Protocol Title:	An Open-label, Single-arm Study to Characterize the Pharmacodynamics and Safety of Repeat Dose SP-102 (Dexamethasone Sodium Phosphate Injectable Gel) Administered by Epidural Injection in Subjects with Lumbosacral Radiculopathy
Protocol Number:	SP-102-03
Clinical Phase:	2
Protocol Version and Date:	Version 1.0, 08 Jun 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: An Open-label, Single-arm Study to Characterize the Pharmacodynamics and Safety of Repeat Dose SP-102 (Dexamethasone Sodium Phosphate Injectable Gel) Administered by Epidural Injection in Subjects with Lumbosacral Radiculopathy

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 Approval:

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: [redacted] Date: [redacted]

Name (print): [redacted]

SYNOPSIS

Protocol Title:	An Open-label, Single-arm Study to Characterize the Pharmacodynamics and Safety of Repeat Dose SP-102 (Dexamethasone Sodium Phosphate Injectable Gel) Administered by Epidural Injection in Subjects with Lumbosacral Radiculopathy
Protocol Number:	SP-102-03
Study Center(s):	Up to 2
Phase of Development:	2
Objectives:	The **primary** objective of the study is to characterize repeat dose pharmacodynamics (PD) of SP-102 (10 mg dexamethasone) administered by epidural injection with respect to hypothalamic-pituitary-adrenal (HPA) suppression using plasma cortisol levels, white blood cell count (WBC), and blood glucose. The **secondary** objectives of the study are to: • Evaluate the safety and tolerability of single and repeat dose SP-102 (10 mg dexamethasone) administered by epidural injection in subjects with lumbosacral radiculopathy. • Evaluate the analgesic effect on leg pain (as measured by the Numeric Pain Rating Scale [NPRS] in the affected leg) following the index (Treatment [T] 1) and repeat (T2) injections.
Study Design:	This is an open-label, single-arm, repeat dose study to characterize the PD and safety/tolerability of SP-102 (10 mg dexamethasone) administered by epidural injection as transforaminal (TF) or interlaminar (IL) injection under fluoroscopic guidance in subjects with lumbosacral radiculopathy. Subjects meeting the eligibility criteria will be enrolled in the study and receive a single 2-mL epidural injection of SP-102 (10 mg dexamethasone) in T1 (index injection) and T2 (repeat injection), separated by 4 to 8 weeks. T2 will only be provided if a repeat injection is warranted and the subject continues to meet applicable study inclusion and exclusion criteria. Subjects who have been using opioids other than high dose opioids within 30 days prior to Screening (see Exclusion #12), 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. The study will include a 21-day screening period (Visit 1), sequential treatments periods T1 and T2, separated by 4 to 8 weeks; each treatment period will consist of a Baseline Visit (Day 0), SP-102 injection (Day 1), and a 4-week follow-up period. Screening, Baseline, and follow-up visits will occur at the research site. Subjects will stay in a restricted environment [redacted]) for each of 5 nights beginning the night before each injection to ensure fasting each evening and on-time collection of PD assessments each morning. Subjects will be permitted to leave the restricted environment [redacted]) and resume normal activities each day after study procedures are performed. The SP-102 injection will be administered in an injection procedure facility. Safety and PD assessments will be collected at Screening, pre-dose, daily for 4 days post dose during the stay in the restricted environment ([redacted]), and at 3 outpatient follow-up visits (on Day 8, Day 15, and Day 28) after each injection. The end of study (EOS) visit (Visit 19) is the final outpatient visit after the second injection. If the subject is not eligible for T2 or chooses to withdraw from further participation in the study, the subject will be scheduled for the EOS visit (Visit 19). From the time of informed consent to the EOS visit, each subject's participation may last up to 15 weeks.

Planned Sample Size:	Enrollment will continue until 12 subjects have each completed two SP-102 injections (T1 and T2).
Key Subject Selection Criteria:	**Inclusion Criteria:** *Treatment 1 Inclusion Criteria:* 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. Subject meets appropriate clinical criteria for lumbar epidural steroid injection per the discretion of a qualified investigator. A qualified investigator is defined as an investigator experienced in performing epidural injections for radicular low back pain. [redacted] 6. 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. Acceptable method of birth control for this study includes: [redacted] 10. Agrees to comply with all study requirements throughout the entire study period including willingness to stay each of 5 nights in a restricted environment ([redacted]). [redacted] *Treatment 2 Inclusion Criteria:* [redacted]

[redacted]

3. The investigator makes a clinical decision that the repeat injection is warranted.

[redacted]

Exclusion Criteria:

1. Body mass index ≥ 40 kg/m^2 without rounding at the Screening Visit.
2. History of Insulin-dependent Diabetes Mellitus and/or Screening Hemoglobin A1c ≥ 7% indicative of diabetes.
3. Any active clinically significant uncontrolled, treated or untreated, medical condition (eg, fungal, bacterial, or viral infections, cardiovascular disease, or renal and/or hepatic disease) at the Screening or Baseline Visit that would preclude the use of dexamethasone in this study.

