attendance requirements for review as defined in the study. 2. Presenting with a history of unilateral pain, radiating into a lower limb, of lancinating, burning, stabbing or electric quality, of duration of 4 weeks to 6 months, having failed conservative therapy. 3. Mean Worst Daily Leg Pain score of ≥5.0 and ≤9.0 being the ***mean*** NRS score (to 1 decimal place) of 5 days (as further defined in the Efficacy Assessments). 4. Demonstration of a disc herniation within 3 months by CT or MRI at the segmental levels of L4-L5, or L5-S1, [redacted] 5. Associated limitation of straight-leg-raise to less than 30 degrees, ***or*** straight-leg raise is measured to 45 degrees with pain history of lancinating pain in the presence of disc herniation confirmed by imaging. 6. The site of the disc herniation must affect L4-5 or L5-S1, with involvement of the L4, L5, or S1 nerve roots unilaterally. 7. [redacted] 9. Women of child-bearing potential must use a medically accepted method of contraception for the duration of the study plus 30 days and register a negative pregnancy test prior to dosing.

	10. Men must agree to abstain from intercourse with women or agree to use a medically accepted method of contraception and refrain from donating sperm for the duration of the study plus 30 days. 11. Willing to comply with all the study activities and procedures throughout the duration of the study.
Exclusion Criteria:	1. Documented history of allergy or intolerance to components of the IMP, relevant radiologic contrast media, or local anaesthetics. 2. Is pregnant or lactating 3. Has been taking corticosteroid medications routinely in the past 6 months *or* has received an epidural corticosteroid injection within 12 weeks of screening. 4. Has a BMI greater than 40 kg/m^2. 5. Has Diabetes Mellitus (Type 1 or Type 2) – prior confirmed HbA_{1c} or OGTT 6. [redacted] 12. Has a history of significant leg pain unrelated to disc herniation that would significantly compromise assessment of back or leg radicular pain. 13. Has radiological evidence of symptomatic disc herniation above L4-L5. 14. Has radiological evidence of clinically significant foraminal stenosis at L4-L5 or L5-S1 or of clinically significant spinal stenosis, or spondylolisthesis (Grade 2 or higher). (Note, asymptomatic foraminal stenosis at other spinal levels is not excluded). 15. Has had lumbar back surgery. 16. [redacted] 22. Has received an implantable device for pain management. 23. [redacted]

Study Procedures:	*Screening*: **Days -28 to Day -1**: This is the screening visit to determine study eligibility, plus baseline measure of Oswestry Disability Index, and recording of all current treatments (medications, physical therapy, etc.), and signing of the Informed Consent Form. ***Day 0:*** The intervention day when TF-EI is performed, and with initial Pharmacokinetic blood sample collections in assigned subjects. *Follow-up Visits:* **Day 1 and Day 7** (telephone assessment) for assessment of adverse events and concomitant medications and therapies. **Day 14, Day 30**, **Day 60**, **Day 90**, **Day 120**, **Day 150**, **Day 180** post-dosing. The following measures will be recorded at each visit • Brief physical examination including weight • Vital signs including supine blood pressure, pulse rate, respiratory rate (breaths/minute), and temperature. • Urine pregnancy test (for females of childbearing potential) • Clinical laboratory tests (haematology, coagulation, serum chemistry) • PK blood sample for dexamethasone quantitation. • Urinalysis • Concomitant medications review • Concomitant therapies review • Adverse events, including serious adverse events • Patient's Global Impression of Change • Functionality Assessment using the Oswestry Disability Index • Quality of Life Assessment using SF-36 questionnaire • Worst Daily Leg Pain electronic diary and paper diary for adverse events and concomitant medications and therapies
Pharmacokinetic Assessments:	NOTE: PK parameters will be based on plasma concentrations that are dependent on the extent of systemic distribution of dexamethasone from the epidural injection. Blood samples for plasma PK will be obtained at the following time points: Pre-dose, 30, 60, 90 minutes, 2, 4, 6, 8, 12, 20, and 24 hours post-epidural injection. A blood sample for drug concentration analysis will also be collected at each follow-up visit (Days 14, 30, 60, 90, 120, 150 and 180) in all subjects. Blood samples in the first 24 hours at the stated times will be collected in a subset of subjects from at least 3 sites, totalling approximately 60 subjects. [redacted] Individual pharmacokinetic parameters for SX600 will be summarized with descriptive statistics. [redacted]

	• [redacted]
Endpoints:	*Primary Efficacy* • The proportion of subjects with a 50% or greater improvement in Mean Worst Daily Leg Pain at 60 days post-dosing (Responders). *Secondary Efficacy* • The proportion of subjects who are Responders (defined as having a 50% or greater improvement in Mean Worst Daily Leg Pain) 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 subjects who are Responders (defined as having a 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. • Reduction in use of concomitant analgesics and supportive health services. • Time to loss of response, in the subset of subjects who are Responders at Day 14 (50% or greater improvement in Mean Worst Daily Leg Pain). *Safety* • 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
Analysis Populations:	Intent to Treat population: All randomized subjects. Subjects will be included in the treatment group to which they were randomized, regardless of treatment received. Safety population: All subjects randomized who proceed to TF-EI (includes patients with attempted but halted or failed TF-EI). In the Safety population, subjects will be included in the treatment group based on the treatment that was received. Modified Intent to Treat (mITT) population: all randomized subjects who receive IMP or placebo by TF-EI. Per Protocol population: all randomized subjects who complete the study without any major protocol violations. PK population: All subjects who received IMP or placebo and with intensive blood collections in the first 24 hours.
Rescue Therapies available:	Any one of the Group 1 and/or any one of the Group 2 rescue medications are available for increases in pain for selection and prescription by the Investigator for up

	to 14 days (once during the study) as addition to the medications currently used by the patient, with special consideration of safety and potential drug interactions. Group 1 (one of): Amitriptyline 5 – 50mg Nocte, *or* Pregabalin 25mg – 300mg BD, *or* Gabapentin 100mg TDS dosage, up to 600mg TDS (Acute withdrawal of gabapentin or pregabalin can result in withdrawal symptoms, with likelihood related to dose and duration of treatment. If appropriate, down-titration should take place over at least a week, starting no later than day 15 after rescue began.) and/or Group 2 (one of): Tramadol 100mg – 200mg (SR) BD, *or* Tapentadol 50 – 200mg (SR) BD If, in the opinion of the Investigator, treatment beyond the above described rescue medication approach is required, for example surgery, the patient will be deemed a non-responder in the efficacy analysis at timepoints after the additional treatment but will continued to be followed in the safety population. [redacted]
Statistical Considerations:	*Sample Size Justification* Limited data are available in the literature on which to base sample size/power considerations. In the study conducted by Ghahreman (Gharheman, 2010), the primary endpoint was the proportion of subjects 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 subjects 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%. *Primary Efficacy Analysis* The primary efficacy endpoint is the proportion of subjects with a 50% or greater improvement from baseline in Mean Worst Daily Leg Pain at 60 days. The primary endpoint will be analysed using a logistic regression model with treatment group (three levels) as a factor. The primary analysis will compare the high dose group to

the placebo group using a two-sided test at the alpha=0.05 level of significance. The odds ratio of the high dose group to the placebo group with a 95% Wald confidence interval will also be reported.

If the comparison between the high dose group and the placebo group is statistically significant ($p<0.05$), then the following analyses will be conducted using a fixed sequence testing procedure to control the overall level of significance:

1. The primary analysis model will be used to compare the low dose group to the placebo group. The odds ratio of the low dose group to the placebo group with a 95% Wald confidence interval will also be reported.
2. Comparing the high dose group to the placebo group, the proportion of subjects with a 50% or greater improvement from baseline in Mean Worst Daily Leg Pain at 90 days will be analysed using the same methodology as the primary analysis.
3. The mean changes from baseline to Day 60 in the Oswestry Disability Index will be compared between the high dose group and the placebo group.
4. Comparing the low dose group to the placebo group, the proportion of subjects with a 50% or greater improvement from baseline in Mean Worst Daily Leg Pain at 90 days will be analysed using the same methodology as the primary analysis.

The change from baseline to Day 60 in the Oswestry Disability Index will be analysed using an analysis of covariance (ANCOVA) model with treatment group (three levels) as a factor.

All of the above analyses will be conducted using two-sided tests at the alpha=0.05 level of significance. However, once a nonsignificant result occurs, all remaining tests will be exploratory rather than confirmatory

Safety Analyses

Treatment-emergent AEs (TEAEs) are defined as any AE occurring during or after initiation of IMP. TEAEs will be summarized using frequency counts and percentages. Treatment-emergent AEs will also be rated according to severity and relationship to IMP. In addition, all SAEs, deaths, and AEs leading to IMP or study discontinuation will be summarized and listed separately.

Safety laboratory test parameters, vital signs, and ECG results will be tabulated and/or listed.

