Protocol Title:	Corticosteroid Lumbar Epidural Analgesia for Radiculopathy (C.L.E.A.R.)
Protocol Number:	SP-102-02
Clinical Phase:	3
Protocol Version and Date:	Version 4.0, 24 May 2018
US Investigational New Drug Number:	[redacted]
Sponsor:	Semnur Pharmaceuticals, Inc. 301 N. Whisman Rd, Suite 100 Mountain View, CA 94043

-CONFIDENTIAL-

SIGNATURE PAGE

Protocol Title: Corticosteroid Lumbar Epidural Analgesia for Radiculopathy (C.L.E.A.R.)

The undersigned have reviewed the format and content of this protocol and have approved the clinical study protocol.

Any modifications of the clinical study protocol must be agreed upon by the sponsor and the investigator and must be documented in writing.

Sponsor Approva

Signature: [redacted] Date: [redacted]

Name (print): [redacted]

Title: [redacted]

Investigator Agreement:

I have read the clinical study protocol and agree to conduct the study as outlined herein.

Signature: _____ Date: _____

Name (print): _____

SUMMARY OF CHANGES incorporated with AMENDMENT 3

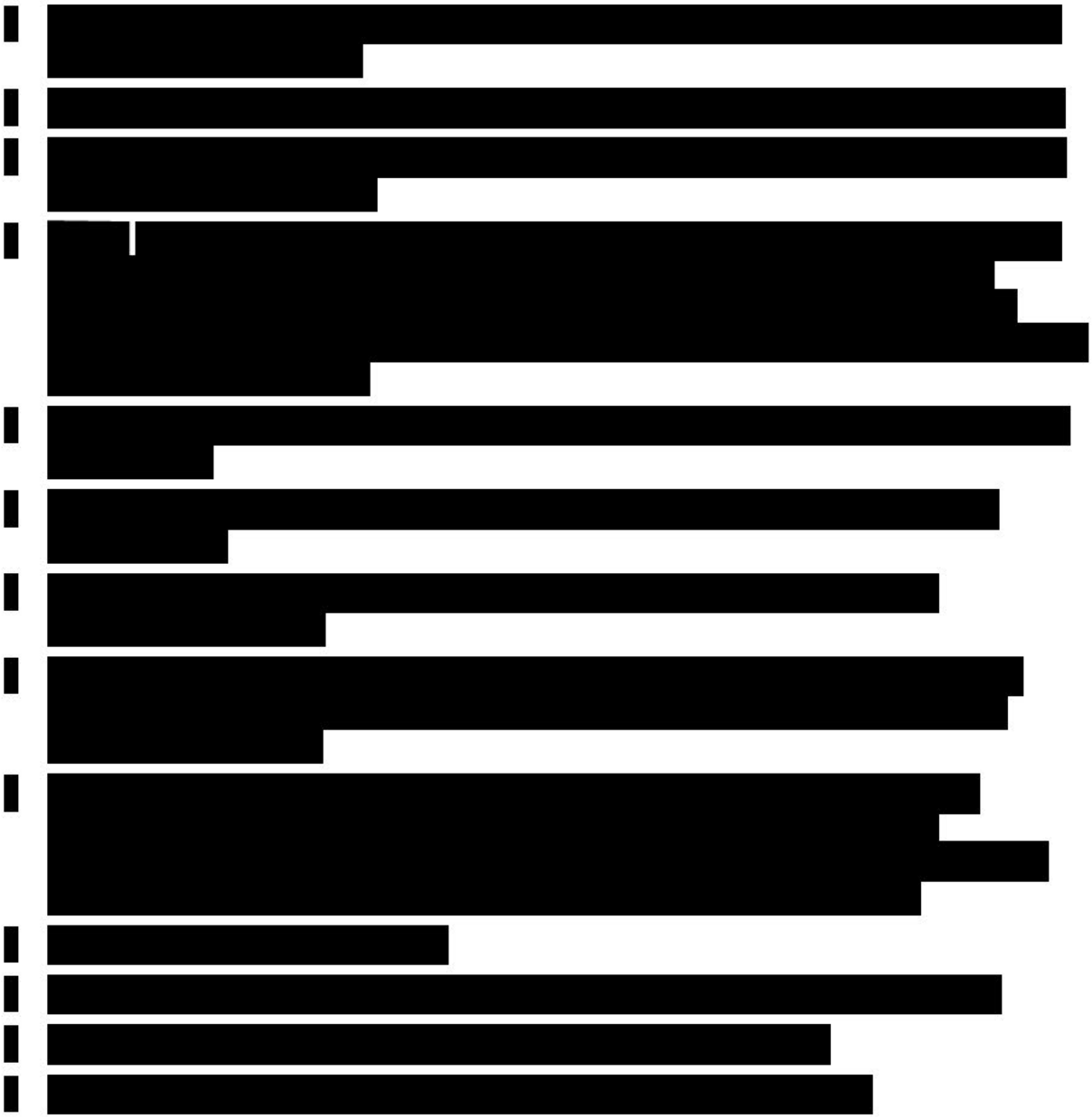
This is a summary of changes from the protocol dated 11 May 2018.

SUMMARY OF CHANGES incorporated with AMENDMENT 2

This is a summary of changes from the Protocol dated 29 Sep 2017. [redacted]

SUMMARY OF CHANGES incorporated with AMENDMENT 1

This is a summary of changes from the Protocol dated 16 Aug 2017 and the rationale for the changes. These additions to the protocol were requested by the United States FDA on 27 Sep 2017:



SYNOPSIS

Protocol Title:	Corticosteroid Lumbar Epidural Analgesia for Radiculopathy (C.L.E.A.R.)
Protocol Number:	SP-102-02
Investigator(s)/Study Center(s):	This study will be conducted at up to approximately 45 study sites in the United States. [redacted] will oversee operational aspects of this study on behalf of Semnur Pharmaceutical, Inc., the sponsor of the study.
Phase of Development:	3
Objectives:	The primary objective of this study is to: • Evaluate the analgesic effect on average leg pain (as measured by the Numeric Pain Rating Scale [NPRS] in the affected leg) following a single transforaminal (TF) injection of SP-102 compared to an intramuscular (IM) injection of placebo over 4 weeks. The secondary objectives of the study are to: • Evaluate degree of disability over time as measured by the Oswestry Disability Index (ODI). • Characterize the change of the subject's radiculopathy symptoms and overall condition using Pain*DETECT*, Brief Pain Inventory–Short Form (BPI-SF), Clinical Global Impression of Change (CGIC), and Patient Global Impression of Change (PGIC). • Evaluate the safety of single and repeat SP-102 TF injections.
Study Design:	This is a double-blind (DB), randomized, placebo-controlled, multicenter study in subjects with lumbosacral radicular pain evaluating the safety and efficacy of a single SP-102 TF injection compared to a single placebo IM injection, followed by an open-label (OL) safety extension, evaluating an optional repeat SP-102 TF injection, if indicated, administered 4 to 20 weeks later. Subjects will be followed for 24 weeks following the initial treatment ("index injection"). After providing informed consent, each subject will complete a Screening Visit between Day (D) -22 and D-8. Subjects who meet the screening eligibility criteria will record their current, worst, and average pain in their lower back, affected, and non-affected leg using the NPRS scale on a handheld electronic clinical outcome assessment (eCOA) device (ie, "eDiary") twice a day (12 ±2 hours apart) from Screening until Baseline (D1). The 7 days immediately prior to Baseline (D1) will be used to determine eligibility. The average and worst NPRS pain scores will reflect the subject's pain over the last 12 hours. During the screening period, subject's medical eligibility will be also reviewed and confirmed by the study Medical Monitor. Subjects can progress to Baseline (D1) only after medical eligibility approval is provided. Subjects who have been using opioids other than high dose opioids within 30 days prior to Screening (see Exclusion #11), may participate in the study if they agree to discontinue the opioid therapy prior to the Screening Visit and sign the pre-screening informed consent form (ICF). At the Baseline Visit (D1), prior to randomization, the Investigator (or designee) will review the subject's eDiary to determine if the subject meets the eligibility requirements for compliance to continue in the study [redacted] To avoid bias, the investigator and study site staff will remain blinded to the NPRS scores entered in the eDiary by the subject. The eDiary vendor will calculate the NPRS scores and provide the site with a notice of eligibility [redacted]

	[redacted] Eligible subjects will then be randomly assigned (in a 1:1 ratio) on D1 to receive a single dose of an SP-102 TF, or placebo [redacted] under fluoroscopic guidance. This first injection is referred to as the "index injection". An appropriately trained physician, hereafter called the Injection Physician, administering the DB investigational product (IP) and other assisting staff (eg, nurse) will, therefore, not be blinded to the treatment assignment, while the rest of study staff involved in assessments and collection of data will remain blinded. Procedures will be in place at each site to ensure blinding, minimizing personnel involved with injection, and guarantee sequestration of imaging data acquired at the time of injection. Each subject will have the option of receiving 1 supplemental OL TF injection of SP-102 ("repeat injection"). To qualify for the repeat injection, subjects must meet Repeat Injection Inclusion Criteria, NPRS pain score in the affected leg, and investigator judgment, which includes a safety evaluation demonstrating no signs or symptoms of adrenal suppression or other safety concerns. The repeat injection may be administered between Weeks (W) 4 and 20. Eligible subjects will receive OL SP-102 repeat injection regardless of their initial treatment assignment (SP-102 or placebo). In case of inadequate control of radicular pain, up to 3 g of acetaminophen as rescue medication will be allowed per day. The subject should be instructed to avoid use of acetaminophen in the 6 hours prior to recording an NPRS score. Doses of rescue medication and time taken will be collected in the eDiaries until W12 and thereafter as a concomitant medication. The subject will complete the eDiary twice daily approximately 12 hours apart (±2 hours) to record their NPRS scores for pain in the previous 12 hours for 12 weeks following index injection. Thereafter, NPRS scores will be recorded at clinic visits. All subjects will be seen at the clinic on D15, and every 4 weeks (ie, W4 [D29], W8 [D57], W12 [D85], W16 [D113], W20 [D141], and W24 [D169]) after the DB index injection for up to 24 weeks. Subjects receiving the OL repeat SP-102 injection will also be seen at the clinic 14 days after the repeat injection and continue the DB planned visits as well. Subjects will also be contacted by telephone by the site staff 2 days after each IP injection to discuss their progress, any medications they are taking, and if they have had any adverse events (AEs).
Planned Sample Size:	Approximately 400 subjects will be randomized in this study. The sample size goal of this study is for 332 subjects to complete W4.
Key Subject Selection Criteria:	**Inclusion Criteria:** <u>Screening Visit Inclusion Criteria (D-22 to D-8)</u> 1. Able and willing to read, write, and understand the English language and provide English-language written informed consent prior to beginning any study procedures. 2. Age 18 to 70 years (inclusive) at the Screening Visit. 3. A diagnosis of lumbosacral radicular pain at the Screening Visit. [redacted]

[redacted]

10. If sexually active and a female of childbearing potential or a male capable of bearing a child, agrees to use an effective method of birth control during the study. [redacted]

[redacted]

12. Reviewed all study-specific educational materials and has, in the opinion of the Investigator, the cognitive abilities to understand and appropriately complete all study-mandated procedures.