[redacted]

6. History of malignancy or evidence of malignancy or lymphoproliferative or neoplastic disease with the exception of successfully treated basal or squamous cell carcinoma of the skin or cervical intraepithelial neoplasia within 5 years of the Screening Visit.
7. History of allergy to corticosteroids or anaphylactoid reaction to any other drug at the Screening or Baseline Visit.
8. Known allergy or idiosyncratic (atopic) reaction to contrast agent, local anesthetic, dexamethasone, any ingredient listed as being present in a study formulation, or any other pain management compound likely to be prescribed in the study.
9. Abnormalities in clinical chemistry that would place the subject at undue risk after epidural steroid injection, per the discretion of the principal investigator. [redacted]

[redacted]

11. Chronic use (ie, more than 5 consecutive days) of oral or parenteral steroid medication during the 2 months prior to the Screening Visit and any oral or parenteral steroid medication in the 2 weeks prior to the Screening Visit or to the Baseline Visit.
12. 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.

	13. An epidural steroid injection for the treatment of the current episode of lumbosacral radicular pain during the 2 months prior to the Screening Visit. 14. History of spine surgery prior to the Screening or Baseline Visit, which may interfere with IL epidural injection, or plans to undergo spine surgical intervention while in the study. 15. Has donated blood exceeding 500 mL during the 45 days before Baseline Visit. 16. Use of any investigational drug or device within 30 days prior to the Screening Visit or is scheduled to receive an investigational drug other than study drug during the course of this study. 17. If female, are lactating/breastfeeding, plan to breastfeed, currently pregnant, or plan to become pregnant while participating in the study. 18. Alcohol dependence, drug abuse, or drug addiction within 1 year of the Screening Visit. 19. 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. 20. The presence of any disorder, condition, laboratory abnormality, or circumstance (with the exception of the condition under study) as determined by a medical and psychiatric history, medical examination, electrocardiogram (ECG), serum chemistry, hematology, and urinalysis that, in the opinion of the investigator, has the potential to compromise subject safety, prevent study completion, and/or to have a confounding effect on outcome measures.
Investigational Product:	SP-102: dexamethasone sodium phosphate injectable gel, 10 mg dexamethasone
Comparator Product:	None
Duration of Treatment:	2 single injections of SP-102.
Main Parameters to Measure Pharmacodynamics:	The following PD assessments will be performed during the study: • Cortisol • Fasting blood glucose • WBC • NPRS measuring current, worst, and average leg and back pain • Brief Pain Inventory (BPI-SF)
Main Parameters of Safety:	The following safety assessments will be performed during the study: • Adverse events (AEs) • Vital signs • Body weight • Physical examinations • General neurological examination • Targeted neurological examination • 12-lead ECGs • Clinical laboratory tests (serum chemistry, hematology, urinalysis, HIV, viral hepatitis screening, and coagulation tests) • Serum or urine pregnancy tests

Pharmacodynamic Endpoints:	• Dexamethasone-induced HPA suppression as measured by:
	  o Observed total blood cortisol levels, change from baseline cortisol levels, and percent change from baseline cortisol levels
	  o Observed glucose levels, change from baseline glucose levels, and percent change from baseline glucose levels
	  o Observed white blood cell counts, change from baseline white blood cell counts, and percent change from baseline white blood cell counts
	• NPRS (average leg pain and back pain) and BPI-SF
	• Change from T1 Day 0 and T2 Day 0 through Day 28 in NPRS (average leg pain and back pain) and BPI-SF over time following the index (T1) and repeat (T2) epidural injections, respectively
	• Percent change from T1 Day 0 and T2 Day 0 through Day 28 in NPRS (average leg pain and back pain) and BPI-SF following the index (T1) and repeat (T2) epidural injections, respectively