6 TABLE OF CONTENTS

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9 LIST OF ABBREVIATIONS

Abbreviation	Definition
AAN	Australian Approved Name
AE	Adverse Event
AKA	Artery of Adamkiewicz
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
APPT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BCC	Basal Cell Carcinoma
BD	Twice a Day
BP	British Pharmacopeia
BMI	Body Mass Index
BUN	Blood Urea Nitrogen

CI	Confidence Interval
CFR	Code of Federal Regulations (USA)
CK	Creatine Kinase
CL/F	Apparent Systemic Clearance
CRF	Case Report Form
CT	Computed Tomography
CTRA	Clinical Trial Research Agreement
DSP	Dexamethasone Sodium Phosphate
DX	Dexamethasone
DXA	Dexamethasone Acetate
ECG	Electrocardiography
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EI	Epidural Injection
FDA	Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practice
GGT	Glutamyl Transferase
GLP	Good Laboratory Practice
GRα	Glucocorticoid Receptor
GRE	Glucocorticoid Response Elements
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ITT	Intent-To-Treat
K_2EDTA	Dipotassium Ethylenediaminetetraacetic Acid
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
NASS	North American Spine Society
NHMRC	National Health and Medical Research Council
NOAEL	No Observed Adverse Effect Limit
NRS	Numeric Rating Scale
OGTT	Oral Glucose Tolerance Test
PA	Posterioranterior
PCR	Polymerase Chain Reaction
PEG	Poly(ethylene glycol)
PK	Pharmacokinetic
PLGA	Poly(lactic-*co*-glycolic acid)
PLGA-PEG	Poly(lactic-*co*-glycolic acid)-*[block]*-poly(ethylene glycol)
PT	Prothrombin Time or Preferred Term
QoL	Quality of Life
QSR	Quality System Regulations
RBC	Red Blood Cell
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCC	Squamous Cell Carcinoma

SIS	Spinal Intervention Society
SOC	System Organ Class
SOP	Standard Operating Procedure
SR	Sustained Release
SRC	Safety Review Committee
TB	Tuberculosis
TDS	Three Times A Day
TEAE	Treatment-Emergent Adverse Event
TENS	Transcutaneous Electrical Nerve Stimulation
TF-EI	Transforaminal Epidural Injection
TGA	Therapeutic Goods Administration
TT	Thrombin Time
Vz/F	Terminal Phase
WBC	White Blood Cell
WHO	World Health Organization
W/W	Weight/Weight

10 INTRODUCTION

SX600 (Dexamethasone acetate microspheres for extended-release injectable micro-suspension) is a sustained release formulation of dexamethasone acetate incorporated into biodegradable poly(lactic-*co*-glycolic acid) (PLGA) and poly(lactic-*co*-glycolic acid-[*block*]-poly(ethylene glycol) (PLGA-PEG) polymeric microspheres and is being developed for transforaminal epidural injection of a synthetic steroid formulation as a treatment for subjects with lumbar monoradiculopathy. [redacted]

Low back pain has been well documented as a very common health problem globally and is the leading cause of activity limitation and work absence throughout most of the world. Low back pain causes more global disability than any other condition. The global age-standardized prevalence of low back pain in 2010 was estimated to be 9.4% (95% CI 9.0 to 9.8) (Hoy, 2014). The prevalence in Australia was 12.9% for men and 11.5% for women. In 2008-2009, around 1.8% of the total health-care expenditure in Australia ($1.2 billion) was attributed to back problems. In 2011, 'back pain and problems' were the third leading cause of disease burden in Australia, accounting for 3.6% of the total burden across all diseases and injuries (AIHW, 2016). Despite widespread clinical use of glucocorticoids for epidural injection, there are currently no steroid drugs on the U.S. or Australian market with an approved indication for epidural administration.

According to SpineThera's proprietary market research, approximately 40% of epidural steroid injections (EIs) performed in the U.S. are repeat injections within 90 days of a subject's first injection, and 33% are repeat injections within 60 days. SX600 is a sustained release formulation of dexamethasone acetate incorporated into biodegradable PLGA polymeric microspheres. This new formulation is intended to provide sustained release of the dexamethasone acetate for greater than 60 days *in vivo* after a single epidural administration, which the Sponsor hypothesizes may provide durable days of pain relief in properly selected subjects. This product may reduce the frequency of epidural steroid injections for the management of lumbar radiculopathy and finally offer physicians and subjects an approved drug for this purpose.

[redacted]

[redacted]

Current Product Name: Dexamethasone acetate microspheres for extended-release injectable micro-suspension (SX600).

This formulation is being evaluated for the indication of lumbar radiculopathy (radiating pain) caused by single intervertebral disc herniation at the L4-5 orL5-S1 levels, involving nerve roots emerging from the L4, L5, and S1 intervertebral foramina. The route of administration of the drug product is identical to that of well-established transforaminal epidural steroid injections that are performed in millions of subjects per year.

[redacted]

For the Phase I/II clinical trial, two doses of SX600 will be tested.

[redacted]

Glucocorticoids work to reduce pain and inflammation by binding to the ligand-binding domain of the glucocorticoid receptor (GRα) after passively entering a cell through the membrane. The newly formed complex moves to the nucleus of the cell through the nuclear pore complex and dimerizes to engage with DNA through glucocorticoid response elements (GREs) where effects on transcription take place. Genomic mechanisms at this location include activation or repression of protein synthesis, including cytokines, chemokines, inflammatory enzymes and adhesion molecules. Thus, inflammation and immune response mechanisms are modified (Czock, 2005).

There is strong, circumstantial evidence from laboratory experiments that inflammatory processes may play a major role in the genesis of symptoms when lumbar nerve roots are affected by disc herniations. Administration of corticosteroids therefore constitutes a logical and attractive form of intervention to relieve the symptoms. The transforaminal route of administration offers the advantage that it delivers

the drug, in maximum concentrations, closer, if not directly, to the site of pathology, which conventional routes of epidural administration do not guarantee. The most common approach is the transforaminal technique (Derby, 1993) and is favoured by the Spinal Intervention Society (SIS), which involves positioning a needle inside the intervertebral foramen to gain access to the nerve root (Bogduk, 2013).

[redacted]

[redacted]

[redacted]

11 NON-CLINICAL STUDIES

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12 SUMMARY OF KNOWN AND POTENTIAL RISKS

No data are available on the relationship of adverse events to administration of SX600 (Dexamethasone acetate microspheres for extended-release injectable micro-suspension) because no studies have yet been conducted in human subjects. The information provided below references known information about the active moiety (dexamethasone), the active ingredient in SX600, and the transforaminal injection procedure.

Since this is a first-in-human study, no adverse events have been reported with SX600. This section will be updated as studies proceed. However, the subject should be aware of the procedural risks that include allergic reactions, haematoma, dural puncture with spinal headache or arachnoiditis, direct nerve injection and injury. Intravascular injection could lead to rare but serious neurological adverse events including spinal cord infarction, paraplegia, stroke and death. Since the lumbar levels defined in this study are below the terminal level of the spinal cord (L2), there is minimal potential risk to the spinal cord.

The subject should be warned that they might experience numbness or weakness in the lower limb following the procedure as a normal effect of the local anaesthetic injected, but this should wear off once the local anaesthetic has ceased to act. This will be monitored in the recovery facility. Because the active moiety is dexamethasone, the known side effects of this drug are well-documented. Known side effects include: anaphylactoid reactions, changes in heart rate and cardiac arrhythmias, congestive heart failure, oedema, thromboembolism, acne and skin changes, including dry scaly skin, ecchymoses and petechiae, impaired wound healing, increased sweating, rash, striae urticaria. Endocrine changes can include decreased carbohydrate and glucose tolerance, hyperglycaemia, glycosuria, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress. Fluid and electrolyte disturbances, including heart failure in susceptible subjects, fluid retention potassium loss and sodium retention have been described. Potential gastrointestinal changes including abdominal distention, elevation in serum liver enzyme levels, hepatomegaly, increased appetite, nausea, pancreatitis and peptic ulcer have been described.

Other rare musculoskeletal changes have been associated with corticosteroids, including aseptic necrosis of the femoral and humeral heads, loss of muscle mass, muscle weakness, and osteoporosis with complications in long bones and vertebral compression fractures, steroid myopathy and tendon rupture, mood swings, depression, euphoria, headache, insomnia, neuritis, neuropathy, personality changes and psychic disorders have been associated with corticosteroid use, as has decreased resistance to infection, hiccups, and weight gain.

Because the IMP is a sustained release formulation of a potent corticosteroid (dexamethasone acetate) and the systemic bioavailability of this product is not yet defined in humans, the subject should be notified that any further corticosteroid administration provided as alternative treatment upon withdrawal

from the study is not recommended for the duration of the study because of the risk of excessive immunosuppression, and that this must be notified to any subsequent physician referral.

Based on the pre-clinical studies conducted to date, epidural injection of SX600 at the chosen doses and in the restricted lower lumbosacral sites is expected to be well tolerated in humans. Its duration of action in producing pain relief is unknown in humans and will be determined by subject assessment out to 180 days following a single treatment.

For this study, medical imaging must demonstrate a cause of radicular pain and radiculopathy amenable to treatment with transforaminal injection of corticosteroids, such as disc herniation, and must exclude causes for which treatment by injection is not appropriate, such as tumours, cysts, and angiomas. Other causes of axial-derived pain, including clinically significant spinal and foraminal stenosis should be excluded.

This study also involves patient exposure to a very small amount of radiation. At the estimated highest radiation dose associated with TF-EI (Braun, 2018) this risk is believed to be very low.

The effects of SX600 in the unborn child and on the newborn baby are not known.

13 CONTRAINDICATIONS

13.1 Steroid Contraindications

Coexisting systemic fungal infection contraindicates the administration of corticosteroids.

13.2 Procedural Absolute Contraindications (SIS practice guidelines)

Absolute contraindications include inability or unwillingness to sign the informed consent for the procedure, history of anaphylaxis to the contrast medium, presence of an untreated or unresolved localized infection in the procedural field, and the subject is unable to cooperate during the procedure.

13.3 Procedural Relative Contraindications (SIS practice guidelines)

- Allergy to any of the drugs that are to be administered.
- Pregnancy
- Concurrent use of anticoagulants
- Anatomical derangements, congenital or surgical, that compromise the safe and successful conduct of the procedure
- Known systemic infection
- Coexisting disease producing significant respiratory or cardiovascular compromise
- Immunosuppression

Risks include but are not limited to infection, allergic reaction, haematoma, no change in pain or increased pain, dural puncture with spinal headache or arachnoiditis, and spinal cord injury. The subject should be fully informed and should understand what to expect: that they might experience numbness or weakness in the lower limb following the procedure. This is a normal effect of the local anaesthetic that is injected, and it should wear off once the local anaesthetic has ceased to act.