[redacted]

[redacted]

Exclusion Criteria:

1. A body mass index ≥ 40 kg/m^2 (without rounding) at the Screening Visit.
2. Significant pain unrelated to the disc herniation that, in the Investigator's and/or Sponsor's opinion, would significantly compromise assessment of the radicular back and leg pain related to the disc herniation.

[redacted]

10. Chronic use (ie, up to 6 consecutive days) of oral or parenteral steroid medication during the 2 months prior to the Screening Visit.
11. Regular use of high dose opioids (> 30 mg morphine equivalents for more than 2 days per week) in the 30 days prior to the Screening Visit. The subject must agree to discontinue all opioids prior to the Screening Visit.
12. Cannot stop use of neuro stimulator for pain control on or before Screening Visit and for the duration of study participation.
13. Cannot interrupt chronic long-acting anticoagulant therapy before index or repeat injection.
14. History of Insulin-dependent Diabetes Mellitus.

	15. History of diabetic neuropathy or peripheral neuropathy other than radiculopathy in the lower extremities. 16. History of malignancy or evidence of malignancy, lymphoproliferative, or neoplastic disease except for successfully treated basal or squamous cell carcinoma of the skin or cervical intraepithelial neoplasia within 5 years of the Screening Visit. 17. Anxiety or depression based on Hospital Anxiety and Depression Scale scores ≥ 15 at Screening Visit, or has a major psychiatric disorder not controlled with medication that would interfere with clinical pain scores or participation in the trial. 18. Known history of any clinically significant or unstable medical condition including disorders of glucocorticoid regulation (eg, Cushing's or pseudo-Cushing's disease, adrenocortical insufficiency), any other disorder, condition or circumstance (including secondary gain) that in the opinion of the Investigator has the potential to prevent study completion and/or to have a confounding effect on outcome assessments. 19. Alcohol dependence, illicit drug use based on urine screen, drug abuse, or drug addiction within 1 year of the Screening Visit. 20. Clinically significant abnormalities that may interfere with participation in the trial such as: [redacted] 22. Use of any investigational drug and/or device within 30 days prior to the Screening Visit or is scheduled to receive an investigational drug other than blinded study drug during this study. 23. If female, are lactating/breastfeeding, plan to breastfeed, or plan to become pregnant while participating in the study. [redacted]
Study Drug(s):	Investigational Product: SP-102 drug product is comprised of [redacted] The drug product is a sterile [redacted] which is intended to be delivered via a TF injection, using 6-inch long microbore/small bore extension tubing. Placebo control: [redacted].

	All IP will be packaged in [redacted]
Duration of Treatment:	One or 2 doses of IP separated by 4 to 20 weeks. Subjects will be followed for 24 weeks after the index injection.

Main Parameters of Efficacy:	Efficacy assessments include:
	• NPRS recorded in the eDiary twice daily approximately 12 hours apart ±2 hours:
	  ○ The NPRS worst pain score in the affected leg
	  ○ The NPRS average pain score in the affected leg
	• NPRS recorded at each study visit:
	  ○ The NPRS current pain score in the affected leg
	  ○ The NPRS average pain score in the lower back
	• ODI
	• Pain*DETECT*
	• BPI-SF
	• PGIC
	• CGIC
	• Use of rescue medication (acetaminophen) as captured in the eDiary

Main Parameters of Safety:	• Physical examination • General Neurological Exam • Targeted Neurological Exam • Vital signs (blood pressure and heart rate) • Electrocardiogram • Laboratory parameters (serum chemistry, hematology, and urinalysis) • AEs
Efficacy Endpoints:	The primary efficacy endpoint is: • The mean change from Baseline (D1) to W4 in the mean NPRS average pain score in the affected leg The key secondary efficacy endpoint is: • The change in ODI total score from Baseline (D1) to W4. Other secondary endpoints are: • The time to repeat injection of SP-102 from index injection. • Proportion of subjects receiving repeat injection. • The mean change from Baseline (D1) to W2, W8, and W12, in the mean NPRS average pain score in the affected leg. • The mean change from Baseline (D1) to W2, W4, W8, and W12, in the mean NPRS worst pain in the affected leg. • The mean change from Baseline (D1) to W2, W4, W8, and W12 in the mean NPRS current pain score in the affected leg. • The mean change from Baseline (D1) in the ODI total score to W12. • The mean change in Pain*DETECT* from Baseline (D1) to W4 and W12. • The mean change in BPI-SF score from Baseline (D1) to W4 and W12.

	• Proportion of subjects achieving a response of 30%, 50%, and 75% reductions from Baseline (D1) in mean NPRS average pain score in the affected leg at W2 and W4. • The mean change from Baseline (D1) to W2, W4, W8, and W12 in the mean NPRS average pain score in the lower back. • PGIC at W2, W4, W8, and W12. • CGIC at W2, W4, W8, and W12. • Cumulative use of rescue medication (mg of acetaminophen) through W4 and W12. • Time to first rescue medication dose. • Proportion of subjects requiring rescue medications.
Safety Endpoints:	• AEs, compared between 4 groups receiving 1 SP-102 injection, 2 SP-102 injections, placebo followed by SP-102 repeat injection, or placebo only. • Change from Baseline (D1) in laboratory parameters. • Change from Baseline (D1) in vital signs. • Change from Baseline (D1) in neurological examination.
Statistical Analyses:	[redacted]

	[redacted] Safety summaries will be provided for proportion of subjects experiencing AEs, clinical laboratory evaluations, vital sign measurements, and neurological examinations. No interim analysis is planned for this study. Note that the study will be unblinded and the primary analysis will be completed after all subjects complete the 12-week assessments and data are cleaned. Subjects in the OL safety extension portion of the study will continue through W24. No efficacy data in the first 12 weeks of the study will change after the primary analysis is completed.

TABLE OF CONTENTS

[redacted]

TABLES

FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
α	alpha
µg	microgram
µmol	micromole
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BMI	body mass index
BPI-SF	Brief Pain Inventory-Short Form
bpm	beats per minute
C	Celsius
CDISC	Clinical Data Interchange Standards Consortium
CD/UT	cognitive debrief and usability testing
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CGIC	Clinical Global Impression of Change
CGIS	Clinical Global Impression-Severity
C_{max}	maximum concentration
CRA	clinical research associate
CRO	contract research organization
CSF	cerebrospinal fluid
CV	coefficient of variation
D	day
DAL	Daily Acetaminophen Log
DB	double-blind
DDE	direct data entry
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
EOS	end of study
ESI	epidural steroid injection
ET	early termination

Abbreviation	Definition
F	Fahrenheit
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HbA1c	Hemoglobin A1c
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
[redacted]	[redacted]
IND	Investigational New Drug
INR	International Normalization Ratio
IP	investigational product
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web recognition system
LFT	liver function tests
MEDD	Mean Equivalent Daily Dose
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat (dataset)
mg	milligram
min	minutes
mIU	milli international unit
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NPRS	Numeric Pain Rating Scale

Abbreviation	Definition
NSAID	nonsteroidal anti-inflammatory drug(s)
ODI	Oswestry Disability Index
OL	open-label
PCS	Pain Catastrophizing Scale
PGIC	Patient Global Impression of Change
po	given by mouth
PP	per-protocol (dataset)
PT	prothrombin time
PTT	partial prothrombin time
REML	restricted maximum likelihood
RLD	Reference Listed Drug
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SOP	standard operating procedure
TEAE	treatment emergent adverse event
TF	transforaminal(ly)
T_{max}	time to maximum concentration
US	United States
V	visit
W	week
WBC	white blood cells
[redacted]	[redacted]

ADMINISTRATIVE STRUCTURE

The Study Team Contact list is provided in a separate document.

1 INTRODUCTION

1.1 Background

1.1.1 Lumbosacral Radicular Pain

Back pain is a widespread, debilitating disorder that results in an enormous socioeconomic burden. The lifetime prevalence of low back pain ranges from 60% to 90%, and the annual incidence is ~5% (Frymoyer-1988, Frymoyer-1992). The annual cost to treat back pain has been estimated to exceed $100 billion, of which it is estimated that up to $50 billion is due to lost productivity (Cleeland-1989).

A specific type of back pain in the distribution of lumbosacral nerves is known as lumbosacral radicular pain, which is frequently referred to as sciatica. It is a common condition with a lifetime incidence varying from 13% to 40% (Stafford-2007). The corresponding annual incidence of an episode of lumbosacral radicular pain ranges from 1% to 5% (Frymoyer-1988, Frymoyer-1992). It is rarely diagnosed before the age of 20, peaks in incidence in the fifth decade of life and declines thereafter (Frymoyer-1992).

Lumbosacral radicular pain is believed to result most commonly from prolapsed disc material causing pain secondary to mechanical impingement and/or inflammation of the anterior primary rami of lumbar nerve roots. Histological changes have been first described in 1951 (Lindahl-1951). Approximately 90% of cases of lumbosacral radicular pain are caused by a herniated disc with nerve root compression, with various other etiologies accounting for the remaining 10% of the cases (Stafford-2007, Valat-2010).

There are several conservative treatments for lumbosacral radicular pain, each with varying levels of effectiveness. These therapeutic approaches include bed rest, staying active (in contrast to bed rest), analgesic or non-steroidal anti-inflammatory drugs (NSAIDs), acupuncture, spinal manipulations, traction therapy, physical therapy, behavioral treatment, and epidural steroid injections (ESIs) (Frymoyer-1992, Koes-2007, Valat-2010). The initial phase of sciatica frequently responds to conservative management with no intervention. For example, in a study of more than 208 subjects with obvious symptoms and signs of a lumbosacral radicular pain (5^{th} lumbar vertebra and 1^{st} sacral vertebra), treated with nonsteroidal anti-inflammatory drug piroxicam or placebo, 70% in active group reported a marked reduction in back and leg pain and improved functionality within 4 weeks and 60% had returned to work at that point in time. However, approximately 30% of subjects in both groups still complained of back pain and 19.5% were out of work after 1 year (Weber-1993). When these more conservative treatments for lumbosacral radicular pain are ineffective, ESIs or surgical interventions are commonly used.