Safety Endpoints:	Safety endpoints are as follows: • Incidence of treatment-emergent AEs (TEAEs) and serious adverse events (SAEs) • Change from baseline in clinical laboratory parameters, vital sign measurements, ECG findings, and physical examination parameters following each treatment
Statistical Analyses:	No formal statistical power calculation was performed for this study; the sample size is based on clinical and practical considerations. TEAEs and SAEs, observed values and changes in clinical laboratory parameters, and vital signs will be summarized descriptively for each treatment. Shifts in laboratory parameters, physical examination findings, general neurological examination findings, and targeted neurological examination findings will be summarized by treatment group. Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to treatments T1 or T2 (reference start date). This includes screening or unscheduled assessments that would have been performed no earlier than 21 days before the reference start date. In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-reference, but AEs and medications commencing on the reference start date will be considered post-reference. Cortisol levels, WBC counts, and fasting blood glucose levels (observed, change from baseline, and percent change from baseline) will be summarized by treatment and measurement time using descriptive statistics. Dexamethasone-induced HPA suppression will be evaluated by using the observed total plasma cortisol level, glucose levels, and WBC count. Other PD analyses may be performed as appropriate. For blood cortisol and glucose levels, and WBC counts (change-from-baseline), PD parameters, ie, area under the effect curve over 28 days ($AUEC_{28\ days}$) and maximum effect (E_{max}) following the T1 (index) and T2 (repeat) injections will be calculated. $AUEC_{28\ days}$ is defined as the change from baseline (for cortisol, glucose, and WBC) and calculated using linear trapezoidal summation from pre-dose to Day 28 in each treatment period. E_{max} is the baseline-adjusted maximum increase in

	glucose level and WBC count or the maximum decrease in cortisol levels over the 28 days post dose in each treatment period. The PD parameters will be analyzed using a mixed model analysis of variance using PROC MIXED with a fixed effect for treatment and a random effect for subject. Estimates and 90% confidence intervals (CIs) will be first constructed in the logarithmic scale. By taking anti-logarithms, estimates and CIs for the geometric means and ratios of geometric means will be calculated. All CIs will be 2-sided. A lack of effect of repeat injection on the PD will be concluded if the 90% CIs for the ratio of T2 (repeat injection; Test) to T1 (index; Reference) for both $AUEC_{28\ days}$ and E_{max} are completely contained within the range of 80 to 125%. The pain assessment closest to and prior to dosing in each treatment period will be used as baseline for each treatment period. The following pain-score endpoints will be summarized over time by treatment using descriptive statistics: • NPRS (average leg pain and back pain) and BPI-SF • Change from T1 Day 0 and T2 Day 0 through Day 28 in NPRS (average leg pain and back pain) and BPI-SF over time following the index (T1) and repeat (T2) epidural injections, respectively • Percent change from T1 Day 0 and T2 Day 0 through Day 28 in NPRS (average leg pain and back pain) and BPI-SF following the index (T1) and repeat (T2) epidural injections, respectively

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
α	alpha
ACTH	adrenocorticotropic hormone
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)
AUC_{inf}	area under the effect time curve from time zero extrapolated to infinity
$AUEC_{28\ days}$	area under the effect time curve at 28 days post dose
BMI	body mass index
BP	blood pressure
BPI-SF	Brief Pain Inventory-Short Form
bpm	beats per minute
C	Celsius
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
C_{max}	maximum concentration
CSF	cerebrospinal fluid
D	day
DDE	direct data entry
ECG	electrocardiogram
eCRF	electronic case report form
E_{max}	maximum effect
EOS	end of study
ESI	epidural steroid injection
ET	early termination
F	Fahrenheit
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice

Abbreviation	Definition
HbA1c	Hemoglobin A1c
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL	interlaminar(ly)
IM	intramuscular(ly)
IND	Investigational New Drug
INR	International Normalization Ratio
IP	investigational product
IRB	institutional review board
IV	intravenous(ly)
LFT	liver function tests
µg	microgram
µmol	micromole
MEDD	Mean Equivalent Daily Dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minutes
mITT	Modified intent-to-treat (dataset)
mIU	milli international unit
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mRNA	messenger ribonucleic acid
MRI	magnetic resonance imaging
NPRS	Numeric Pain Rating Scale
NSAID	nonsteroidal anti-inflammatory drug(s)
OL	open-label
PD	pharmacodynamic
PT	prothrombin time
PTT	partial prothrombin time

Abbreviation	Definition
RLD	Reference Listed Drug
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SOP	standard operating procedure
T	treatment
TEAE	treatment-emergent adverse event
TF	transforaminal(ly)
T_{max}	time to maximum concentration
US	United States
WBC	white blood cells
WOCBP	women of childbearing potential
[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.

Epidural cocaine injections were reported as early as 1901 via the sacral hiatus for lumbosacral radicular pain (Nelson-2001). In the 1950s, physicians began injecting corticosteroids into the epidural and extradural space as a treatment for lumbosacral radicular pain (Barry-1962, Benzon-2015).