[redacted]

[redacted]

15 JUSTIFICATION OF THE STUDY

The design and choice of the trial population for this first-in-human, clinical Phase I/II study, is based on the need to initially demonstrate the safety and efficacy of SX600 in humans. In addition, the PK and efficacy outcome measures in this study may also answer questions concerning the duration of action in a clinical setting. The study should also assist with the choice of dose for subsequent single dose studies in subjects.

This first-in-human study is a Phase I/II, double-blind, parallel-group, randomized, placebo-controlled multi-centre trial in 180 subjects randomized 1:1:1 to 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. Only the on-site dedicated person(s) designated to prepare and administer the IMP or placebo, will be aware of treatment assignment. Each subject will be followed by a blinded, independent Investigator and site staff 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 AEs.

16 JUSTIFICATION OF THE ROUTE OF ADMINISTRATION AND DOSE

Steroids have been widely used to treat radicular pain both in cervical and lumbar radiculopathies and have been used as an off-label therapeutic modality, since no steroids are approved for epidural administration at this time. The most common approach is the transforaminal technique (Derby, 1993) and is favoured by the SIS, which involves positioning a needle inside of the intervertebral foramen to gain access to the nerve root (Bogduk, 2013). In this study, only a single transforaminal injection into

foramen at the L4-5, L5-S1, or the S1 foramen will be used. Many reports, including a few randomized controlled trials, have documented the clinical utility of transforaminal epidural steroid injections. [redacted]

Dose selection:

[redacted]. **Based upon these values, the proposed human doses of SX600 will be 12.5 mg and 25.0 mg DXA for the Phase I/II clinical study.** [redacted]

17 STUDY PURPOSE

One hundred and eighty (180) subjects, aged 18 to 65 years, male and female, for the study will be sourced from those presenting to the investigative sites, where the participation in the study is offered for the management of monoradicular pain of severity (Mean Worst Daily Leg Pain of ≥5.0 and ≤9.0 being the *mean* NRS score (to 1 decimal place) of 5 days (as further defined in the Efficacy Assessments), of duration 4 weeks to 6 months that requires interventional treatment, having failed conservative therapies.

This study represents the first-in-human study and seeks to characterize the safety of SX600 (Dexamethasone acetate microspheres for extended-release injectable micro-suspension) when administered by TF-EI in a highly selected patient population in terms of specificity of the position of a single nerve root, and in the absence of axial contributions to the pain. Systemic pharmacokinetics are included to provide surrogate evidence of the duration of corticosteroid release from the microspheres as validation for the potential extended duration of action.

18 STUDY OBJECTIVES

18.1 Primary Objectives

- To assess the safety of two doses (12.5mg and 25.0mg) 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) 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.

18.2 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

19 STUDY DESIGN

19.1 Duration

Following informed consent, subjects will be randomized 1:1:1 to receive SX600 (Dexamethasone acetate microspheres for extended-release injectable micro-suspension) 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. Each subject 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.

The study is expected to enrol over a period of 9 months. Each subject is expected to be in the study for 7 months. The total duration of the study is expected to be 19 months (9 months enrolment + 7 months follow-up + 3 months reporting).

Subjects will be screened within 28 days (Day -28 to -1) prior to Day 0. On Day 0, following final pre-dose qualifications and pre-dose collection of blood for PK, subjects will receive a single dose of SX600 (Dexamethasone acetate microspheres for extended-release injectable micro-suspension) at 12.5mg or 25.0mg or Placebo (0.9% Sodium Chloride for Injection, BP) via TF-EI at time zero (0).

In a subset of approximately sixty (60) subjects, blood for PK analysis will be collected at 30, 60, 90 minutes, and at 2, 4, 6, 8, 12, 20 and 24 hours, and, in all subjects, will be collected at each follow-up visit. Those subjects consenting to PK assessment will remain at the investigational Site from admission to 24 hours after IMP or placebo administration.

19.2 Rationale

Safety parameters will be collected pre-dose and at intervals specified in the schedule of procedures. Safety parameters will be collected, including ECG, vital signs, clinical laboratory panels, physical exam, urinalysis, adverse events, concomitant medications, etc. at each visit, as will functionality and quality of life assessments.

This is a first-in-human study to assess the safety and efficacy of two doses (12.5 mg or 25.0 mg) of Dexamethasone acetate microspheres for extended-release injectable micro-suspension, SX600 (IMP) administered by transforaminal injection to the lumbosacral epidural space at the L4- L5, L5-S1 level, or the S1 nerve root, as an outpatient procedure, 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.

Subjects enrolled in the study must have a defined Mean Worst Daily Leg Pain of ≥5.0 to ≤9.0 (being the *mean* NRS score, to 1 decimal place, of 5 days as further defined in the Efficacy Assessments) after at least 4 weeks but less than 6 months of conservative therapy. Validation of the single herniated disc consistent with the clinical features requires an MRI or CT scan of the lesion within 3 months of planned IMP administration. The pain history must be that of unilateral pain, radiating into a lower limb, of lancinating, burning, stabbing or electric quality, of duration 4 weeks to 6 months, and in the absence of significant axial contribution to the source of the pain.

Despite widespread clinical use of glucocorticoids for epidural injection, there are currently no steroid drugs on the U.S. or Australian market with an approved indication for epidural administration. Additionally, approximately 40% of EIs performed in the U.S. are repeat injections within 90 days of a subject's first injection, and 33% are repeat injections within 60 days. This new formulation is intended to provide sustained release of the dexamethasone acetate for greater than 60 days *in vivo* after a single epidural administration, which the Sponsor hypothesizes may provide durable pain relief in properly selected patients. This product

may reduce the frequency of epidural steroid injections for the management of lumbar radiculopathy and finally offer physicians and patients an approved drug for this purpose.

As secondary measures, functionality as measured by the Oswestry Disability Index and quality of life (SF-36 scoring) will be measured, and subjects will be followed for 180 days with 30-day visits measuring the pain response compared to baseline measures, with a Responder defined as subjects whose Mean Worst Daily Leg Pain (*mean* NRS score, to 1 decimal place, of 5 days), is ≥50% lower than that recorded at baseline (in the week pre-treatment.) The primary efficacy endpoint will be at 8 weeks post-treatment, but all measures will be recorded at each 30-day visit, thus providing some evidence of the duration of treatment efficacy.

19.3 Minimisation of Bias

Potential sources of bias have been considered and minimised through the study design, including:

- Eligibility of subjects will be confirmed by screening against all of the inclusion and exclusion criteria
- Investigational sites will be encouraged to enrol at least 5 subjects and enrolment at any one site will be capped at 50 subjects
- Investigational site staff who are involved in administration of IMP will not be involved in subsequent subjects' visits or assessments, in order to maintain the blind
- All investigational sites will utilize this Protocol and standardized CRFs for collection of data
- All subjects will be provided with standardised method for collection of patient-reported outcomes
- All Sponsor and Site personnel will be trained in study-specific procedures according to standardised training materials
- A Safety Review Committee, including an independent Medical Monitor will be used to assess safety
- A Statistical Analysis Plan will be developed prior to unblinding of the study.

20 STUDY ENDPOINTS

20.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with a 50% or greater improvement in Mean Worst Daily Leg Pain at 60 days post-dosing.

20.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- The proportion of subjects who are Responders (defined as having a 50% or greater improvement in Mean Worst Daily Leg Pain) 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 subjects who are Responders (defined as having a 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.
- Reduction in use of concomitant analgesics and supportive health services.
- Time to loss of response, in the subset of subjects who are Responders at Day 14 (50% or greater improvement in Mean Worst Daily Leg Pain).

20.3 Safety Endpoints

The Safety outcome will be assessed by:

- Subjects reporting AEs from treatment day through study conclusion
- The number of subjects reporting serious adverse events (SAEs) considered product or procedure-related throughout the study
- Neurological consequences of the TF-EI
- Number of subjects experiencing non-laboratory AEs following TF-EI throughout the study
- Number of subjects experiencing laboratory AEs 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

20.4 Pharmacokinetic Parameters

Individual pharmacokinetic parameters for SX600 will be summarised with descriptive statistics. Pharmacokinetic parameters will be calculated using non-compartmental analyses and PK modelling, [redacted]

21 SUBJECT ELIGIBILITY

One hundred and eighty subjects, male and female aged 18 to 65, will be sourced from those presenting to the investigative sites, where the participation in the study is offered for the management of monoradicular pain of severity (Mean Worst Daily Leg Pain of ≥5.0 and ≤9.0) and of duration 4 weeks to 6 months, that requires interventional treatment, having failed conservative therapies.

Subjects will be screened to ensure they meet all the inclusion and none of the exclusion criteria. Subjects 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.

21.1 Inclusion Criteria

1. Adult aged 18 to 65 years, capable of providing informed consent, capable of complying with the outcome instruments, and meeting the attendance requirements for review as defined in the study.
2. Presenting with a history of unilateral pain, radiating into a lower limb, of lancinating, burning, stabbing or electric quality, of duration of 4 weeks to 6 months, having failed conservative therapy.
3. Mean Worst Daily Leg Pain score of ≥5.0 and ≤9.0 being the *mean* NRS score (to 1 decimal place) of 5 days (as further defined in the Efficacy Assessments).

4. Demonstration of a disc herniation within 3 months by CT or MRI at the segmental levels of L4-L5, or L5-S1, [redacted]
5. Associated limitation of straight-leg-raise to less than 30 degrees, *or* straight-leg raise to 45 degrees with pain history of lancinating pain in the presence of disc herniation confirmed by imaging.
6. The site of the disc herniation must affect L4-5 or L5-S1, with involvement of the L4, L5, or S1 nerve roots unilaterally
7. [redacted]
9. Women of child-bearing potential must use a medically accepted method of contraception for the duration of the study plus 30 days and register a negative pregnancy test prior to dosing.
10. Men must agree to abstain from intercourse with women or agree to use a medically accepted method of contraception and refrain from donating sperm for the duration of the study plus 30 days.
11. Willing to comply with all the study activities and procedures throughout the duration of the study.