[redacted]

[redacted]

1.1.3 SP-102

[redacted]

1.2 Preclinical Studies

[redacted]

[redacted]

Another study (UPD003-IS21) was conducted to evaluate organs, particularly the brain,

[redacted]

1.3 Clinical Studies

[redacted]

[redacted]

1.5 Study Rationale

The proposed clinical use of SP-102 is in the treatment of lumbosacral radicular pain. SP-102 is designed to produce an immediate effect from [redacted] SP-102 contains [redacted] which is expected to result in better safety profile, [redacted] as demonstrated in animal toxicology studies [redacted]

1.6 Dose Rationale

[redacted]

1.7 Study Endpoint Rationale

1.8 Risks and Benefits for Subjects

Pain relief is expected following TF administration of SP-102 based on [redacted]. In April 2014, the FDA issued a requirement that all injectable glucocorticoid product labels carry a warning stating that "serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids" and that the "safety and effectiveness of epidural administration of corticosteroids have not been established and corticosteroids are not approved for this use" (FDA-2014). As part of the FDA's ongoing effort to investigate the issue, an Advisory Committee was convened in November 2014 to discuss the benefits and risks of epidural corticosteroid injections and determine if further FDA actions are needed beyond the warnings already incorporated into the labels of steroids for injection. The committee reviewed the data from between 1997 and 2014 where the Department

of Pharmacovigilance II (DPV) identified 131 FAERS cases of neurological AEs, including 41 cases of arachnoiditis and other serious neurological AEs (FDA-2014). Given the large number of ESIs, an estimated 9 million are performed annually in the US, these events are rare (Benzon-2015). Even though serious neurological AEs were reported with both types of preparation, the case series for FAERS review contained many more reports for particulate steroids (n=116) compared with nonparticulate steroids (n=4), with 11 cases not reporting a formulation. All catastrophic events (those resulting in permanent disability or death) reported to FAERS were associated with injection of a suspension, whereas only a few cases involving temporary symptoms were reported with glucocorticoid solutions (including dexamethasone) (Racoosin-2015).

As SP-102 has been formulated as [redacted], safety issues are not anticipated.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to:

- Evaluate the analgesic effect on average leg pain (as measured by the NPRS in the affected leg) (Appendix E) following a single TF injection of SP-102 compared to an [redacted] of placebo over 4 weeks.

2.2 Secondary Objectives

The secondary objectives of the study are to:

- Evaluate degree of disability over time as measured by the Oswestry Disability Index (ODI) (Appendix F).
- Characterize the change of the subject's radiculopathy symptoms and overall condition using Pain*DETECT* (Appendix G), Brief Pain Inventory – Short Form (BPI-SF) (Appendix H), Clinical Global Impression of Change (CGIC) (Appendix I), and Patient Global Impression of Change (PGIC) (Appendix J).
- Evaluate the safety of a single and repeat SP-102 TF injection.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a double -blind (DB), randomized, placebo-controlled, multicenter study in subjects with lumbosacral radicular pain evaluating the safety and efficacy of a single SP-102 TF injection compared to a single placebo IM injection, followed by an open-label (OL) safety extension, evaluating an optional repeat SP-102 TF injection, if indicated, administered 4 to 20 weeks later. Subjects will be followed for 24 weeks following the initial treatment ("index injection".).

After providing informed consent, each subject will complete a Screening Visit between Day (D) -22 and D-8. Subjects who meet the screening eligibility criteria will record their current, worst, and average pain in their lower back, affected, and non-affected leg using the NPRS scale on a handheld electronic clinical outcome assessment (eCOA) device (ie, "eDiary") twice a day (12 ±2 hours apart) from Screening until Baseline (D1). The 7 days immediately prior to Baseline (D1) will be used to determine eligibility. The average and worst NPRS pain scores will reflect the subject's pain over the last 12 hours. During the screening period, subject's medical eligibility will be also reviewed and confirmed by the study Medical Monitor. Subjects can progress to Baseline (D1) only after medical eligibility approval is provided.

Subjects who have been using opioids other than high dose opioids within 30 days prior to Screening (see Exclusion #11), may participate in the trial if they agree to discontinue the opioid therapy prior to the Screening Visit and sign the pre-screening informed consent form (ICF).

At the Baseline Visit (D1), prior to randomization, the Investigator (or designee) will review the subject's eDiary to determine if the subject meets the eligibility requirements for compliance to continue in the study (ie, the subject must have completed [redacted] To avoid bias, the investigator and study site staff will remain blinded to the NPRS scores entered in the eDiary by the subject. The eDiary vendor will calculate the NPRS scores and provide the site with a notice of eligibilit [redacted] Eligible subjects will then be randomly assigned (in a 1:1 ratio) on D1 to receive a single dose of an SP-102 TF, or placebo [redacted] in the vicinity of the epidural space or [redacted] under fluoroscopic guidance (for instructions on study drug injection see Appendix D). This first injection is referred to as the "index injection". An appropriately trained physician, hereafter called the Injection Physician, administering the DB investigational product (IP) and other assisting staff (eg, nurse) will, therefore, not be blinded to the treatment assignment, while the rest of study staff involved in assessments and collection of data will remain blinded. Procedures will be in place at each site to ensure blinding, minimizing personnel involved with injection, and guarantee sequestration of imaging data acquired at the time of injection.

Fluoroscopic imaging guidance is required by this protocol to ensure proper placement of the injection needle (see instructions in Appendix D). Long-term persistent AEs are rarely seen with fluoroscopically-guided lumbosacral TF injections, however immediate and delayed AEs may include vasovagal episodes, procedure interruption from intravascular flow, pain exacerbation, injection site soreness, headache, and insomnia (Plastaras-2015). Avoidance of risk of procedural AEs in the placebo group by implementing an [redacted]

[redacted] is consistent with ethical considerations and use of [redacted] in interventional/surgical clinical trials (Wartolowska-2014). In addition to safety considerations and lowering the risk of procedural complication in the control group, the choice of an [redacted]

The choice of the TF injection approach with direct deposition of drug near the ventral epidural space at the affected level is selected based on published reviews documenting better effectiveness as compared to other approaches. For lumbar disc herniation with unilateral symptoms, the evidence for analgesic effect and ability to prevent surgery is greater for TF epidural injections as compared to caudal or interlaminar approaches (Manchikanti-2012; Cohen-2013).

Each subject will have the option of receiving 1 supplemental OL TF injection of SP-102 ("repeat injection"). To qualify for the repeat injection, subjects must meet Repeat Injection Inclusion Criteria, NPRS pain score in the affected leg, and investigator judgment, which includes a safety evaluation demonstrating no signs or symptoms of adrenal suppression or other safety concerns. The repeat injection may be administered between Weeks (W) 4 and 20. Eligible subjects will receive OL SP-102 repeat injection regardless of their initial treatment assignment (SP-102 or placebo).

In case of inadequate control of radicular pain, up to [redacted] will be allowed per day. The subject should be instructed to avoid use of acetaminophen within 6 hours prior to recording an NPRS score. Doses of rescue medication and time taken will be collected in the eDiaries until W12 and thereafter as a concomitant medication.

The subject will complete the eDiary twice daily approximately 12 hours apart (±2 hours) to record their NPRS scores for pain in the previous 12 hours for 12 weeks following index injection. Thereafter, NPRS scores will be recorded at clinic visits.

All subjects will be seen at the clinic on D15, and every 4 weeks (ie, W4 [D29], W8 [D57], W12 [D85], W16 [D113], W20 [D141], and W24 [D169]) after the DB index injection for up to 24 weeks. Subjects receiving the OL repeat SP-102 injection will also be seen at the clinic 14 days after the repeat injection and continue the DB planned visits as well. The subject will also be contacted by telephone by the site staff 2 days after each IP injection to discuss their progress, any medications they are taking, and if they have had any adverse events (AEs).

The study visits and the planned efficacy analysis after all enrolled subjects have completed W12 are depicted in Figure 3.1.

Figure 3.1: Study Schematic

3.2 Study Duration

Subjects will undergo screening for up to 3 weeks before the index injection and will be followed for 24 weeks after the index injection; therefore overall duration of a subject's participation in the study is approximately 26 weeks.

3.3 Selection of Study Population

Specific entry criteria are detailed in Section 3.3.1 and Section 3.3.2.

3.3.1 Inclusion Criteria

Subjects meeting all the following inclusion criteria should be considered for admission to the study.

3.3.1.1 Screening Visit Inclusion Criteria (D-22 to D-8)

1. Able and willing to read, write, and understand the English language and provide English-language written informed consent prior to beginning any study procedures.
2. Age 18 to 70 years (inclusive) at the Screening Visit.
3. A diagnosis of lumbosacral radicular pain at the Screening Visit.

[redacted]

10. If sexually active and a female of childbearing potential or a male capable of bearing a child, agrees to use an effective method of birth control during the study. [redacted]

[redacted]

12. Reviewed all study-specific educational materials and has, in the opinion of the Investigator, the cognitive abilities to understand and appropriately complete all study-mandated procedures.

3.3.1.2 Randomization Inclusion Criteria (D1)

[redacted]

[redacted]

3.3.1.3 Repeat Injection Inclusion Criteria (4 to 20 weeks following index injection)

[redacted]

3.3.2 Exclusion Criteria

1. A body mass index (BMI) $\geq$ 40 kg/m^2 (without rounding) at the Screening Visit.
2. Significant pain unrelated to the disc herniation that, in the Investigator's and/or Sponsor's opinion, would significantly compromise assessment of the radicular back and leg pain related to the disc herniation.