1.1.2 Epidural Steroids

The first controlled trial evaluating ESIs was performed in 1970 (Sullivan-1995) and since then there have been many controlled trials evaluating the effectiveness of different corticosteroids injected into the epidural space for the treatment of radicular pain. Despite differences in injection route, anatomical region of injection, control group, injectate characteristics, and

individual pathology, the clinical consensus across multiple practice specialties is that ESIs provides at least short-term benefit in selected people (Cohen-2013).

The mechanisms by which steroids exert their analgesic effects have been debated, but it is established that corticosteroids inhibit phospholipase A2, which catalytically hydrolyzes the bond converting membrane phospholipids into arachidonic acid and lysophospholipids (Cohen-2013). In addition to the anti-inflammatory effects, steroids may also inhibit pain via their ability to suppress ectopic discharges from injured nerve fibers and depress conduction in normal unmyelinated C fibers (Devor-1985, Johansson-1990). Epidural steroids are now considered a standard treatment regimen for lumbosacral radicular pain (Cohen-2013). The comparative effectiveness of the various treatment modalities has been a topic that has been frequently addressed in the literature, but there is currently no United States (US) Food and Drug Administration (FDA)-approved epidural steroid treatment for lumbosacral radicular pain.

Epidural injection of corticosteroids is a common procedure performed in the US for the management of lumbar radicular pain caused by disc herniations. They have been shown effective in reducing pain, restoring function, reducing the need for other health care, and avoiding surgery (MacVicar-2013). Recent review of randomized controlled clinical trials using ESIs for treatment of radicular pain demonstrate Level II clinical evidence of long-term benefits (Kaye-2015). ESIs are relatively safe procedures, containing lower risks than opioid therapy (Cohen-2013).

Because injectable corticosteroids are not FDA-approved for this route of administration, the epidural injection of corticosteroids is considered an off-label use of approved injectable steroid formulations.

In 2009, the FDA began evaluating serious neurologic events associated with epidural glucocorticoid injections. Between 1997 and 2014, a total of 90 serious and sometimes fatal neurologic events were reported to the FDA Adverse Event Reporting System (FAERS), including cases of paraplegia, quadriplegia, spinal cord infarction, and stroke. There is concern that in glucocorticoids formulated as suspensions rather than solutions, particulate matter may pose an increased risk of embolism after inadvertent intravascular injection. 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 (Racoosin-2015). In 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” (Food and Drug Administration-2014).

The Anesthetic and Analgesic Drug Products Advisory Committee held a meeting on November 24-25, 2014 to discuss the risk of serious neurologic adverse reactions associated with ESIs administered to reduce inflammation for pain management. The Committee considered the efficacy of ESI and the overall risk-benefit balance of injecting steroids in the epidural space to treat pain. The committee acknowledged the benefits of ESIs. The safety concerns are related to particulate-containing formulations leading to 131 neurological adverse events (AEs), including 41 cases of arachnoiditis, identified by the FDA, and 700 cases of fungal meningitis following

injection of contaminated steroids. These events were associated with inadvertent intravascular injection of particulates-containing suspensions, contaminants, inadequate sterility, neurotoxic preservatives, and surfactants in steroid formulations, developed for intramuscular (IM) and intraarticular use (Manchikanti-2015).

1.1.3 SP-102

[redacted]

1.2 Preclinical Studies

[redacted]

[redacted]

1.3 Clinical Studies

[redacted]

[redacted]

1.4 Use of Epidural Injection of Dexamethasone for Radicular Pain in the Clinical Setting

[redacted]

1.5 Study Rationale

The rationale for the present study is to characterize the PD of SP-102 following a repeat epidural SP-102 administration on the hypothalamic pituitary adrenal (HPA) axis suppression, particularly plasma cortisol levels, WBC count, and blood glucose levels.

1.6 Dose Rationale

[redacted]

1.7 Study Endpoint Rationale

[redacted]

1.8 Risks and Benefits for Subjects

Pain relief is expected following epidural administration of SP-102 based on previous epidural administration of ESI, particularly dexamethasone. 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" (Food and Drug Administration-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 adverse events (AEs), including 41 cases of arachnoiditis and other serious neurological AEs (Food and Drug Administration-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).

[redacted]

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to characterize repeat dose PD of SP-102 (10 mg dexamethasone) administered by epidural injection with respect to HPA suppression using plasma cortisol levels, WBC count, and blood glucose.