21.2 Exclusion Criteria

Subjects who meet any of the exclusion criteria at Visit 1 will be excluded from study participation and may be replaced. Exclusion criteria must be assessed by a study investigator who is also a clinician licensed to make medical diagnoses. Subjects will not be able to participate if they have any of the following:

1. Documented history of allergy or intolerance to components of the IMP, relevant radiologic contrast media, or local anaesthetics.
2. Is pregnant or lactating.
3. Has been taking corticosteroid medications routinely in the past 6 months *or* has received an epidural corticosteroid injection within 12 weeks of screening.
4. Has a BMI greater than 40 kg/m^2.
5. Has Diabetes Mellitus (Type 1 or Type 2) - prior confirmed HbA_{1c} or OGTT
6. [redacted] significant leg pain unrelated to disc herniation that would significantly compromise assessment of back or leg radicular pain.
13. Has radiological evidence of symptomatic disc herniation above L4-L5.
14. Has radiological evidence of clinically significant foraminal stenosis at L4-L5 or L5-S1 or of clinically significant spinal stenosis, or spondylolisthesis (Grade 2 or higher). (Note, asymptomatic foraminal stenosis at other spinal levels is not excluded).
15. Has had lumbar back surgery.
16. [redacted]

18. [redacted]

22. Has received an implantable device for pain management
23. [redacted]

22 STUDY SCHEDULE AND PROCEDURES

Prior to commencing any study-related procedures it is the Principal Investigator's responsibility to ensure that the study and the Investigational Site has received Ethics approval and Regulatory Authority approval (where relevant) *and* has received written authorization to commence study-related procedures for the Sponsor *and* the Participant Informed Consent Form has been signed by the subject and a study Investigator (who is also a clinician)

[redacted]

[redacted]

[redacted]

22.1 Consent

A subject can only consent to participation in this study after all aspects of the study have been explained to the subject, the subject has had adequate time (in their opinion) to consider the information relating to the study and that any questions they may have related to the study are answered adequately. Participation in the study is entirely voluntary and a subject may withdraw consent to participate at any time with no consequences to their standard care regimen provided by their usual treating clinician.

Sponsor and Human Research Ethics Committee approval of the Participant Informed Consent Form (including any required privacy language) is required prior to the enrolment of any subjects in this study. Any changes to the Participant Informed Consent Form language must be approved by the Sponsor and the Human Research Ethics Committee prior to being used to consent or re-consent subjects.

The Investigator must notify all subjects, including completed and withdrawn subjects, of any significant new information that becomes available during the course of the study. All previously consented subjects may be required to consider and provide reconsent.

A subject is considered enrolled in the study when the Participant Informed Consent Form has been signed by the subject and a study Investigator (who is also a clinician).

22.2 Study Visits

***Screening*: Day -28 to Day -1:**

This is the screening visit to determine study eligibility, plus baseline measure of Oswestry Disability Index, and recording of all current treatments (medications, physical therapy etc).

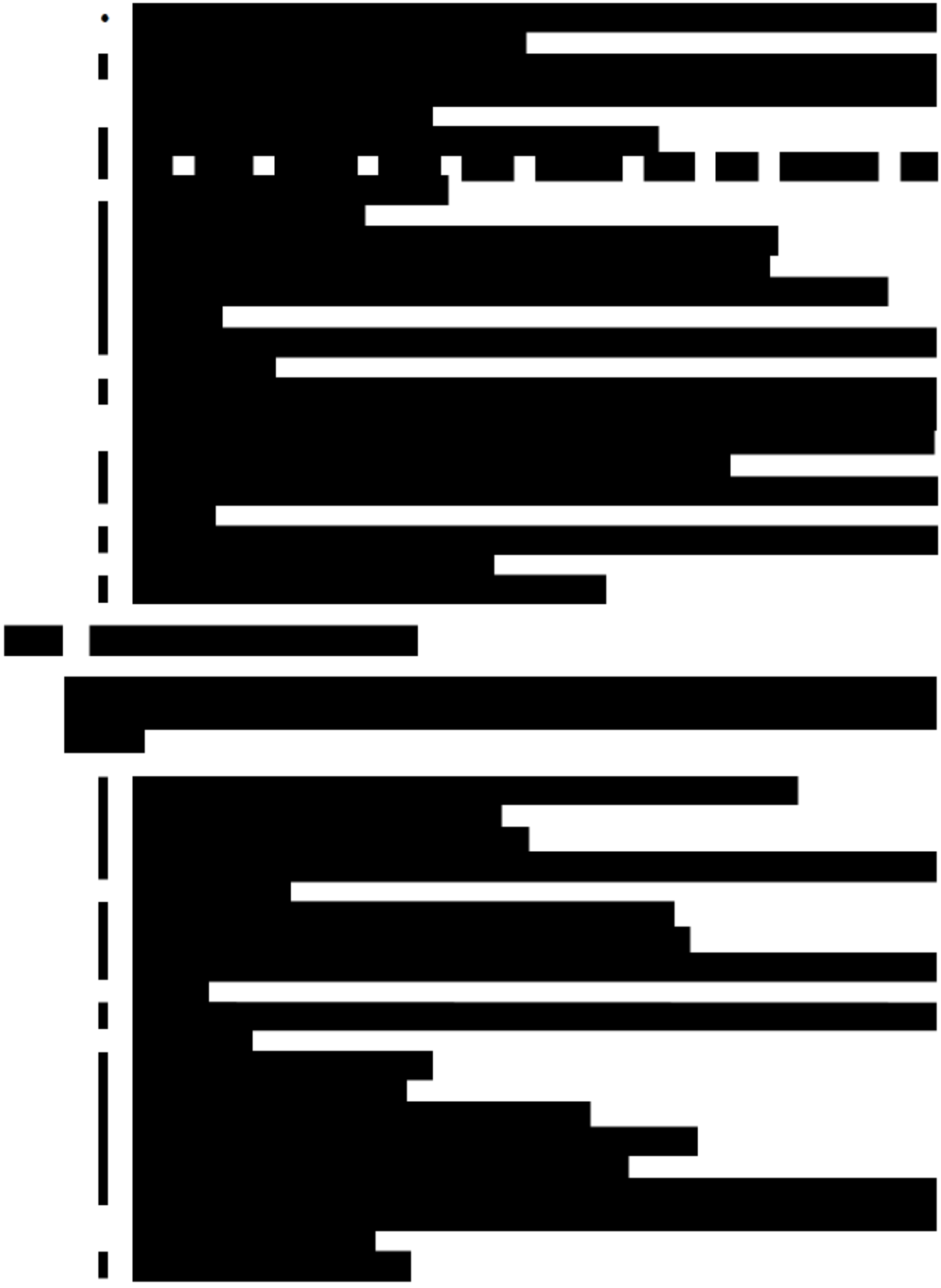
***Baseline/Treatment Day 0*:**

The intervention day when TF-EI is performed, and with initial Pharmacokinetic blood sample collections in the assigned subject population.

Follow-up Visits:

Post-dosing at Day 1 and Day 7, a telephone call will review subject status, and seek reporting of any AEs. At Days 14, 30, 60, 90, 120, 150, and 180 post-treatment, the subject will return to the Investigational Site for detailed assessment of both efficacy measures and safety assessments.

[redacted]



[redacted]

22.2.3.1 TF-EI Procedure

[redacted]

NOTE: If injection into an artery has been demonstrated, the procedure should be terminated, and the subject exited from the study. Physicians should not assume that simply repositioning the needle will avoid subsequent intra-arterial injection or uptake of the steroid preparation. The subject may be replaced in the study. The subject will be followed per standard of care.

8. [redacted]

[redacted]

22.2.3.5 Procedures for Identifying Inadvertent Administration

Validation of the appropriate position of the needle tip is based on:

1. Absence of flash-back of clear fluid (CSF) or blood in the needle cavity. Further validation can be sought by aspiration of the needle.
2. Interpretation of the radiologic screening of the injection through the needle of a small volume of contrast agent while continuously screening.

[redacted]

22.2.3.6 Pharmacokinetic Sampling

Following IMP/placebo administration, subjects allocated to the Pharmacokinetic population, will remain in-patient for the scheduled venous blood collection over 24 hours for pharmacokinetic analysis.

After the pre-dose baseline blood sample, post-dose blood samples for the measurement of the dexamethasone concentration in systemic circulation will be collected at the following time-points post-dose: 30, 60, 90 minutes, 2, 4, 6, 8, 12, 20, and 24 hours. Subjects will be discharged from the Investigational Site following collection of the 24 hr PK sample and all 24-hour safety measures (as listed below for other subjects (Telephone call 1) have been conducted and recorded.

[redacted]

[redacted]

22.3 RANDOMISATION

Subjects who are eligible for enrolment 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 Neuroscience Trials Australia. Subjects 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 final assignment of 60 subjects/group. The list of randomized treatment assignments will be prepared by statisticians assigned to the study and included in the enrolment module of the Electronic Data Capture (EDC) System. EDC will assign each subject a treatment code from the list after demographic and eligibility data have been entered into the system.

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 subject 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.

22.4 UNBLINDING

Unblinding is allowed where relevant to the acute clinical management of the subject.

Sites will be instructed to break the blind only in situations in which the Investigator determines that adequate medical care cannot be provided without knowing the treatment assignments. If a code break must occur, the Investigator or designee must contact the study Medical Monitor before unblinding.

Contact Information for Emergency Unblinding

[redacted]

If the blind has been broken, the Investigator must document the date and the reason the blind was broken in the source notes and CRF.