[redacted]

10. Chronic use (ie, up to 6 consecutive days) of oral or parenteral steroid medication during the 2 months prior to the Screening Visit.
11. Regular use of high dose opioids (> 30 mg morphine equivalents for more than 2 days per week; see Appendix B) in the 30 days prior to the Screening Visit. The subject must agree to discontinue all opioids prior to the Screening Visit.
12. Cannot stop use of neuro stimulator for pain control on or before Screening Visit and for the duration of study participation.
13. Cannot interrupt chronic long-acting anticoagulant therapy before index or repeat injection.
14. History of Insulin-dependent Diabetes Mellitus.
15. History of diabetic neuropathy or peripheral neuropathy other than radiculopathy in the lower extremities.
16. History of malignancy or evidence of malignancy, lymphoproliferative, or neoplastic disease except for successfully treated basal or squamous cell carcinoma of the skin or cervical intraepithelial neoplasia within 5 years of the Screening Visit.
17. Anxiety or depression based on Hospital Anxiety and Depression Scale (HADS, Appendix L) scores ≥ 15 at Screening Visit, or has a major psychiatric disorder not controlled with medication that would interfere with clinical pain scores or participation in the trial.
18. Known history of any clinically significant or unstable medical condition including disorders of glucocorticoid regulation (eg, Cushing's or pseudo-Cushing's disease, adrenocortical insufficiency), any other disorder, condition or circumstance (including secondary gain) that in the opinion of the Investigator has the potential to prevent study completion and/or to have a confounding effect on outcome assessments.
19. Alcohol dependence, illicit drug use based on urine screen, drug abuse, or drug addiction within 1 year of the Screening Visit.
20. Any Clinically significant abnormalities that may interfere with participation in the trial such as:

21. Known allergy or idiosyncratic (atopic) reaction to contrast agent, lidocaine,

22. Use of any investigational drug and/or device within 30 days prior to the Screening Visit, or is scheduled to receive an investigational drug other than blinded study drug during this study.
23. If female, are lactating/breastfeeding, plan to breastfeed, or plan to become pregnant while participating in the study.

24. Involvement in an ongoing worker's compensation claim, disability claim, or litigation related to any pain problem, receiving payments for a settled claim, awaiting pending payment for a settled claim, or any secondary gain in the opinion of the investigator.

3.3.3 Stopping Rules

A single occurrence of an adverse event of special interest (AESI) precludes the subject receiving a repeat injection. Three occurrences of the AESI of the same type across the study will trigger stopping of all further dosing until implementation of a safety review.

3.3.4 Removal of Subjects from Therapy or Assessment

A subject will be considered to have completed the study when he or she completes the W24 (D169) visit. If a subject is discontinued at any time after randomization into the study, the investigator will make every effort to follow the subject and complete the End of Study (EOS)/Early Termination (ET) assessments as shown in Section 3.5.1. Sufficient subjects will be enrolled such that 332 subjects complete the study through W4.

A termination electronic case report form (eCRF) page should be completed for every subject who receives IP, whether the subject completes the study or not. The reason for any early discontinuation should be indicated on this form. The primary reason for a subject discontinuing early should be selected from the following standard categories of ET:

- *Adverse Event*: Clinical or laboratory events occurred that, in the medical judgment of the investigator for the best interest of the subject, are grounds for discontinuation. This includes serious, nonserious AEs and AESI regardless of relation to the IP.
- *Death:* The subject died.
- *Withdrawal of Consent*: The subject desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for withdrawing, it should be recorded in the eCRF.
- *Protocol Violation*: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (eg, drug noncompliance, failure to return for defined number of visits). The violation necessitated early discontinued from the study.
- *Lost to Follow-Up*: The subject stopped coming for visits and study personnel were unable to contact the subject.
- *Other*: The subject was discontinued for a reason other than those listed above, such as theft, loss of IP, or termination of study by sponsor.

3.4 Treatments

3.4.1 Details of Study Treatments

Information about the IPs is provided in Table 3.1.

Table 3.1: Details of Investigational Products

	SP-102	Placebo
Ingredient	[redacted]	
Manufacturer		
Dose(s)		
Route		
Formulation		
Strength(s)		

SP-102 drug product is comprised of [redacted]

The drug product is a sterile [redacted] which is intended to be delivered via a TF injection, using 6-inch long extension tubing. The placebo, [redacted]. While the drug is sterile manufactured and is sterile for injection, the outside of the syringes is not sterile; thus, attachment of the syringe and IP injection should be the last step prior to removal of needle and finishing the procedure.

Under Good Manufacturing Practices, SP-102 was manufactured by [redacted]. All IP will be kept in a locked area with limited access. [redacted] Deviations of storage temperature outside this range should be documented and Semnur or designee should be promptly notified. IP kits should not be frozen. If any component of the IP kit is damaged, Semnur or designee must be notified as soon as possible.

3.4.2 Dosage Schedule

Index Injection: The subject will receive a single DB TF injection of SP-102 [redacted] based on the randomization schedule. The DB IP will be administered by the Injection Physician. The Injection Physician and any assisting study personnel (eg, nurse) will not be blinded to the IP being administered, while the rest of the study staff involved in assessments and collection of data, will remain blinded to treatment assignment. In case of questions or safety issues related to the index injection, the unblinded Injection Physician or study staff may contact the unblinded [redacted] Medical Monitor.

Repeat Injection: If a subject receives the repeat SP-102 injection, this injection will be administered TF and will not be blinded. The repeat injection may be administered by the

Injection Physician or by the Investigator. Specific instructions for IP administration are found in Appendix D.

3.4.3 Treatment Assignment

Using an Interactive Web Response System (IWRS), on D1, the site staff or research pharmacist will contact the IWRS after the Investigator has confirmed that the subject fulfills all the inclusion/exclusion criteria. The IWRS will assign a randomization number to the subject, which will be used to link the subject to a treatment arm. The research pharmacist will prepare the appropriate IP and deliver it to study staff in preparation for injection.

A randomization schedule will be employed to facilitate effective randomization and allocation concealment. The schedule will involve a block randomization technique, randomly assigning participants within blocks based on a 1:1 allocation ratio. The randomization schedule will be stratified by study site.

3.4.4 Drug Packaging and Blinding

The DB IP will be provided to the pharmacy in a blinded fashion. From the pharmacy, following randomization assignment and prior to the injection procedure, a single drug package will be dispensed to site staff. [redacted]. Only the Injection Physician and other designated unblinded staff will be unblinded to the contents of the [redacted] All other site staff must entirely avoid visibility to the contents of the [redacted] when it is opened by the Injection Physician, during the injection, and following the injection to ensure they remain blinded to each subject's drug assignment. Following injection, the Injection Physician will return the used active or placebo syringe to the [redacted] thus, ensuring the contents of the used drug package are blinded from any staff handling and accounting for the dispensed IP.

The repeat SP-102 will be provided to the pharmacy in an unblinded fashion. [redacted]

Following injection, the Investigator will return the used active syringe [redacted] No protection of the blind is required for study staff as the repeat SP-102 injection is OL.

All IP will be labeled in accordance with US regulations.

Figure 3.2: Picture of Investigational Product

3.4.5 Drug Inventory and Accountability

The investigator must keep an accurate accounting of the number of IP units delivered to the site, dispensed to subjects, and returned to the sponsor or other disposition during and at the completion of the study. The IP must be dispensed to subjects only by an appropriately qualified person. The IP is to be used in accordance with the protocol by subjects who are under the direct supervision of the investigator. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all IPs received at the site before final disposition. At the end of the study, or as directed, all study drugs, including unused, partially used, and empty containers, will be destroyed or returned to the sponsor or its designee.

3.4.6 Treatment Compliance

Administration of IP will be performed by study personnel to ensure compliance.

3.4.7 Rescue Medication

3.4.8 Prior and Concomitant Illnesses and Medications

3.4.8.1 Prior and Concomitant Illnesses

Investigators should document in the eCRF all significant illnesses that the subject has experienced within 3 months of the Screening Visit in the eCRF Medical History. Additional illnesses present at the time informed consent is given are to be regarded as concomitant

illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF.

3.4.8.2 Prior and Concomitant Medications

All prescription and non-prescription medications (eg, over-the-counter drugs and herbal supplements) that subjects report taking during the 30 days prior to the Screening Visit will be assessed and recorded in the eCRF Concomitant Medication. For each medication, documentation should list the trade or generic name, the total daily dose including units (or the dose, units and scheduled and actual frequency of administration if the medication is not taken daily), the route of administration, and the reason for use.

Concomitant medication refers to all drugs and therapies used from the time of informed consent through the EOS participation. For D1 to Week 12, rescue medication (acetaminophen) use will be recorded only in the eDiary by the subject. After W12, when the eDiary is returned to the clinic, subjects will report acetaminophen use to study staff, and reported use will be documented in the Concomitant Medication eCRF.

[redacted]

Changes, additions, or discontinuations to medications will be assessed and recorded in the eCRF during each study visit and at the EOS/ET Visit (D169). All as needed (*pro re nata, PRN*) prescriptions should be converted to reflect actual number of pills and dose taken per day.

To be eligible for this study, each subject agrees that any oral, non-opioid analgesic medication regimen for or indications other than radiculopathy pain (eg, neuropathic pain, cardiac prophylaxis) will not be altered from the Screening Visit throughW12. The Investigator must inform the Medical Monitor (in advance, if possible) if a subject requires analgesic medications contrary to the protocol during the study.

3.4.8.3 Prohibited Medications and Substances

[redacted]

[redacted]

This decision must be noted in medical records.