2.2 Secondary Objectives

The secondary objectives of the study are to:

- Evaluate the safety and tolerability of single and repeat dose SP-102 (10 mg dexamethasone) administered by epidural injection in subjects with lumbosacral radiculopathy.
- Evaluate the analgesic effect on leg pain (as measured by the Numeric Pain Rating Scale [NPRS] in the affected leg) following the index (Treatment [T] 1) and repeat (T2) injections.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

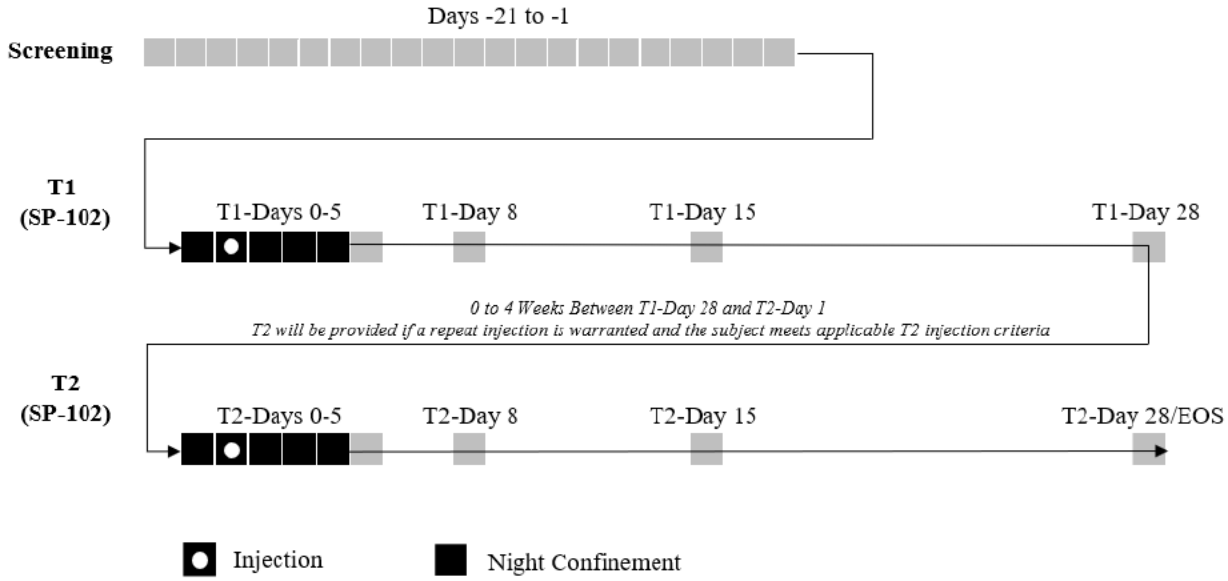
This is an open-label, single-arm, repeat dose study to characterize the PD and safety/tolerability of SP-102 (10 mg dexamethasone) administered by TF or IL injection under fluoroscopic guidance in subjects with lumbosacral radiculopathy.

Subjects meeting the eligibility criteria will be enrolled in the study and receive a single 2-mL epidural injection of SP-102 (10 mg dexamethasone) in T1 (index injection) and T2 (repeat injection), separated by 4 to 8 weeks. T2 will only be provided if a repeat injection is warranted and the subject continues to meet applicable study inclusion and exclusion criteria.

Subjects who have been using opioids other than high dose opioids within 30 days prior to Screening (see Exclusion #12), 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).

The study will include a 21-day screening period (Visit 1), sequential treatments periods T1 and T2, separated by 4 to 8 weeks; each treatment period will consist of a Baseline Visit (Day 0), SP-102 injection (Day 1), and a 4-week follow-up period. Screening, Baseline, and follow-up visits will occur at the research site. Subjects will stay in a restricted environment ([redacted]) for each of 5 nights beginning the night before each injection to ensure fasting each evening and on-time collection of PD assessments each morning. Subjects will be permitted to leave the restricted environment [redacted]) and resume normal activities each day after study procedures are performed. The SP-102 injection will be administered in an injection procedure facility. Safety and PD assessments will be collected at Screening, pre-dose, daily for 4 days post dose during the stay in the restricted environment ([redacted]), and at 3 outpatient follow-up visits (on Day 8, Day 15, and Day 28) after each injection. The end of study (EOS) visit (Visit 19) is the final outpatient visit after the second injection. If the subject is not eligible for T2 or chooses to withdraw from further participation in the study, the subject will be scheduled for the EOS visit (Visit 19).

Figure 3.1 Study Schematic



Abbreviations: EOS=End of Study; T = treatment

3.2 Study Duration

From the time of informed consent to the EOS visit, each subject's participation may last up to 15 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 Treatment 1 Inclusion Criteria

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. Subject meets appropriate clinical criteria for lumbar ESI per the discretion of a qualified investigator. A qualified investigator is defined as an investigator experienced in performing epidural injections for radicular low back pain.

[redacted]

6. 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]

10. Agrees to comply with all study requirements throughout the entire study period including willingness to stay each of 5 nights in a restricted environment ([redacted]).