22.5 EARLY WITHDRAWAL

Subjects will be encouraged to complete the study and all assessments. A subject may withdraw consent to participate in the study at any time. A subject may be withdrawn from the study for the following reasons:

- Subject withdraws consent
- Subject is lost to follow-up
- Investigator deems early withdrawal necessary
- Other
- Study is terminated

Subjects who withdraw or are withdrawn prior to TF-EI procedure will be replaced. Subjects who withdraw or are withdrawn after IMP administration will NOT be replaced. An Early Withdrawal visit will be completed where possible. Upon withdrawal from the study and completion of the early withdrawal visit, no further study data will be collected, nor study visits occur for the subject. Subjects will be included in analyses up to the time that consent was withdrawn.

Refer to Section 22.2.12 Early Termination or Subject Early Withdrawal Visit for procedures to be followed if a subject withdraws or is withdrawn from the study.

In the case of subjects who fail to appear for a follow-up assessment, efforts to contact should include at least one telephone call and one letter, which should be documented in the subjects' records. Any additional requirements of the Human Research Ethics Committee should be followed. Lost to follow-up subjects will be withdrawn.

23 ASSESSMENTS

23.1 Efficacy Assessments.

Efficacy assessment will be based on the categorical measure of a Responder, defined as the proportion of subjects at Day 60 post-dosing in each active dose group compared to placebo with a 50% or greater improvement in Mean Worst Daily Leg Pain score compared to baseline. This pain scoring data will be

derived from the E-Diary recordings entered by the subjects. Subjects will be trained and reminded at each study visit to enter a measure of worst daily leg pain in the evening of each day. This is to establish a learned behaviour that ensures appropriate recording of the essential time period from which the mean values are derived. The data from intervening periods will not be analysed.

It is important that the critical levels of Mean Worst Daily Leg Pain (NRS Score of 5.0-9.0) is NOT communicated to the patient at any stage so that they remain unprogrammed and objective in any daily scoring.

If, in the opinion of the Investigator, additional treatment beyond the rescue medication approach provided in this protocol is required, for example surgery, the patient will be deemed a non-responder in the efficacy analysis at timepoints after the additional treatment but will continued to be followed in the safety population. In this case, the patient shall not continue to report worst daily leg pain score in the electronic diary but shall continue to record concomitant therapy and safety measures in the paper diary.

[redacted]

23.2 Functional Outcomes

Functional outcomes following treatment will be assessed by the Oswestry Low Back Pain Disability Questionnaire (Oswestry Disability Index) which provides information as to how the pain has affected the subject's ability to manage everyday life. This test has been in use since 1980 and is considered a "gold standard" of low back pain functional outcome tools. The Questionnaire will be completed by the subject at each study visit. The Disability Index will be calculated from each completed Questionnaire by the study personnel.
Interpretation of scores is:

- 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

Another supporting measure of efficacy will be reflected in the ability of the subject to reduce their use of concomitant analgesics and supportive health services. Measure of the use of the defined rescue medications will be included in this analysis, and any subject who "drops out" of the study will be noted and included in a separate analysis. They will of course be Non-Responders and included as such in the efficacy analysis.

23.3 Patient Clinical Global Impression of Change

A Patient Clinical Global Impression of Change will be assessed using the following 5-point scoring classification:

- Greatly improved = 1
- Improved = 2
- No change = 3
- Worse = 4
- Much worse = 5

23.4 SF-36 Assessments

SF-36 is a set of generic, coherent, and easily administered quality-of-life measures., presented as a questionnaire that addresses six domains:

- General Health
- Limitation of Activities
- Physical Health Problems, such as work and daily activities
- Emotional Health Problems
- Social Activities
- Pain

The Quality of Life patient questionnaire Short Form (36) Health Survey (SF-36) will be completed by patients at each visit.

23.5 Safety Assessments

23.5.1 Adverse Events

Adverse events will be collected throughout the study duration, starting at Visit 2 (Baseline/Treatment, Day 0) and ending at Visit 9 (Day 180 post-dosing) or until all ongoing adverse events are deemed resolved or stable by the Principal Investigator.

Resolution of an AE is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

Adverse events will be reported by the study subjects in the subject diary and/or to the study staff at each study visit. Recording of AEs will occur on an Adverse Event eCRF which will include the reported verbatim term (diagnosis where possible), Start Date, End Date, Outcome, Severity, Causality, Action Taken with IP and procedure and Seriousness.

Any SAE or subject death that occurs from and including Visit 2 (Baseline/Treatment onwards, whether or not related to IMP/Placebo, must be reported to Neuroscience Trials Australia (within 24 hours) via e-mail at the address noted below. A completed Serious Adverse Event Report Form with as much detail as possible must be included with the email, while ensuring that the SAE report contains the minimum criteria for reporting (participant ID, adverse event term, suspected investigational product, reason for meeting serious criteria and relationship to investigational product, name of the reporter). The Investigator must report all SAEs occurring from the time of Visit 2 (Baseline/Treatment) until 30 days after last treatment with the IMP/Placebo.

Contact Information for SAE Reporting

[redacted]

Pre-existing conditions or planned treatment (such as hospitalization) for pre-existing conditions are not considered adverse events unless the nature and severity of the condition has worsened.

Details of AE definitions, collection, recording, and reporting are found in Section 26.2

23.5.2 Demographic/Medical History

Information relating to the subject's age, sex, and race, will be recorded at Screening on the appropriate CRF.
Medical history will be recorded at Screening on the appropriate CRF, and brief physical review seeking to record changes in medical history will be collected at Baseline on the day the TF-EI is performed, and at all subsequent clinic visits.

23.5.3 Physical Examination

An abbreviated physical examination will be performed at Screening and Baseline visits, but with special attention to examination of the lower back and neurologic assessment of the lower limbs. This will particularly seek to determine motor function in the affected leg and will assess and record any sensory change that might coincide with the dermatomal representation of the affected nerve root. Examination of the lower back will seek to assess axial sources of pain that may contribute to the presenting pain and are therefore exclusionary.

If the characteristics of the pain or its intensity increases during the study, a detailed peripheral neurology examination should be performed to include motor strength and function, proprioception, sensation, reflexes, and gait and balance for the clinical assessment of a significant change in the original presenting pathology or the potential occurrence of newly-presenting co-morbidity. This can include new radiological investigation at the discretion of the Investigator, and treatment be recommended to provide "standard-of-care" management.

Careful examination of the skin in the area of potential TF-EI will be performed to identify any skin infection or inflammation that may contraindicate the procedure. Straight-leg-raising in the affected lower limb should be measured and recorded in the CRF.

The physical examination will include brief assessment of the head and neck, abdomen, chest, cardiovascular system and heart, respiratory, musculoskeletal, skin, general neurologic assessment, and any gross evidence of endocrine dysfunction. The physical assessment is mandatory at all unscheduled visits and at early termination visits per the Investigator's discretion. Body weight will also be recorded at Screening and Baseline and subsequent study visits, but subject height will be recorded at Screening Visit only.

23.5.4 Vital Signs

Blood pressure and pulse rate will be recorded at study visits and will be taken preferably using an automated recording machine programmed to take preferably 3 consecutive readings at least 2 minutes apart, with the subject seated comfortably for at least 3 minutes prior to blood pressure readings. Respiratory rate and temperature will be measured at all study visits.

23.5.5 Concomitant Medications/Therapies.

All concomitant medications and therapies in the preceding 30 days will be recorded at the Screening Visit and any changes or additions to medications or therapies must be recorded at each subsequent study visit.

The pain-relief needs of the subject should be carefully assessed at each study visit following IMP/placebo administration and prescribed medications and therapies tailored to the needs of the subject.

If, in spite of continued therapies, the subject requires additional analgesic medication, then a choice of rescue medication as listed in Section 25.8.1 can be added as deemed necessary and safe by the Investigator.

23.5.6 Electrocardiography (ECG)

A 12-lead ECG will be recorded in triplicate and assessed at the Screening and Baseline Visits, and again at the final Visit 9. The assessment is optional at unscheduled visits and at early termination visits, per the Investigator's discretion.

23.5.7 Laboratory Assessments

Clinical laboratory evaluations will be performed by the local Clinical Pathology Laboratory. Specific tests to be performed are described below:

- Haematology [redacted]
- Coagulation [redacted]
- Clinical chemistry (non-fasting serum) [redacted]
- Urinalysis: [redacted].

23.5.8 Virus Serology

HIV, Hepatitis A, Hepatitis B and Hepatitis C testing will be performed at Visit 1, D-28 – D-1 Screening, on a blood sample sent to the local Clinical Pathology Laboratory. HIV testing will be performed as per local standards. It is recommended that an antibody or antibody/antigen test be used for screening. If antibody or antibody/antigen testing results in an indeterminate test, HIV PCR may be used to further evaluate the HIV status of the subject.

23.5.8.1 Pregnancy Screen

Pregnancy testing will be performed in all female subjects of child-bearing potential at Visit 1, D-28 – D-1, Screening (serum and urine). Serum pregnancy testing will be performed at the local Pathology Laboratory. At Visit 2 and all subsequent visits, urine pregnancy test will be performed. Urine pregnancy test in females of childbearing potential will be performed in the research clinic, or Local Pathology. Any pregnancy in a subject or partner of a subject must be reported to Neuroscience Trials Australia within 24 hours per Section 26.3.

23.5.9 Urine Drug Screening

Urine drug screen (cocaine, cannabinoids, opiates, benzodiazepines, and amphetamines) will be tested at Visit 1 Screening visit Treatment on a sample sent to the local Clinical Pathology Laboratory, and at Visit 2 Baseline using a urine dip test at the study site. Subjects with a positive screen test results for any of the

above substances will be excluded from the study (with the exception of positive testing for prescribed ADHD therapy). Positive drug tests cannot be repeated.

23.5.10 Pharmacokinetic Assessments

In this study, systemic blood levels reflect a surrogate measure of drug concentration released locally from the drug depot in the transforaminal site.