3.4.9 Allowed Medications and Treatments

[redacted]

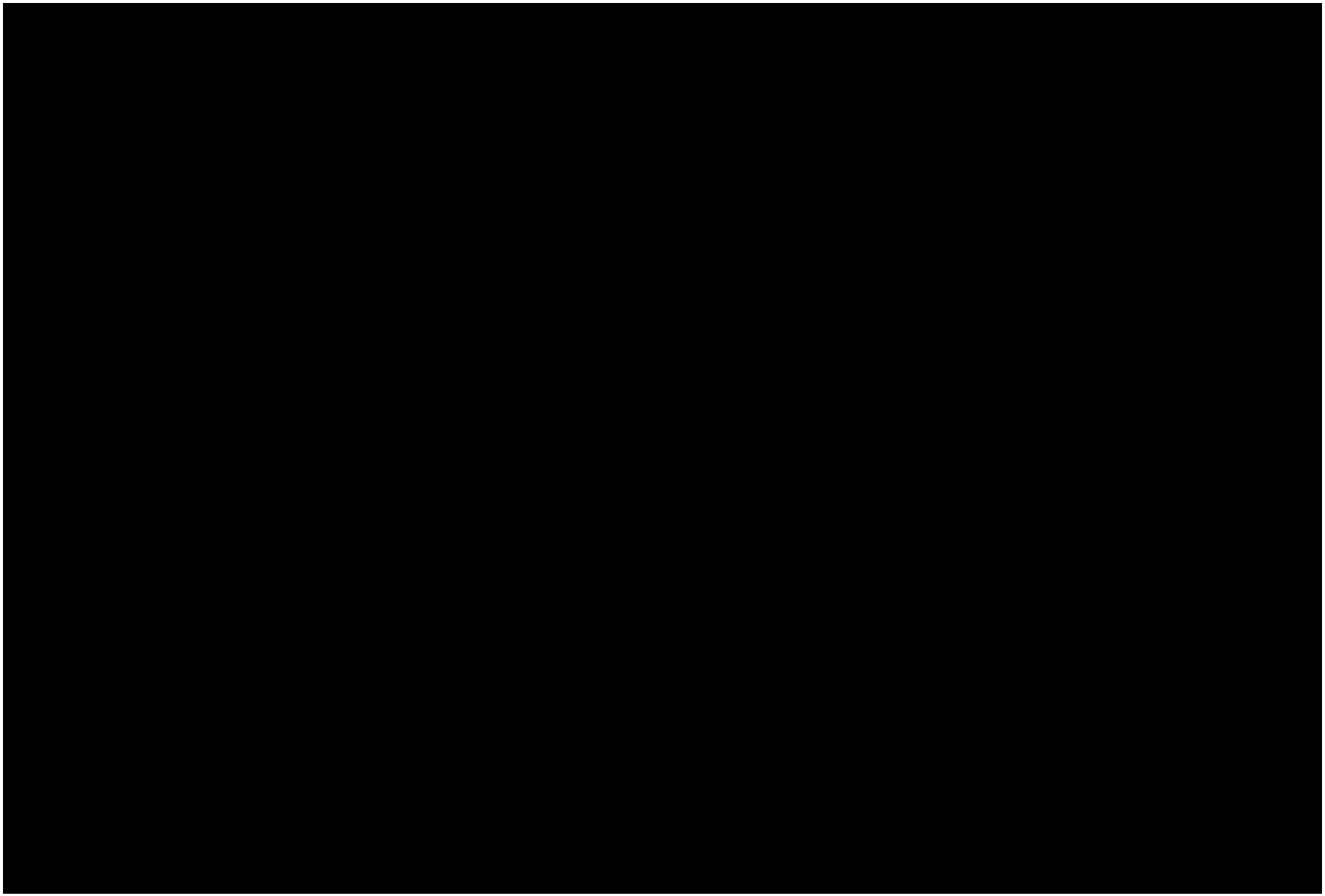
[redacted]

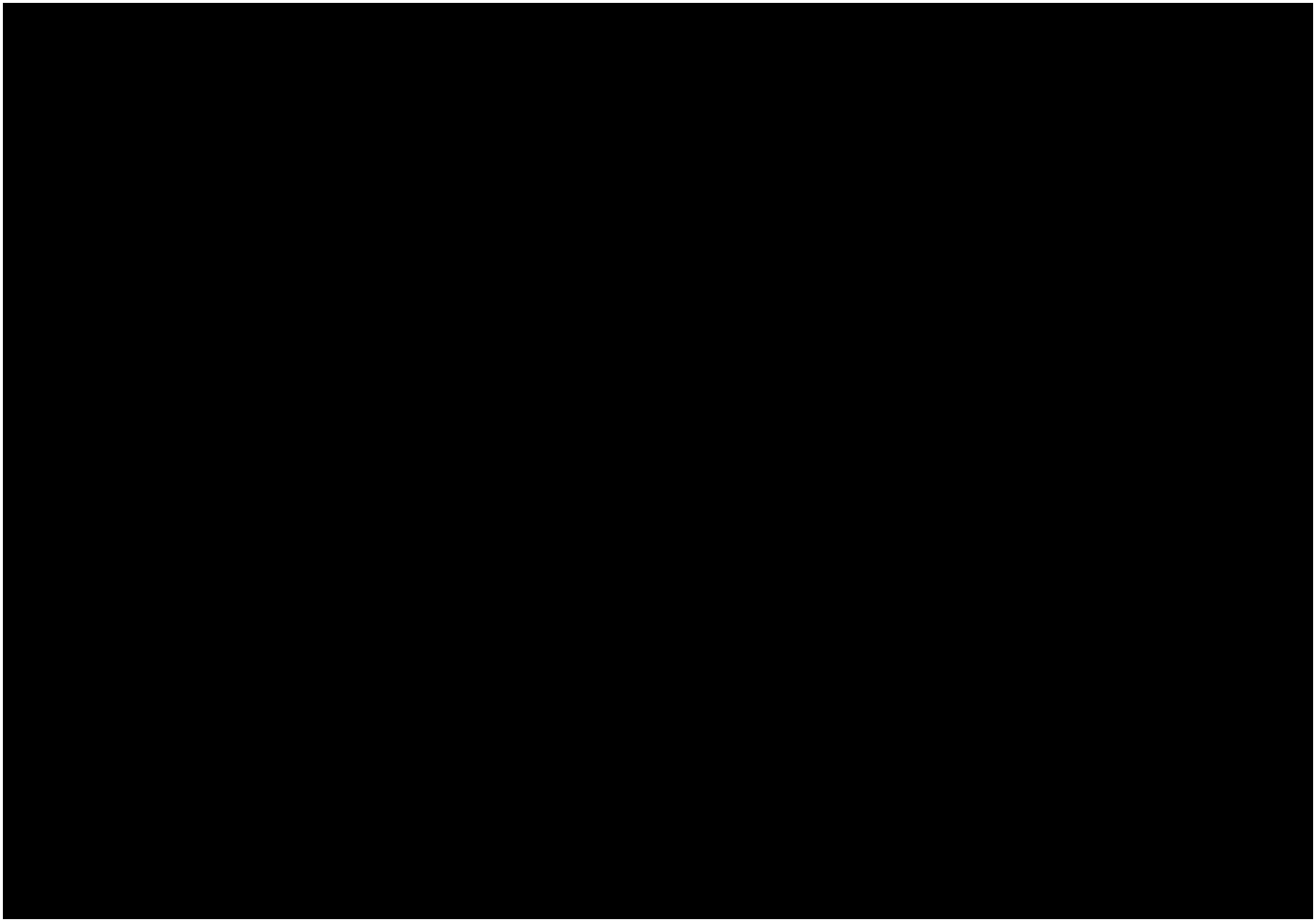
3.5 Assessments

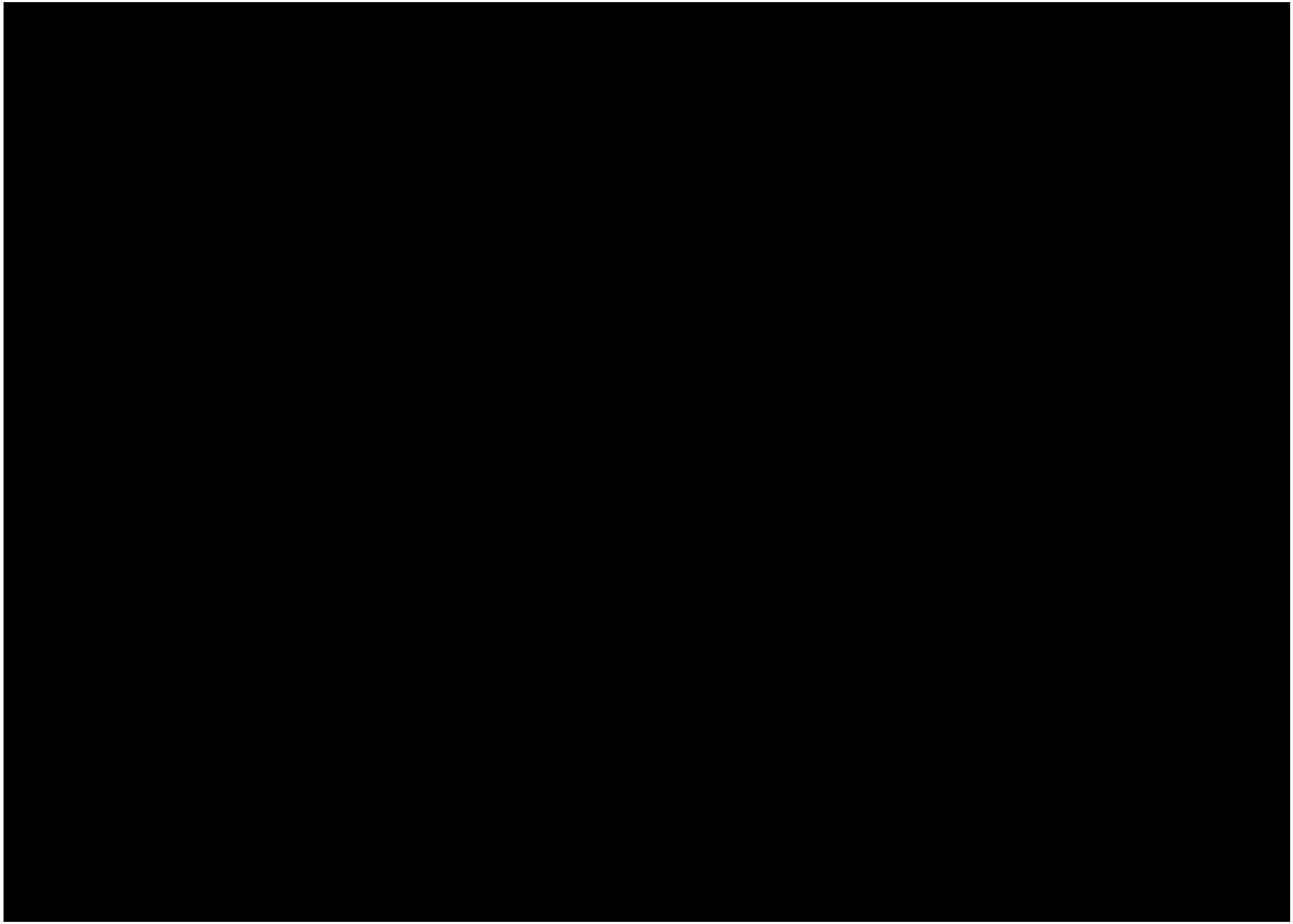
Unless otherwise indicated, all assessments will be performed by the investigator or designated study personnel and captured into eCRFs.