3.3.1.2 Treatment 2 Inclusion Criteria

[redacted]

3. The investigator makes a clinical decision that the repeat injection is warranted.

[redacted]

3.3.2 Exclusion Criteria

1. Body mass index (BMI) $\geq$ 40 kg/m^2 (Appendix A) without rounding at the Screening Visit.
2. History of Insulin-dependent Diabetes Mellitus and/or Screening Hemoglobin A1c (HbA1c) $\geq$ 7% indicative of diabetes.
3. Any active clinically significant uncontrolled, treated or untreated, medical condition (eg, fungal, bacterial, or viral infections, cardiovascular disease, or renal and/or hepatic

disease) at the Screening or Baseline Visit that would preclude the use of dexamethasone in this study.

4. Has a major psychiatric disorder not controlled with medication at the Screening or Baseline Visit that would interfere with clinical pain scores or participation in the trial.
5. History of any disorder related to cortisol production (eg, hyper- or hypo-cortisolism, Cushing's syndrome, pituitary tumor, Addison's disease, Nelson syndrome) at the Screening or Baseline Visit.
6. History of malignancy or evidence of malignancy or lymphoproliferative or neoplastic disease with the exception of successfully treated basal or squamous cell carcinoma of the skin or cervical intraepithelial neoplasia within 5 years of the Screening Visit.
7. History of allergy to corticosteroids or anaphylactoid reaction to any other drug at the Screening or Baseline Visit.
8. Known allergy or idiosyncratic (atopic) reaction to contrast agent, local anesthetic, dexamethasone, any ingredient listed as being present in a study formulation, or any other pain management compound likely to be prescribed in the study.
9. Abnormalities in clinical chemistry that would place the subject at undue risk after epidural steroid injection, per the discretion of the principal investigator. These abnormalities include but are not limited to:
    a. serum glutamic-oxaloacetic transaminase/aspartate aminotransferase (AST) or serum glutamic-pyruvic transaminase/alanine aminotransferase (ALT) ≥ 3 times the upper limit of the reference range at the Screening Visit
    b. Coagulation abnormalities: INR > 1.5 or platelet count < 100,000/mm^3)
    c. HIV, Hepatitis B, or Hepatitis C virus infection
10. Creatinine clearance < 60 mL/min as estimated by Cockcroft-Gault equation (Appendix B) at the Screening Visit.
11. Chronic use (ie, more than 5 consecutive days) of oral or parenteral steroid medication during the 2 months prior to the Screening Visit and any oral or parenteral steroid medication in the 2 weeks prior to the Screening Visit or to the Baseline Visit.
12. 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 (Appendix C). The subject must agree to discontinue all opioids prior to the Screening Visit.
13. An epidural steroid injection for the treatment of the current episode of lumbosacral radicular pain during the 2 months prior to the Screening Visit.
14. History of spine surgery prior to the Screening or Baseline Visit, which may interfere with IL epidural injection, or plans to undergo spine surgical intervention while in the study.
15. Has donated blood exceeding 500 mL during the 45 days before Baseline Visit.
16. Use of any investigational drug or device within 30 days prior to the Screening Visit or is scheduled to receive an investigational drug other than study drug during the course of this study.

17. If female, are lactating/breastfeeding, plan to breastfeed, currently pregnant, or plan to become pregnant while participating in the study.
18. Alcohol dependence, drug abuse, or drug addiction within 1 year of the Screening Visit.
19. 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.
20. The presence of any disorder, condition, laboratory abnormality, or circumstance (with the exception of the condition under study) as determined by a medical and psychiatric history, medical examination, electrocardiogram (ECG), serum chemistry, hematology, and urinalysis that, in the opinion of the investigator, has the potential to compromise subject safety, prevent study completion, and/or to have a confounding effect on outcome measures.

3.3.3 Stopping Rules

A single occurrence of an adverse event of special interest (AESI) (Section 4.2.2) precludes the subject from 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 Visit 19 (End of Study [EOS]/Early Termination [ET]) 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 EOS/ET assessments as shown in Section 3.5.1. Enrollment will continue until 12 subjects have each completed two SP-102 injections (T1 and T2).

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 SAEs, nonserious AEs, and AESIs 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 IP is provided in Table 3.1.

Table 3.1: Deta

[redacted]

3.4.2 Dosage Schedule

The subjects will receive 2 single epidural injection of SP-102 (10 mg in 2 mL) separated by 4 to 8 weeks. The IP will be administered by the Investigator. Specific instructions for IP administration are found in Appendix D.

3.4.3 Treatment Assignment

This is an open-label study; there is no blinding. All subjects will receive SP-102 for each of the injections.