Every study subject will have an aliquot of blood collected at each clinic visit to assess drug release duration from the microspheres. At the completion of the study, a reduced sample of placebo subject samples will be analysed, and if a timepoint is reached where no dexamethasone is measured in any of the active dose group subjects, then further analysis may be discontinued.

In the subset of subjects from at least 3 sites, totalling approximately sixty (60) in number, subjects will be assigned to a "PK Population".

Plasma PK: PK parameters based on plasma concentration will be dependent on the extent of systemic absorption of dexamethasone from the epidural depot.

Blood samples for plasma PK will be obtained at the following time points: Pre-dose, 30, 60, 90 minutes, 2, 4, 6, 8, 12, 20- and 24-hours post- epidural injection. A blood sample for drug concentration analysis will be collected at each follow-up visit (14, 30, 60, 90, 120, 150 and 180-days post-dosing) in all subjects.

[redacted]

Individual pharmacokinetic parameters for SX600 will be summarized with descriptive statistics.

[redacted]

[redacted]

23.5.11 TF-EI Imaging

Available imaging of transforaminal contrast spread during TF-EI will be collected as source and may be used for efficacy and safety analysis where relevant.

24 DEVIATION HANDLING

Deviations will be defined by NHMRC Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods 2018.

All deviations will be recorded on the Deviation page of the eCRF. Additionally, Serious Breaches will be reported on the NHMRC Serious Breach Report Form (Sponsor) and Suspected Breaches will be reported on the NHMRC Suspected Breach Report Form (Third Party).

Table 5. Deviation Definitions.

Deviation	Any breach, divergence or departure from the requirements of Good Clinical Practice or the clinical trial protocol.
Serious Breach	A breach of Good Clinical Practice or the protocol that is likely to affect to a significant degree: a) The safety or rights of a trial participant, or b) The reliability and robustness of the data generated in the clinical trial.
Suspected Breach	A report that is judged by the reporter as a possible serious breach but has yet to be formally confirmed as a serious breach by the sponsor

Table 6. Deviation Reporting Requirements and Timeframes.

Sponsor	
Serious Breach	Report to **HREC** within **7 calendar days** of confirming a serious breach has occurred and provide follow-up reports when required
	Notify trial **site**'s Principal Investigator within **7 calendar days** of confirming a serious breach has occurred
	Report to **HREC** within **7 calendar days** of the decision, where a Sponsor determines a third-party report, provided to it by the HREC, meets the definition of a serious breach
	Report to **HREC** by letter or e-mail, including a justification for this decision, within **7 calendar days** of confirming a serious breach has not occurred where the Sponsor determines a third-party report, provided to it by the HREC, does not meet the definition of a serious breach
	Notify the **TGA** and **HREC** if the serious breach leads to the closure of the site
	Report to the **TGA** any serious breach that involves a defective product that may have wider implications for the supply chain for that marketed product
Investigator	
Serious Breach or Suspected Breach	Report to Sponsor within **72 hours** of awareness

Serious Breach (that have been confirmed by the Sponsor as occurring at the site)	Report to the **Institution** within **72 hours** of being notified of the serious breach

25 INVESTIGATIONAL DRUG INFORMATION AND MANAGEMENT

25.1 Investigational Drug Regimen

In SX600, the dexamethasone acetate (DXA) is dispersed in a biodegradable polymer matrix and formed into solid microspheres to slowly release the drug and potentially provide durable pain relief in subjects. [redacted]

A dose volume of 1.0 mL (SX600 in 0.9% Sodium Chloride Injection, BP) was selected as the ideal volume for the IMP. [redacted] wo doses of SX600 will be tested in the Phase I/II clinical trial, 12.5 mg and 25.0 mg dexamethasone acetate reconstituted in 0.9% Sodium Chloride for Injection, BP, and delivered in 1.0 mL to the subjects.

[redacted]

[redacted]

The Placebo product for the clinical trial will be 0.9% Sodium Chloride for Injection, BP.

25.2 Dose Rationale

SX600 (Dexamethasone acetate microspheres for extended-release injectable micro-suspension) is a microsphere formulation of dexamethasone acetate, a corticosteroid, to be administered by transforaminal epidural injection. The route of administration of the IMP is identical to that of well-established transforaminal epidural steroid injections that are performed off-label in millions of subjects per year. Dosing in this study will involve a single administration of a 1 ml dose delivered to the transforaminal epidural space adjacent to an affected nerve root.

Based on the NOAEL doses identified in the nonclinical studies conducted in beagle dogs and rats, and the toxicokinetic profile [redacted]

[redacted] it has been calculated that human doses of 12.5 mg and 25.0 mg as single doses are safe and will fulfil the expectation of prolonged release.

25.3 Investigational Drug Packaging and Labelling

All IMP used in this study will be prepared, packaged, and labelled in accordance with the Standard Operating procedures (SOPs) of the Sponsor or its qualified subcontractors, Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonization (ICH) guidelines for GCP, guidelines for Quality System Regulations (QSR), and applicable regulations.

[redacted]

25.4 Investigational Drug Storage

[redacted]

25.5 Investigational Drug Preparation

[redacted]

25.6 Investigational Drug Administration

A detailed description of the Transforaminal procedure has been presented in Section 22.2.3.1.

25.7 Investigational Drug Accountability

It is the responsibility of the Principal Investigator to ensure IMP/Placebo accountability, reconciliation and record maintenance at the investigational site. All discrepancies in IMP/Placebo accountability must be accompanied by a written account from the Investigator.

In accordance with all applicable regulatory requirements, the Investigator and/or designated site staff must maintain IMP/Placebo accountability records throughout the course of the study. Details IMP/Placebo received at site will be documented. Details of IMP/Placebo supplied and/or administered to subjects will be documented by investigational site staff who are listed on the Delegation of Authority log as 'unblinded' to treatment assignment.

An unblinded study Monitor will verify all accountability records during periodic monitoring visits. Unused and used IMP/Placebo must be stored on site until such accountability has taken place and authorization is received from the Sponsor or Sponsor's designee that the study drug may be returned for destruction.

25.8 Treatment of Subjects

25.8.1 Rescue Medication

All subjects entering this study are required to keep all analgesic medication and other therapy usage [such as physiotherapy, acupuncture, or TENS] stable or decreased during the study, and only use the rescue pain medication as needed and specified by the protocol.

If pain control is unsatisfactory, the Investigator has a range of Rescue medications that can be added to the maintenance therapy that the subject takes as concomitant medications.

Any one of the Group 1 and/or any one of the Group 2 rescue medications are available for increases in pain for selection and prescription by the Investigator for up to 14 days (once during the study) as addition to the medications currently used by the patient, with special consideration of safety and potential drug interactions.

Group 1 (one of):

Amitriptyline	5 – 50mg Nocte, *or*
Pregabalin	25mg – 300mg BD, *or*
Gabapentin	100mg TDS dosage, up to 600mg TDS

(Acute withdrawal of gabapentin or pregabalin can result in withdrawal symptoms, with likelihood of withdrawal related to dose and duration of treatment. If appropriate, down-titration should take place over at least one week, starting no later than day 15 after rescue began.)

and/or Group 2 (one of):

Tramadol	100mg – 200mg (SR) BD, *or*
Tapentadol	50 – 200mg (SR) BD

[redacted]

[redacted]

Because the IMP is a sustained release formulation of a potent corticosteroid (Dexamethasone) and the systemic bioavailability of this product is not yet defined in humans, the Investigator is advised not to order, refer, or perform another epidural steroid injection of any type during the study beyond the TF-EI that is performed per this protocol. If the Investigator is aware that subject will seek another epidural steroid injection elsewhere during the study, Investigator shall advise patient of the sustained-release nature of the IMP and its unknown duration of drug exposure in humans and shall further advise patient to inform any physician offering an epidural steroid injection of the patient's participation in this study.

25.9 Treatment Compliance

Treatment compliance with the IMP is not an issue, because this involves a single administrative procedure via the transforaminal epidural injection on Day 0 of the study. However, compliance with protocol requirements for concomitant medications and supportive therapies will be aided using a paper diary provided to each subject at study commencement that will seek to record changes in maintenance treatments (doses up or down, or missed), or the recording of any additional medication.

26 SAFETY

It is the responsibility of the Sponsor and Investigational site to follow local regulatory requirements and guidelines with respect to safety.

26.1 Adverse Event Definitions

Adverse events will be defined by the NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (November 2016).

Table 7. Adverse Event Definitions.

Seriousness	
Adverse event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and that does not necessarily have a causal relationship with this treatment.
Adverse reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Safety Critical Adverse Events	Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations that should be reported to the sponsor according to the reporting requirements specified in the protocol.
Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)	Any adverse event/adverse reaction that results in death, is life-threatening*, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
Significant Safety Issue (SSI)	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
Urgent Safety Measure (USM)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.
Severity	

Mild	event requires minimal or no treatment and does not interfere with the participant's daily activities
Moderate	event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe	event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
Life-threatening	event in which the subject was at risk of death *at the time of the event**
Fatal	event that resulted in death
Relatedness	
Definitely related	There is a reasonable possibility that the IMP caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the TF-EI procedure or the IMP and the AE.
Probably related	
Possibly related	
Not related	There is not a reasonable possibility that the TF-EI procedure or the IMP caused the event
Expectedness	
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction that is both serious and unexpected.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the Reference Safety Information (RSI)
Timing	
During TF-EI procedure	
Post TF-EI procedure	

*Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgement should be exercised in deciding whether an adverse event/ reaction should be classified as serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must be assessed for seriousness, severity, relatedness, expectedness and timing by a study Investigator (who is also a clinician). All changes to an AE must be documented. AEs characterized as intermittent require documentation of onset and duration of each episode.

26.2 Reporting Procedures

Adverse events will be reported according to local regulatory requirements. It is the responsibility of the Investigator to meet any additional AE reporting requirements stipulated by the HREC responsible for oversight of the study.

Table 8. Adverse event reporting requirements and timeframes.