3.5.1 Schedule of Assessments

The procedures to be performed throughout the study are outlined in the Schedule of Assessments (Table 3.2). A detailed description of each assessment may be found in Section 3.5.2.







3.5.2 Study Procedures

3.5.2.1 Prescreening

[redacted]

3.5.2.2 Screening Visit – (Day -22 to Day -8)

[redacted]

[redacted]

3.5.2.3 Baseline Visit – (Day 1): Randomization and Index Injection

[redacted]

[redacted]

3.5.2.4 Telephone Call (D3)

[redacted]

3.5.2.5 Clinic Visit (Week 2, Day 15)

[redacted]

[redacted]

3.5.2.6 Clinic Visit (Week 4, Day 29)

On D29 ± 3 days, the subject should return to the site for a follow-up visit. This is the last visit

[redacted]

[redacted]

3.5.2.7 Clinic Visit (Week 8, Day 57)

[redacted]

[redacted]

3.5.2.8 Clinic Visit (Week 12, Day 85)

[redacted]

[redacted]

3.5.2.9 Clinic Visit (Week 16, Day 113)

On D113 ± 3 days, the subject should return to the site for a follow-up visit. The following [redacted]

3.5.2.10 Clinic Visit (Week 20, Day 141)

[redacted]

[redacted]

3.5.2.11 Clinic Visit (Week 24, Day 169) – End of Study or Early Termination

On D169 ± 3 days, the subject should return to the site for a follow-up visit. The following [redacted]

3.5.3 Repeat SP-102 Administration

[redacted]

3.5.3.1 Day of Repeat SP-102 Administration

[redacted]

[redacted]

3.5.3.2 Telephone Call 2 Days after Repeat SP-102 Injection

The subject should be contacted 2 days ±1 day after the repeat SP-102 injection. The following [redacted]

3.5.3.3 Clinic Visit 14 Days after Repeat SP-102 Injection

[redacted]

3.5.4 Unscheduled Visit

[redacted]

3.5.5 Assessments for Early Termination

If the subject's participation in the study is terminated prematurely for any reason, the reason for such ET should be documented and the W24 (D169) procedures should be performed. If the ET occurs prior to W4 (D29), the subject should be encouraged to continue in the study until W4 (D29), if possible. In case of ET, the subject should be encouraged to return to the site for ET procedures, or failing a return visit, a telephonic visit should be arranged to encourage the subject to complete the W24 (D169) procedures (Section 3.5.2.11).

An EOS eCRF page should be completed for every subject who receives IP, whether the subject completes the study or not. The reason for any ET should be indicated on this form. The primary reason for the ET should be selected as noted in Section 3.3.3.

3.5.6 Efficacy Assessments

Medical advisors, psychometricians, and clinical research associates (CRAs) may request to review subject evaluations occurring as part of this protocol. A site and subject rater training program and a surveillance mechanism for protocol outcome measures will be implemented and described in separate operational plans. Site raters will receive didactic scale trainings and placebo response training either by webinar or through a designated study web portal. A subject training video, specific to the subject reported outcome measures in this protocol and placebo response training, will be provided to all study subjects for review and completion. The data surveillance program to be implemented will be specific to identified data flags, to be reviewed on a regular basis for identification of potential scoring anomalies and variability. The data surveillance program to be implemented will be specific to identified data flags, to be reviewed on a regular basis by a reviewer (blinded to treatment arm) for identification of potential scoring anomalies and variability. If clinically significant anomalies are detected on subject-rated scales, sites may be requested to show the video to the subject again for re-training.

[redacted]

3.5.6.1 Numeric Pain Rating Scale

The NPRS (Appendix E) is an 11-point scale (0 to 10-point scale where 0 is no pain and 10 is worst pain imaginable) that allows the subject to rate the severity of their pain intensity at various points in time (Turk-2003). Twice daily in the morning and evening (approximately 12 hours apart), the subject will use the NPRS to record their average and worst pain in the past 12 hours. [redacted] After the Screening Visit, the NPRS will be collected twice daily using the eDiary through W12; thereafter, the NPRS will be collected at clinic visits only. The eDiary

subject assignment should remain the same throughout the trial, and eDiaries should only be re-assigned for completed/withdrawn subjects. The current pain intensity "pain now" will be measured at every clinic visit and used for assessment of accuracy of pain reporting and monitoring of outlier values. Morning and afternoon pain measurements will be investigated for predictability of response.

3.5.6.2 Oswestry Disability Index

The ODI (Appendix F) is a validated questionnaire that was first published in 1980 but it was updated in 2000 (Fairbank-1980, Fairbank-2000). The ODI is currently the gold standard for measuring degree of disability and estimating quality of life in a person with low back pain. The ODI is questionnaire completed by the subject which contains 10 topics concerning intensity of pain, lifting, ability to care for oneself, ability to walk, ability to sit, sexual function, ability to stand, social life, sleep quality, and ability to travel. Each topic category is followed by 6 statements describing different potential scenarios in the subject's life relating to the topic. The subject then checks the statement which most closely resembles their situation. Each question is scored on a scale of 0-5 with the first statement being zero and indicating the least amount of disability and the last statement is scored 5 indicating most severe disability. The scores for all questions answered are summed, then multiplied by 2 to obtain the index (range 0 to 100). Zero is equated with no disability and 100 is the maximum disability possible. The ODI will be obtained at Screening, Baseline, W4, W12, and W24.

3.5.6.3 PainDETECT

Pain*DETECT* (Appendix G) is a 7-question validated tool to determine the prevalence of neuropathic pain in individuals with lower back pain. The 7 responses are summed for a possible score ranging from 0-35. In addition to the 7 questions, subjects note the course of pain (Persistent pain with slight fluctuations; Persistent pain with pain attacks, Pain attacks without pain between them; Pain attacks with pain between them) for a total, overall scale score of 0-38. Since its development, 4 additional questions have been added but do not contribute to scoring. They ask the patient to rate their pain now and over the last for weeks, and to mark on a body chart if their pain is radiating to other parts of the body. Pain*DETECT* will be collected at Screening, Baseline, W4, W12, and W24.

3.5.6.1 Brief Pain Inventory - Short Form

The BPI-SF (Appendix H) is a 15-item self-rating scale assessing use of medications, as well as sensory, and reactive components of pain. The BPI-SF includes items that will address components of sensory pain, including severity, location, chronicity, and degree of relief due to therapy. The BPI-SF also has items that address reactive pain components, including depression, suffering, and perceived availability of relief. Respectable reliability has been demonstrated over short intervals using test-retest correlation; worst pain, r=0.93; usual pain, r=0.78; pain now, r=0.59. The BPI-SF will be collected at Screening, Baseline (D1), W4, W12, and W24.

3.5.6.2 Clinical and Patient Global Impression Scales

The CGIS (Appendix I) is rated on an 8-point scale, with responses ranging of responses from 0 (not assessed) and 1 (normal) through 7 (amongst the most severely ill subjects) (to be completed prior to IP administration at the Baseline (D1) Visit). The CGIC (Appendix I) scores

range from 0 (not assessed) and 1 (very much improved) through 7 (very much worse) as determined by the trained site rater. The PGIC scores range from 1 (very much improved) through 7 (very much worse) as assessed by the subject. The CGIC and PGIC are obtained at each clinic visit following Baseline (D1).

3.5.7 Safety Assessments

3.5.7.1 Physical Examination:

A complete physical examination, including examination of general appearance, skin, neck, eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and musculoskeletal system, will be performed at Screening. Specific musculoskeletal examination focusing on lumbar spine and lower extremities to exclude musculoskeletal sources of the predominant pain, such as SI joints and trigger points, will be performed in standardized manner and recorded. Height (in inches without shoes) and weight (in pounds) will be recorded at Screening.

3.5.7.2 General Neurological and Targeted Neurological Examinations:

A general neurological examination will include evaluation of mental status (awareness of person, place, and time), cranial nerves, motor function and balance, sensory exam (ability to feel) and reflexes. A targeted neurological examination demonstrating findings of, focusing on signs and symptoms of lumbosacral radiculopathy, including straight leg raise test, will be performed according to the checklist (see Appendix A). Both general and targeted neurological exams are to be performed by the same trained clinician throughout the study, if possible. Training for conducting examination will be available on video. General and targeted neurological examinations will be performed at Screening, Baseline (D1), W2, W4, W12, and W24, as well as if the repeat injection is administered.

The blinded Investigator will summarize and document the MRI findings based on the Lumbar Disc Nomenclature, the clinical presentation, and the Injection Plan in the eCRF prior to Baseline (D1).

3.5.7.3 Vital Signs and Body Weight:

Vital signs will include systolic and diastolic BP and heart rate. During the usual clinic visits, the subject is to be seated for approximately 3 mins before vital signs are recorded. During the injection procedure, the vital signs will need to be collected while the subject is in prone position on the fluoroscopy table (Appendix D). Vital signs will be recorded at each clinic visit.

3.5.7.4 Electrocardiogram:

Standard 12-lead ECGs will be measured on the site machines at Screening. The ECG results will be documented in the eCRF.

3.5.7.5 Laboratory Parameters:

The following clinical laboratory tests are to be performed at Screening and W24 unless noted below:

Hematology: Hemoglobin, hematocrit, red blood cell count, WBC count (with differential [lymphocytes, neutrophils, eosinophils, basophils, and monocytes]), and platelet count.

Blood Chemistry: albumin, alkaline phosphatase, AST, ALT, direct bilirubin, total bilirubin, blood urea nitrogen, calcium, chloride, creatine kinase (Screening only), creatinine, gamma-glutamyl transferase, glucose, lactate dehydrogenase, potassium, sodium, and uric acid.

Other tests: HbA1c, HIV, hepatitis B, and hepatitis C at Screening. Coagulation tests at Screening: activated PTT, PT, and INR. Coagulation tests may be repeated prior to the index and repeat injection, if deemed necessary by the Investigator.

Urinalysis: Dipstick analysis: color, turbidity, specific gravity, pH, glucose, protein, ketones, urobilinogen, bilirubin, blood nitrate, leukocyte esterase, and microscopic examination when indicated by dipstick results.

Urine drug screen: Includes opiates, barbiturates, benzodiazepines, tricyclic antidepressants, cannabinoids, PCP, cocaine, ecstasy, and amphetamines. A urine drug screen will be obtained at Screening, Baseline (D1), W2, and W4. A urine drug screen may be repeated if deemed necessary by the Investigator.