3.4.4 Drug Packaging and Blinding

The open-label IP will be provided to the pharmacy. [redacted]

Figure 3.2: Picture of Investigational Product

[redacted]

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 IP 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 on site 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

[redacted]

[redacted]

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. [redacted]

Concomitant medication refers to all drugs and therapies used from the time of informed consent through the EOS/ET participation. Changes, additions, or discontinuations to medications will be assessed and recorded in the eCRF during each study visit and at Visit 19/EOS/ET. All as needed (*pro re nata, PRN*) prescriptions should be converted to reflect actual number of pills and dose taken per day.

Subjects who have been using opioids other than high dose opioids within 30 days prior to Screening (see Exclusion #12), may participate in the study if they agree to discontinue the opioid therapy prior to the Screening Visit and sign the pre-screening ICF.

3.4.8.3 Prohibited Medications and Substances

[redacted]

[redacted]

3.4.9 Allowed Medications and Treatments

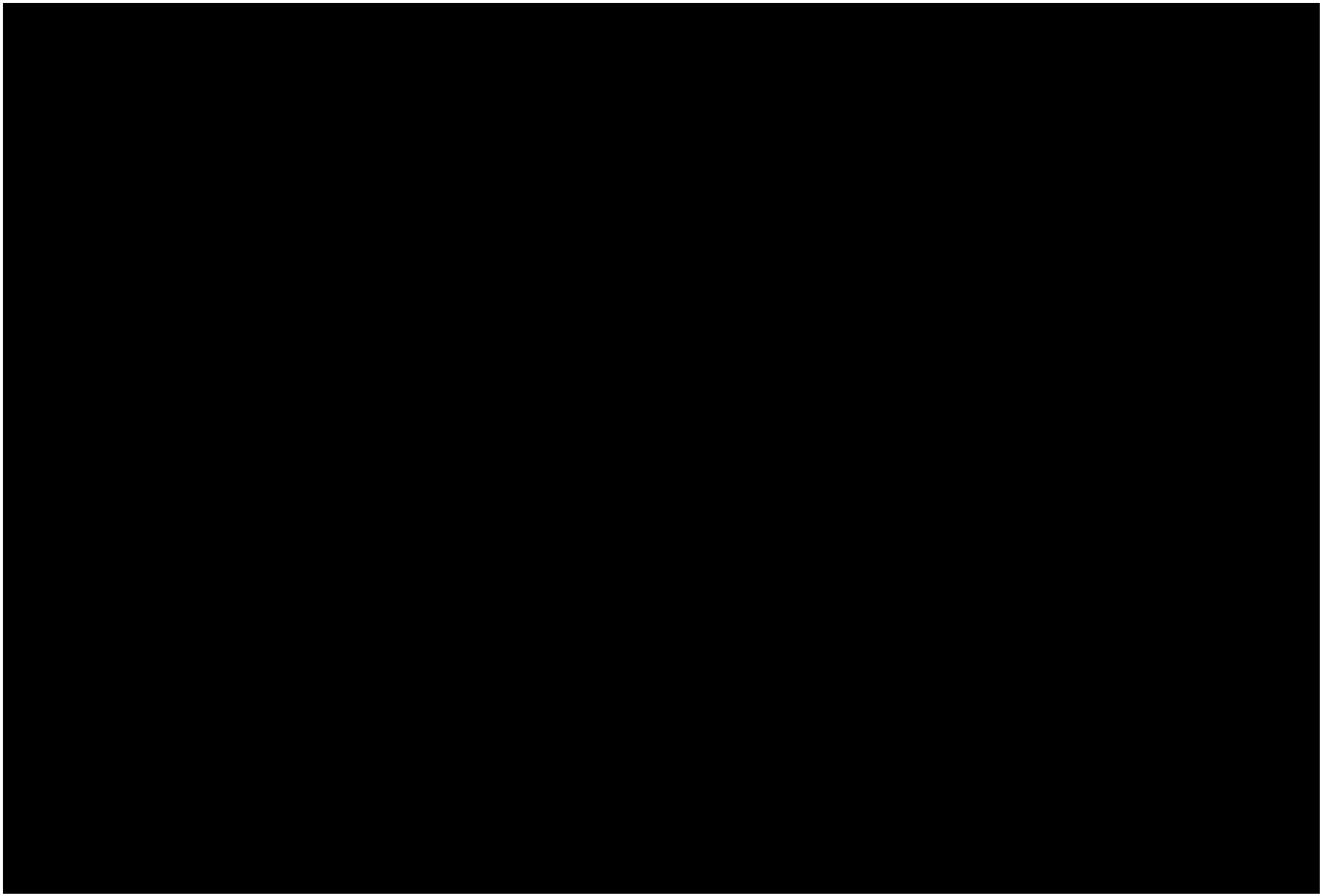
[redacted]