Sponsor	

Significant Safety Issue (SSI) Including SSIs that arise from overseas reports relating to a clinical trial in Australia	Notify **TGA, HREC and all Investigators** without undue delay and no later than **15 calendar days** of the sponsor instigating or being made aware of the issue
Urgent Safety Measure (USM)	Notify **TGA** within **24 hours**. Notify the HREC and all Investigators within **72 hours** of the Sponsor instigating or being made aware of the issue
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Report to the **TGA** Fatal or life threatening Australian SUSARs, immediately, but no later than **7 calendar days** after being made aware of the case, with any follow-up information within a further **8 calendar days** For all other Australian SUSARs, no later than **15 calendar days** after being made aware of the case
Notification of amendment, temporary halt or early termination of trial for safety reasons	Notify **TGA, HREC and all Investigators** without undue delay and no later than **15 calendar days** of the sponsor instigating or being made aware of the issue
Action with respect to safety that has been taken by another country's regulatory agency (relevant to an ongoing clinical trial in Australia	Report to the **TGA** without undue delay and no later than **72 hours** of the trial Sponsor becoming aware of the action
Other single case adverse events (AEs)	Report to the **TGA** at their request
Annual Safety Reports	Report to the **TGA** at their request
Investigator	
Adverse Events (AEs) and Adverse Reactions (ARs)	Report to the **Sponsor** as soon as practicable
Serious Adverse Events (SAEs)	Report to the **Sponsor as soon as possible** and without unjustified delay and **within 24 hours** of the event
Urgent Safety Measure (USM) instigated at the site	Report to the **Sponsor** within **24 hours**
Significant Safety Issues (SSIs) and SUSARs arising from the local site	Report to the **Institution and the Sponsor** without undue delay and no later than **72 hours** of the Principal Investigator becoming aware of the event
Annual Safety Reports	Report to the **HREC** as per the HREC requirements

Any SAE or subject death that occurs from and including Visit 2 (Baseline/Treatment onwards, whether or not related to IMP/Placebo, must be reported to Neuroscience Trials Australia (within 24 hours) via e-mail at the address noted below. A completed Serious Adverse Event Report Form with as much detail as possible must be included with the email while ensuring that the SAE report contains the minimum criteria for reporting (participant ID, adverse event term, suspected investigational product, reason for meeting serious criteria and relationship to investigational product, name of the reporter) The Investigator must report all SAEs occurring from the time of Visit 2 (Baseline/Treatment) until 30 days after last treatment with IMP/Placebo.

Contact Information for SAE Reporting

NTA-Pharmacovigilance@florey.edu.au

Other supporting documentation of the event may be requested by the Sponsor via Neuroscience Trials Australia Pharmacovigilance Group or additional information may be received by the Sponsor (e.g., evolution of the SAE, other signs or symptoms, final diagnosis, final outcome, hospital discharge summary,

or autopsy report).and should be provided as soon as possible to ensure compliance of reporting with local regulatory requirements. The same procedures and timelines as for initial reporting, listed above, should be followed for any follow-up information. If necessary, the study site will be visited to collect additional information.

Follow-up information is required on all SAEs until one of the following criteria is satisfied:

- The final outcome of the case is known.
- The event is resolved, or the medical condition of the subject has stabilized.
- No further information is available.
- Sponsor assessment has been finalized.

The SpineThera Chief Medical Officer will be notified of the SAE by the Neuroscience Trials Australia Pharmacovigilance Group. The Sponsor is responsible for reporting of safety information to the Regulatory Authority. The Safety Review Committee will provide safety oversight per Section 26.4.

At any time after completion of the study, if the Investigator becomes aware of an SAE that is suspected to be related to study product, the Investigator will report the event to the Sponsor.

The Investigator has a responsibility to ensure the conduct of the trial, including the monitoring of safety and reporting of adverse events, complies with the study protocol. Initial safety reports should be followed by detailed written reports including comments on potential confounding factors, results of investigations, treatment required and outcome. The Sponsor and Principal Investigator should review the adverse outcome in the context of known information on the medicine and make a determination as to whether the event was drug-related (i.e. an adverse reaction).

The Sponsor will review all adverse events for completeness and accuracy and request clarification and/or additional information from the Investigator where necessary. The Sponsor will utilize MedDRA, the Medical Dictionary for Regulatory Activities, to assign a MedDRA term for each adverse event based on the information provided by the investigator.

26.3 Pregnancy

Pregnancy in a subject or partner of a subject must be reported to Neuroscience Trials Australia (within 24 hours) via e-mail at the address noted below. A completed Pregnancy Report Form with as much detail as possible must be included with the email. It is the responsibility of the Investigator to follow-up any pregnancy, including pregnancies of partners of subjects, until outcome (e.g. birth or spontaneous abortion) and report any incidents of congenital abnormality/birth defect as an SAE, dependent on local privacy laws. The outcome of the pregnancy should be reported to Neuroscience Trials Australia. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by emailing a completed SAE Report Form to the Sponsor within 24 hours of knowledge of the event. Subjects will remain in the study and undertake all study-related procedures, unless the subject chooses to withdraw from the study.

Contact Information for Pregnancy Reporting

[redacted]

26.4 Safety Oversight: Safety Review Committee

A Safety Review Committee (SRC) assigned the responsibility of safety of the participants will provide medical oversight and expertise to the Sponsor and sites concerning the continuation, modification, or termination of the trial. The SRC will monitor subject 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 the safety oversight of the study per the NHMRC Guidance on Data Safety Monitoring Boards 2018. The SRC will be composed of three to four members including a 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.

The SRC will be charged with reviewing the protocols with respect to ethical and safety standards and making recommendations if necessary. During the study, the SRC will meet via teleconference or web-based meetings at least every 3 months to review safety issues and to monitor Investigational Site performance in execution of the protocol. Prior to each meeting, a safety report on all subjects will be generated.

In addition, an SRC review will occur after at least 30 subjects have received their one dose of IMP/Placebo and have completed Visit 5 (Day 60). The SRC will either recommend continued enrolment of the remaining subjects or discontinuation of enrolment/termination of the study. Though the timing of the SRC review will be expedited, enrolment may continue while awaiting the SRC review. In addition, a computerized system will be used to acquire any data regarding halting criteria throughout the study.

If any of the halting rules are met, the study will not proceed with the remaining enrolment without a review by and recommendation from the SRC to proceed. Upon completion of this review and receipt of the advice of the SRC, SpineThera will determine if study entry or study dosing should be interrupted or if study entry and study dosing may continue according to the protocol, documenting reason(s) for decision taken

27 STUDY SUSPENSION OR EARLY TERMINATION

Suspension is a temporary pause in study activities. Early termination is the closure of the study prior to the defined endpoint. Suspension or early termination can occur either at an Investigational Site or across the entire study and may be at the direction of the Sponsor, the HREC or the Regulatory Authority.

Reasons for suspension or early termination of the study may include, but are not limited to, the following:

- Incidence or severity of adverse events represent a significant medical risk. Severity of adverse events will be determined per Table 9: Adverse Event Definitions Specifically, but not limited to:
    - three or more subjects experience the same serious adverse event as evaluated by a licensed clinician.
    - three or more subjects who received one treatment dose experience a severe, treatment-related laboratory abnormality in the same laboratory parameter.
    - an overall pattern of symptomatic, clinical, or laboratory events that the Safety Review Committee consider to be associated with IMP and that may collectively represent a serious potential concern for safety.
- An issue relating to IMP manufacturing or distribution.
- Failure to obtain Human Research Ethics approval or HREC annual report acknowledgement for the study.
- Failure of the Investigator/Investigational Site to comply with the protocol, the Clinical Trial Research Agreement or applicable regulatory guidelines in conducting the study.
- Failure of the Investigator/Investigational Site to accurately and completely collect and record study related data as per GCP.

In the case of study suspension, it is the responsibility of the Sponsor to notify all Investigators and the Human Research Ethics Committee, including the reason for suspension. It is the responsibility of the Investigator to ensure enrolment and treatment (IMP/Placebo administration) of subjects ceases

immediately and until the suspension is lifted by the Sponsor and acknowledged by the Human Research Ethics Committee. Enrolled *and* treated subjects will continue to be managed per protocol.

In the case of termination, it is the Sponsor's responsibility to notify all Investigators, the Regulatory Authority and Human Research Ethics Committee immediately, including the reason for termination. It is the Investigator's responsibility to inform the subjects and ensure appropriate care and follow-up is provided.

28 ETHICS

28.1 Statement of Compliance

The study will be conducted according to ICH Harmonised Guideline Integrated Addendum to ICH E6(R1): Guideline For Good Clinical Practice ICH E6(R2) – annotated with TGA comments, and in accordance with the national and local laws, regulations, standards, and requirements of the country/ies in which the study is conducted.

The study will follow and comply with:

- The principles of Good Clinical Practice
- 21 CFR Part 11
- 21 CFR Part 50 (informed consent)
- 21 CFR Part 54 (financial disclosure by clinical investigators)
- Local Ethics Committee and Regulatory Authority requirements
- The Clinical Trial Research Agreement (CTRA)
- This subject eligibility and study procedures as outlined in this protocol

This study will only commence once Ethics Committee approval and Regulatory Authority acknowledgement has been received, where relevant. The Protocol and any subsequent amendments must be approved by the Sponsor and the Ethics Committee prior to any study-related procedures being undertaken at an investigational site. The CIP and any subsequent amendments must be acknowledged by the site Principal Investigator prior to any study-related procedures being undertaken at the Investigational Site.

The investigators shall make written commitments to comply with GCP and this protocol.

The study will be publicly registered prior to first enrolment.

29 STUDY ADMINISTRATION

29.1 Study Monitoring

It is the responsibility of the Sponsor to ensure monitoring of this clinical study. Site monitoring will be conducted by trained Sponsor personnel or delegates to ensure the study is conducted in accordance with the GCP, the Protocol, Clinical Trial Research Agreements and local laws and regulatory requirements, as specified in the study Monitoring Plan.