For females of childbearing potential: Serum pregnancy test at Screening. Urine pregnancy test at Baseline (D1) and at Repeat Injection. A urine pregnancy test may be repeated if deemed necessary by the Investigator.

Laboratory samples will be analyzed by a central laboratory [redacted] to ensure consistent interpretation of results. Samples are to be shipped to [redacted], [redacted] In the event of an unexplained clinically noteworthy abnormal laboratory test value, the test should be repeated immediately and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

3.5.7.6 Adverse Events:

All AEs occurring after the subject signs the ICF through W24, D169 will be recorded.

See Section 4 for additional information.

3.5.7.7 Rescue Medication Use

[redacted]

3.5.8 Other Assessments

Pain Catastrophizing Scale: PCS (Appendix K) is used to assess pain as a baseline characteristic only at Screening (Sullivan-1995). It was developed to quantify a subject's pain experience by asking how they feel and what they think about when they are in pain. Items on this scale were developed from clinical and experimental research on catastrophic thinking and its relation to experience of pain. The PCS is a 13-item instrument that can be completed and scored in less than 5 mins. The PCS requires a reading level of approximately Grade 6.

Hospital Anxiety and Depression Scale: HADS (Appendix L) is commonly used to determine a subject's anxiety and depression levels. The scale is comprised of 14 items rated on a scale of 0-3; 7 items focused on anxiety symptoms and 7 items focused on depression symptoms. The HADS will be used for inclusion criteria and completed at Screening only. A score of 11-14 on either the depression or anxiety subscale is indicative of moderate symptomatology. A score of ≥15 on either the depression or anxiety subscale is indicative of severe symptomatology (Snaith-1994, Turk-2015). Subjects with HADS scores ≥ 15 will be excluded from this study (Zigmond-1983).

3.5.9 Appropriateness of Measurements

All assessments to be used in this study are commonly used, standard measurements frequently seen in radiculopathy studies.

4 ADVERSE EVENT REPORTING

Throughout the course of the study, after signing the ICF, all AEs will be monitored and recorded on an AE eCRF, including the AE's description, start and end date, seriousness, severity, action taken, and relationship to the IP. If AEs occur, the first concern will be the safety of the study subjects. All AEs will be followed until resolved or stable and the outcome documented on the eCRF.

4.1 Definitions and Criteria

4.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH-E2A-1996). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product or not.

Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat the medical condition. They should be recorded as treatment of the AEs.

4.1.2 Serious Adverse Events

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse; malignancy tumors [histologically different from primary tumor])

Note: The term "life-threatening" in the definition of "serious" 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 judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. An SAE is not necessarily severe; eg, an overnight hospitalization for a diagnostic procedure must be reported as an SAE even though the occurrence is not medically serious. By the same token, a severe AE is not necessarily serious: nausea of several hours' duration may be rated as severe but may not be considered serious.

4.1.3 Unexpected Adverse Drug Reactions

An unexpected adverse drug reaction (ADR) is a reaction for which the nature or severity is not consistent with the applicable product information (IB, SP102-IB-2015). Until product information is amended, expedited reporting is required for additional occurrences of the reaction. Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the IB would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

Guidance on reporting AEs and SAEs is described in Section 4.2.

4.1.4 Abnormal Laboratory Values

Any abnormality (Appendix N) in a laboratory value that is new in onset or which has worsened in severity or frequency from the baseline condition and meets 1 of the following criteria will be recorded on the AE pages of the eCRF:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of IP
- Has accompanying or inducing symptoms or signs
- Is judged by the investigator as clinically significant

4.1.5 Assessing Intensity and Relationship

All AEs will be assessed on 2 descriptive parameters: intensity and relationship to the IP:

- Intensity refers to the severity of an event and references impact on a subject's functioning.
- Relationship refers to the likelihood that the event being assessed was caused by the IP.

Intensity

Each AE will be classified according to Appendix N.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over a number of days, those changes should be recorded separately (with distinct onset dates).

Relationship

Each AE will be assessed as to its relationship to the IP, based on the following criteria. Although the attribution by the investigator will be collected for reported events, for analytic purposes a temporal association with the use of the IP will be assumed sufficient for at least plausible association.

Investigators are required to assess the causal relationship (ie, whether there is reasonable possibility that the study drug caused the event) using the following definitions:

Unrelated:	A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations of the event.
Possibly Related:	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the study drug, but that could also be explained by concurrent disease or other drugs or chemicals. Information on study drug causality may be lacking or unclear.
Probably Related:	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the study drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge) of the study drug.
Definitely Related:	A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship definite and is clearly related to use of the IP.

When assessing the relationship to the IP, the following criteria will be considered:

- Positive rechallenge
- Positive dechallenge (resolution upon stopping suspect the IP, in absence of other intervention or treatment)
- Known class effect
- Biological plausibility
- Lack of alternative explanation—concomitant drug or disease

4.2 Reporting Procedures and Requirements

4.2.1 Adverse Events

AEs occurring after the subject signs the ICF until the 30 days after the last study visit will be recorded. Any AEs occurring before the start of treatment (ie, before the first dose of the IP)" will be recorded in the medical history. Also, the sign, symptom, or disease present before starting the treatment period are only considered AEs if they worsen after starting the treatment period.

If a subject has new or worsening pain, or onset of new neurological symptoms, a follow-up MRI may be obtained after consultation with the Medical Monitor.

If the investigator detects an AE in a study subject within 30 days after the last scheduled follow-up visit and considers the event possibly related or related to prior study treatment, the investigator should report it to the sponsor[redacted]

The investigator should report all AEs on the AE page(s) of the eCRF and source documents (if the eCRF is unavailable for direct data entry [DDE]), regardless of seriousness, severity, and causality. Whenever possible, an AE will be reported using a diagnostic term, (eg, "common cold" or "upper respiratory infection" rather than "runny nose, cough, mild fever") and should be described with the attributes described in Section 4.1.5.

4.2.2 Adverse Events of Special Interest

If any of the following AESIs occur at time after the procedure that are attributable (ie, possibly related or related) to IP the Medical Monitor is to be contacted immediately and the reporting procedures for SAE to be followed (Section 4.2.3):

- Infection in the epidural space that requires surgical intervention
- Hematoma in the epidural space that requires surgical intervention, or
- Paraplegia

4.2.3 Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria (Section 4.1.2). If the AE is considered serious, the investigator should report this event to [redacted] as outlined below and also to the IRB/IEC according to its standard operating procedures.

If the investigator detects an SAE in a study subject within 30 days after the last scheduled study visit, and considers the SAE related or possibly related to prior study treatment, the investigator should report it to sponsor[redacted]

The investigator should report all SAEs to [redacted] on the eCRF within 24 hours of the Investigator, designee or site staff's knowledge of the event regardless of relationship to study drug.

If the site experiences a temporary disruption of the eCRF system, a back-up paper SAE Report Form will be available for site staff to complete.

- Site staff will complete the paper SAE report form and email it within 24 hours to the following address [redacted]
- Only in cases where the email system is unavailable, site staff will send the SAE by fax to: [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

All recorded SAEs, regardless of relationship to study treatment, will be followed up until resolution, stabilization, or the subject is lost to follow-up and cannot be contacted. In circumstances where the Investigator is unable to contact the subject, the Investigator must provide a written statement to [redacted] confirming that the subject is lost to follow-up. SAEs that are ongoing at V5 (D29) should be followed until resolved.

Additional follow-up information must be reported in the eCRF within 24 hours of awareness following Investigator (or site) awareness of the information. The Investigator should not delay reporting an SAE to obtain additional information. Additional information, when available, should be reported to [redacted] by the reporting procedures described above.

The sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities per the applicable regulatory requirements.

4.3 Procedures for Documenting Pregnancy during the Study

Pregnancy occurring in a female subject should be reported to [redacted] within 24 hours of becoming aware of the event using the pregnancy eCRF. The investigator will also: (1) notify the subject's physician that the subject may have been treated with SP-102 and (2) follow the progress of the pregnancy to term and document the outcome of the pregnancy. Pregnancy outcome information should be forwarded to sponsor/[redacted] when available.

Any pregnancies will be followed through delivery or premature termination. If a subject becomes pregnant during the study, any complications of that pregnancy such as abortion (spontaneous or induced), premature birth, or congenital abnormality will be captured as SAEs. In the event the eCRF system is unavailable, a back-up paper Pregnancy Reporting Form will be available for site staff to complete following reporting guidelines as outlined in Section 4.2.2.

5 DATA MANAGEMENT AND STATISTICAL ANALYSIS

5.1 Data Management Considerations

eCRFs will be employed for this study. Completed eCRFs for this study will be forwarded to the sponsor or its representative at the end of the study. Queries will be issued for any inconsistencies, omissions, and discrepancies and will be resolved by the appropriate parties. The statistical analysis of these data will be performed by the sponsor or its representative. All AEs will be coded using the latest version of the Medical Dictionary for Regulated Activities (MedDRA). Concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary. Data management details will be outlined in a separate data management plan.

5.2 Statistical Considerations

The statistical analysis will be undertaken by [redacted] in collaboration with Semnur.

A detailed Statistical Analysis Plan (SAP) will be finalized and signed before database lock and the code for all subjects is broken and before analysis of the study being carried out. Any deviations from the analyses described below will be included in the SAP, which will be included in the clinical study report.

5.2.1 Sample Size Justification

[redacted]

5.2.2 Study Data

[redacted]

To comply with the requirement to maintain accurate case histories, clinical investigator(s) should review and electronically sign the completed eCRF for each subject before the database is locked.

All study data will be formulated into data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study data will be mapped to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model architecture.

5.2.3 Definition of a Completed Subject

For the purposes of analysis, there are 2 types of completers in this trial:

- A Primary Efficacy Endpoint Completer is defined as one who receives an injection of study drug and completes the study though W4.
- A 24-week Completer is defined as one who receives an injection of study drug and completes the study through W24.

5.2.4 Analysis Methods

[redacted]

5.2.5 Analysis Populations

The Safety Analysis population is defined as all randomized subjects who receive a study drug injection. For safety analyses, subjects will be grouped based upon the treatment received (even if different from what they were randomized to).

[redacted]

5.2.6 Protocol Deviations

Protocol deviations should be collected by site and grouped into different categories, such as those who:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Major protocol violations that impact the primary efficacy analysis may lead to exclusion from the PP population. Full details regarding these will be provided in the SAP.