It is the responsibility of the Investigator to allow monitors access to the clinical trial records including regulatory files, IMP accountability records, laboratory records and Participant Informed Consent Forms, *and* subjects' medical records including clinic and hospital records, in accordance with the Participant Informed Consent Form. The Principal Investigator must also make every effort to be available to meet with the Sponsor and/or study monitors during monitoring visits to discuss any problems and actions to be taken and document visit findings and discussions. Further, it is the Principal Investigators responsibility to comply with Sponsor requests relating to GCP or protocol compliance issues identified as the result of monitoring.

29.2 Source Documents

It is the responsibility of the Principal Investigator to ensure source documents listed below are appropriately prepared and maintained at the Investigational Site, including security and limited access to personal or sensitive information of subjects.

- Regulatory Authority notification or approval
- Ethics Committee approval documentation including Ethics Committee composition and certification.
- All correspondence between the Ethics Committee, Regulatory Authorities, the Institution, Sponsor or delegate, Monitor and the investigator relating to the clinical study
- Subjects' records including, but not limited to:
    - Signed and dated Participant Informed Consent Form for all subjects, including revisions or updates
    - Subject identification log
    - Adverse events
    - Concomitant medications and therapies
    - Medical history
    - Procedure-related information
    - Efficacy Information
- Deviations from the protocol with rationale
- Fully executed Clinical Trial Research Agreement, Form of Indemnity, Insurance Certificates and Financial Disclosures
- All approved versions of the Protocol and Investigator Brochure including completed Acknowledgment of Receipt
- Participant Informed Consent Form master, Patient Reported Outcomes master and other information given to the subject.
- Current signed and dated curriculum vitae of all Investigational Site staff undertaking study-related procedures
- Documentation of delegated tasks for all Investigational site staff undertaking study-related procedures
- Study training records for all Investigational Site staff.
- IMP shipping records, accountability records and environmental monitoring logs
- Equipment maintenance records, where applicable
- Any other document that local or international Regulatory Agencies may require to be maintained

It is the responsibility of the Sponsor to ensure the documents listed below are appropriately prepared and maintained:

- Regulatory Authority notification or approval
- Ethics Committee approval documentation including Ethics Committee composition and certification.
- All correspondence relating to the clinical study
- fully executed Clinical Trial Research Agreements, Form of Indemnity, Insurance Certificates and Financial Disclosures
- All approved versions of the Protocol and Investigator Brochure including completed Acknowledgments of Receipt
- Participant Informed Consent Form master, Patient Reported Outcomes master and other information given to the subject.
- List of Investigator and Investigational Sites/Institutions
- Current signed and dated curriculum vitae of all Investigational Site staff undertaking study-related procedures
- Documentation of delegated tasks for all Investigational site staff undertaking study-related procedures

- Study training records for all Sponsor/delegate staff.
- List of study Monitors, all Monitoring Visit Reports and follow-up letters
- IMP shipping records, accountability records
- All approved versions of study management reports and plans including the Monitoring Plan, Statistical Analysis Plans, Document Management Plan, Safety Management Plan etc.
- Case Report Forms
- Clinical Study Report
- Any other document that local or international Regulatory Agencies may require to be maintained

Records will be retained by the Sponsor and the Investigational Sites for a minimum of 15 years after product approval or the date on which the study is terminated.

The Principal Investigator, Investigational Site and Institution will allow access to all source documents for monitoring, Ethics Committee review, assessment, audits or regulatory inspections from commencement of the study and at least through to the end of the minimum retention period.

29.3 Data Collection and Management

Data will be collected using an electronic data management system which is 21 CFR Part 11 compliant.

Data generated within this clinical study will be handled according to the relevant SOPs and/or the Data Management Plan of the Sponsor and/or their delegate(s). An electronic CRF (eCRF) will be created by the data management group for recording of the required data. Automated and manual checks will be run against the data to ensure completeness and consistency.

Data collection and entry into the eCRF will be completed by authorised study site personnel designated by the Investigator, following appropriate training. The Investigator must verify that all data recorded in the eCRFs are accurate and correct and he/she will be required to sign off on the final clinical data.

Data in the eCRFs shall be derived from source documents. Source documents are documents used by the Investigator or study site that relate to the subject's medical record, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study.

Adverse events will be coded using the MedDRA and medications will be coded using the WHO Drug Dictionary.

eCRFs will be completed for subjects who have signed the ICF, are eligible for this study and have been randomized in the study.

30 CONFIDENTIALITY

All subject data will be treated as confidential as per local laws and guidelines. Subjects will be identified to the Sponsor in a key-coded form only. As the Investigational Site will maintain a master subject log, all data will be potentially re-identifiable. Source documents requested by the Sponsor (for example, medical records related to a SAE) will have personal and sensitive information redacted by the Investigational Site prior to transfer to the Sponsor. Subjects will not be identified by name in any publications arising from this study.

31 STATISTICAL CONSIDERATIONS

31.1 Introduction

Data will be summarized descriptively by treatment arm and overall. The descriptive summary for categorical variables will include counts and percentages. The descriptive summary for continuous variables will include number of subjects, means, medians, standard deviations and minimum and maximum values.

All collected data will be listed for all subjects.

Unless otherwise specified, all statistical tests will be conducted at the two-sided 0.05 alpha level with 95% confidence intervals. A comprehensive statistical analysis plan (SAP) will be prepared prior to database lock and unblinding. Further analytical details will be provided in the SAP.

31.2 Sample Size Justification

Limited data are available in the literature on which to base sample size/power considerations. In the study conducted by Ghahreman (Gharheman, 2010), the primary endpoint was the proportion of subjects 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 subjects 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%.

31.3 Data Analysis Populations

The Intent-to-Treat (ITT) population includes all randomized subjects. In the ITT population, subjects will be included in the treatment group to which they were randomized, regardless of treatment received. A safety analysis will be conducted in the ITT population, which includes patients in which a TF-EI procedure was attempted but abandoned prior to drug delivery and patients who received IMP or placebo, thereby differentiating the effects of the procedure.

The Safety population includes all randomized subjects who proceed to TF-EI (including patients with attempted but halted or failed TF-EI). In the Safety population, subjects will be included in the treatment group based on the treatment that was received. All safety analyses will be conducted in the Safety population.

The modified Intent to Treat population includes all randomized subjects who receive IMP or placebo by TF-EI. This population forms the basis of the primary efficacy and safety analyses. In the mITT population, subjects will be included in the treatment group to which they were randomized, regardless of treatment received. All efficacy analyses will be conducted in the mITT population.

The Per-Protocol (PP) efficacy analysis population includes all randomized subjects 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. Supportive efficacy analyses will be conducted in the PP population.

PK population: All subjects 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.

In order to minimize bias, the PP population will be defined prior to unblinding.

31.4 Study Disposition

The number and percent of subjects in each analysis population will be summarized. The number of subjects who complete the study, discontinue prematurely, and their reason for study discontinuation will be tabulated.

31.5 Baseline Characteristics and Demographics

Summary descriptive statistics for baseline and demographic characteristics will be provided for all subjects. Demographic data will include age, race, sex, body weight and height. Other baseline and background characteristics will also be summarized.

31.6 Efficacy Analyses

31.6.1 Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of subjects with a 50% or greater improvement from baseline in Mean Worst Daily Leg Pain at 60 days. The primary endpoint will be analysed using a logistic regression model with treatment group (three levels) as a factor. The primary analysis will compare the high dose group to the placebo group using a two-sided test at the alpha=0.05 level of significance. The odds ratio of the high dose group to the placebo group with a 95% Wald confidence interval will also be reported.

31.6.2 Key Secondary Efficacy Analysis

If the comparison between the high dose group and the placebo group is statistically significant ($p<0.05$), then the following analyses will be conducted using a fixed sequence testing procedure to control the overall level of significance:

1. The primary analysis model will be used to compare the low dose group to the placebo group. The odds ratio of the low dose group to the placebo group with a 95% Wald confidence interval will also be reported.
2. Comparing the high dose group to the placebo group, the proportion of subjects with a 50% or greater improvement from baseline in Mean Worst Daily Leg Pain at 90 days will be analysed using the same methodology as the primary analysis.
3. The mean changes from baseline to Day 60 in the Oswestry Disability Index will be compared between the high dose group and the placebo group.
4. Comparing the low dose group to the placebo group, the proportion of subjects with a 50% or greater improvement from baseline in Mean Worst Daily Leg Pain at 90 days will be analysed using the same methodology as the primary analysis.

The change from baseline to Day 60 in the Oswestry Disability Index will be analysed using an analysis of covariance (ANCOVA) model with treatment group (three levels) as a factor.

All of the above analyses will be conducted using two-sided tests at the alpha=0.05 level of significance. However, once a nonsignificant result occurs, all remaining tests will be exploratory rather than confirmatory.

[redacted]

[redacted]

[redacted]

31.7 Safety Analyses

Adverse events will be coded using the MedDRA.

Treatment-emergent AEs (TEAEs) are defined as any AE occurring during or after initiation of IMP. TEAEs will be summarized using frequency counts and percentages. Treatment-emergent AEs will also be rated for severity and relationship to IMP. In addition, all SAEs, deaths, and AEs leading to IMP or study discontinuation will be summarized and listed separately.

Safety laboratory test parameters, vital signs, and ECG results will be tabulated and/or listed.

31.8 PK Analyses

Individual pharmacokinetic parameters for SX600 will be summarized with descriptive statistics. Individual measures will be calculated using non-compartmental analyses and PK modelling.

32 REFERENCES

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33 ATTACHMENTS

Attachment #	Title	# of Pages
01	Major antipsychotic or major antidepressant drugs	01
02	TF-EI Procedure & IMP/Placebo Preparation (CLIN-0022)	07