5.2.7 Demographic and Baseline Characteristics

Treatment groups will be compared with respect to subject demographics and baseline characteristics and will be summarized using descriptive statistics, but no formal statistical analysis testing will be performed.

5.2.8 Efficacy Analyses

All efficacy analyses will use the mITT as the primary analysis population, and all primary and secondary endpoints will additionally be analyzed with the PP population.

Efficacy variables include:

- NPRS: The NPRS is an 11-point scale (0 to 10-point scale where 0 is no pain and 10 is most severe pain) that allows the subject to rate the severity of their pain intensity at various points in time. [redacted]

- CGIC: The CGIC is an 8-point scale (0 to 7, where 0 is not assessed, 1 is very much improved, and 7 is very much worse) that allows clinicians to rate the subject's global impression of change. CGIC will be collected after randomization at W2, W4, W8, W12, W16, W20, and W24, or until administration of the repeat injection and at subsequent visits following the repeat injection. For analysis, the CGIC response will be grouped into 1 of 2 categories, 1) very much improved or much improved (recorded as a 1 or 2 in the scale), and 2) all other responses (recorded as 3-7 in the scale). The number and percentage of subjects reporting each of the 7 CGIC response levels will also be provided by visit and treatment.
- PGIC: The PGIC is a 7-point scale (1 to 7, where 1 is very much improved and 7 is very much worse) that allows patients to rate their global impression of change. PGIC will be collected after randomization at W2, W4, W8, W12, W16, W20, and W24, or until administration of the repeat injection and at subsequent visits following the repeat injection. For analysis, the PGIC response will be grouped into 1 of 2 categories, 1) very much improved or much improved (recorded as a 1 or 2 in the scale), and 2) all other responses (recorded as 3-7 in the scale). The number and percentage of subjects reporting each of the 7 PGIC response levels will also be provided by visit and treatment.
- ODI: The ODI is a measure of disability associated with low back and leg pain with 10 topics, with each topic having a response ranging from 0-5. The 10 responses are then summed and multiplied by 2 resulting in an ODI score ranging from 0-100. The ODI will be collected after randomization at W4, W12, and W24, or until administration of the repeat injection and at subsequent visits following the repeat injection.
- Pain*DETECT*: Pain*DETECT* is a 7-question validated tool to determine the prevalence of neuropathic pain in individuals with lower back pain. The 7 responses are summed for a possible score ranging from 0-35. In addition to the 7 questions, subjects note the course of pain (Persistent pain with slight fluctuations; Persistent pain with pain attacks, Pain attacks without pain between them; Pain attacks with pain between them; and Radiating pains marked on a body chart) for a total, overall scale score of 0-38. Pain*DETECT* will be collected at Screening, Baseline (D1), W4, W12, and W24.
- BPI-SF: The BPI assesses pain at its "worst," "least," "average," and "now" (current pain). The pain severity domain will be derived by summing items 3-6.

  The BPI also measures how much pain has interfered with 7 daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. BPI pain interference is typically scored as the mean of the 7 interference items. The pain interference domain will be derived by summing items 9A - 9G.

- Rescue Medication: In this study, acetaminophen is the permitted and study provided rescue medication. The time to first rescue medication dose and number of mg taken will be collected and analyzed.

5.2.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from Baseline (D1) to W4 in the mean NPRS average pain score in the affected leg.

[redacted]

[redacted] in the mean change from baseline NPRS average pain score in the affected leg over 4 weeks

5.2.8.2 Principal Analysis

[redacted]

5.2.8.3 Secondary Efficacy Endpoints

The key secondary efficacy endpoint is:

- The change in ODI total score from Baseline (D1) to W4.

Other secondary endpoints are:

- The time to repeat injection of SP-102 from index injection.
- Proportion of subjects receiving repeat injection.
- The mean change from Baseline (D1) to W2, W8, and W12, in the mean NPRS average pain score in the affected leg.
- The mean change from Baseline (D1) to W2, W4, W8, and W12, in the mean NPRS worst pain in the affected leg.

- The mean change from Baseline (D1) to W2, W4, W8, and W12 in the mean NPRS current pain score in the affected leg.
- The mean change from Baseline (D1) in the ODI total score to W12.
- The mean change in Pain*DETECT* from Baseline (D1) to W4 and W12.
- The mean change in BPI-SF score from Baseline (D1) to W4 and W12.
- Proportion of subjects achieving a response of 30%, 50%, and 75% reductions from Baseline (D1) in mean NPRS average pain score in the affected leg at W2 and W4.
- The mean change from Baseline (D1) to W2, W4, W8, and W12 in the mean NPRS average pain score in the lower back.
- PGIC at W2, W4, W8, and W12.
- CGIC at W2, W4, W8, and W12.
- Cumulative use of rescue medication (mg of acetaminophen).
- Time to first rescue medication dose.
- Proportion of subjects requiring rescue medications during first 4 weeks.

Other possible exploratory analyses may be added, such as percent of rescue medication free days, or evaluating certain endpoints only including those data collected prior to a second treatment injection (of SP-102). Any such exploratory additions will be provided in the SAP prior to unblinding.

5.2.8.4 Secondary Efficacy Endpoint Analyses

[redacted]

5.2.8.5 Multiplicity

[redacted]

5.2.9 Safety Analyses

Safety endpoints are:

- AEs, compared between 4 groups receiving one SP-102 injection, two SP-102 injections, placebo followed by SP-102 repeat injection, or placebo only.
- Change from Baseline (D1) in laboratory parameters.
- Change from Baseline (D1) in vital signs.
- Change from Baseline (D1) in neurological examination.

5.2.9.1 Adverse Events

All AEs will be coded using the most current version of MedDRA.

The incidence of treatment-emergent AEs (TEAEs) (number and percent of subjects reporting the AE at least once during the study), SAEs, AEs related to study treatment, SAEs related to treatment, and AEs leading to study discontinuation will be summarized by treatment.

A TEAE is defined as any AE that has an onset on or after the dose of IP, or any pre-existing condition that has worsened on or after the first dose of IP.

The incidence of TEAEs and treatment-related AEs will also be summarized by maximum severity and most-related relationship to IP by MedDRA primary system organ class and preferred term. The summary will include the total number and percentage of subjects reporting an event. In counting the number of events reported, a continuous event, ie, reported more than once and which did not cease, will be counted only once; non-continuous AEs reported several times by the same subject will be counted as multiple events.

Any TEAEs will be summarized by treatment group, for each post-randomization treatment period:

- Occurring after the randomization injection, but prior to a second injection (of SP-102)
- Occurring after the second injection (of SP-102)

5.2.9.2 Electrocardiographic Data

A listing of 12-lead ECG parameter results obtained at Screening will be presented.

5.2.9.3 Laboratory Data

Mean changes from Baseline (D1) at each post-baseline time point for each laboratory variable will be presented. In addition, each reading will be classified as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables for the baseline and follow-up measurements will be presented.

5.2.9.4 Vital Signs

Summary statistics for the absolute vital sign value and the changes from baseline will be presented by treatment group for each visit, for each of the following vital signs:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (bpm)

Vital sign values will be categorized into the following potential clinical concern categories if applicable and summarized.

Vital Sign	Potential Clinical Concern Categories
Systolic blood pressure	≥ 160 mmHg
Diastolic blood pressure	≥ 100 mmHg
Heart rate	< 60 or > 100 bpm

5.2.9.5 Neurological Examinations

General neurological and targeted neurological examination results will be summarized descriptively over time and included in listings.

5.2.10 Interim Analyses

No interim analysis is planned for this study. Note that the study will be unblinded and the primary analysis will be completed after all subjects complete the 12-week assessments and data are cleaned. Subjects in the OL safety extension portion of the study will continue through W24. No efficacy data in the first 12 weeks of the study will change after the primary analysis is completed.

6 STUDY MANAGEMENT

6.1 Ethics and Consent

6.1.1 Regulations and Guidelines

The study will be performed in accordance with this protocol, US investigational new drug (IND) regulations (21 CFR 312), ICH guidelines for Good Clinical Practice (GCP), the regulations on electronic records and electronic signature (21 CFR 11), and the most recent guidelines of the Declaration of Helsinki.

6.1.2 Institutional Review Board/Independent Ethics Committees

Conduct of the study must be approved by an appropriately constituted institutional review board (IRB). Approval is required for the study protocol, protocol amendments, ICFs, subject information sheets, and advertising materials. No IP will be shipped to a site until written IRB authorization has been received by the sponsor or its representative.

6.1.3 Informed Consent

For each trial subject, a written ICF will be obtained before any protocol-related activities. As part of this procedure, the investigator or a designated representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the IP in such a manner that the subject and (if applicable) appointed guardian are aware of the potential risks, inconveniences, or adverse effects that may occur. Subjects should be informed that they may withdraw from the study at any time. They will receive all information that is required by federal regulations and ICH guidelines. The principal investigator or a designated representative will provide the sponsor or its representative with a copy of the IRB-approved ICF before the start of the study.

6.2 Discontinuation of the Study by the Sponsor

The sponsor reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. A site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated, and/or the site closed for whatever reason, all documentation and IP pertaining to the study must be returned to the sponsor or its representative.

6.3 Study Documentation

By signing a copy of Form FDA 1572, the principal investigator acknowledges that he/she has received a copy of the IB on SP-102 and assures the sponsor that he/she will comply with the protocol and the provisions stated in Form FDA 1572. No changes in this protocol can be made without the sponsor's written approval.

6.4 Study Monitoring and Auditing

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel employed by the sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted per the protocol, standard operating procedures, Guidelines of GCP, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Remote and on-site review of eCRFs

will include a review of forms for completeness and clarity, and consistency with electronic or paper source documents (if used) for each subject.

Medical advisors and CRAs or assistants may request to witness subject evaluations occurring as part of this protocol. The investigator and appropriate personnel will be periodically requested to attend meetings/workshops organized by the sponsor to assure acceptable protocol execution. The study may be subject to audit by the sponsor or by regulatory authorities. If such an audit occurs, the investigator must agree to allow access to required subject records. By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

6.5 Retention of Records

The investigator must arrange for retention of study records at the site for 2 years after the IP's New Drug Application is approved or the IND is withdrawn, as required by FDA regulations. The investigator should take measures to prevent accidental or premature destruction of these documents.

6.6 Use of Study Findings

By signing the study protocol, the investigator agrees to the use of results of the study for the purposes of national and international registration. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the sponsor or its representative.

6.7 Publications

[redacted]

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