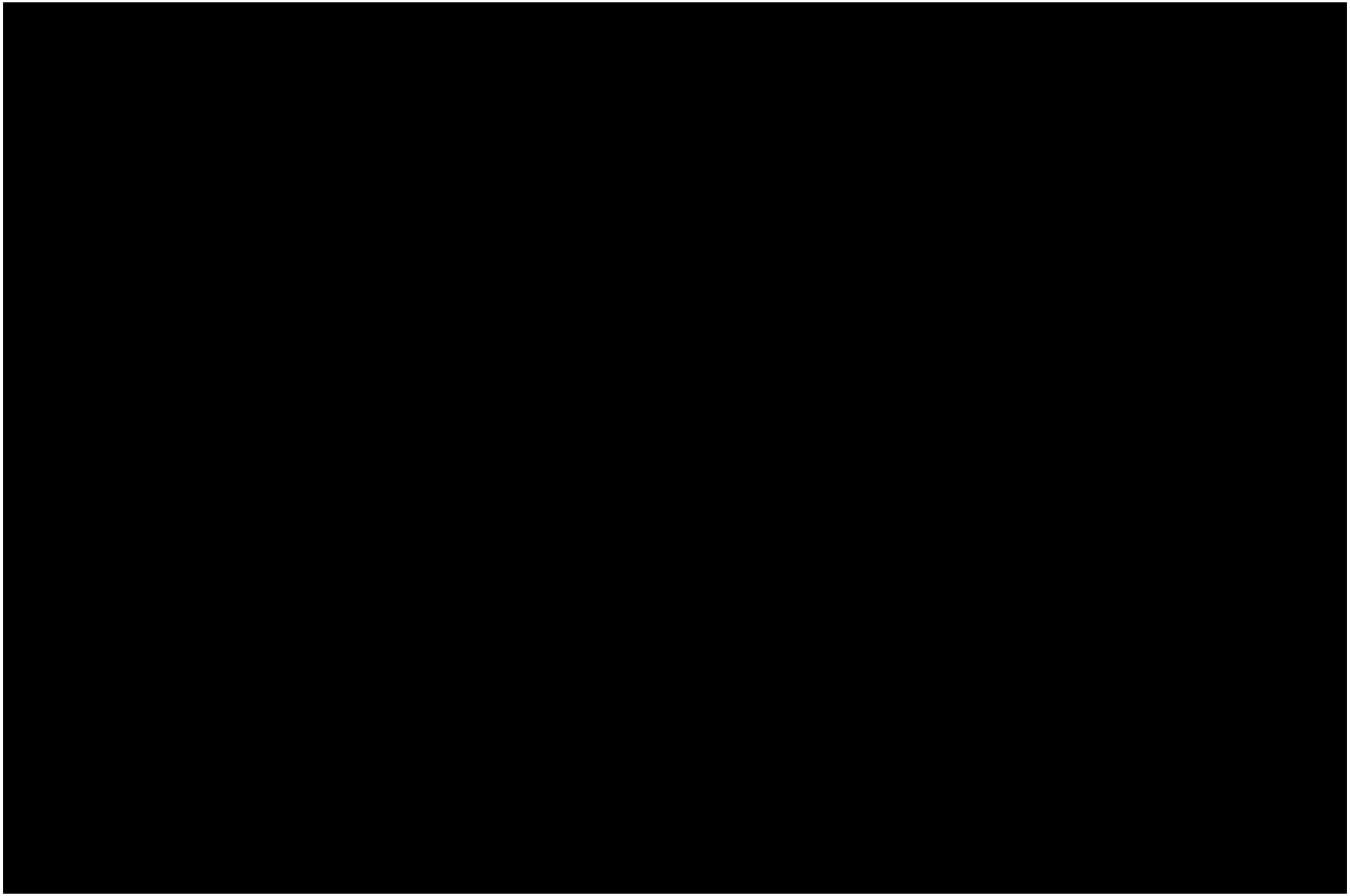
3.5 Assessments

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 and Table 3.3). 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 Visit 1 – Screening Visit – (Day -21 to Day -1)

[redacted]

[redacted]

3.5.2.3 Visit 2 – T1 Baseline Visit – Day 0

[redacted]

3.5.2.4 Treatment 1

3.5.2.4.1 Visit 3 (Treatment 1 – Day 1, Day of SP-102 Injection)

[redacted]

[redacted]

3.5.2.4.2 Visit 4 through Visit 7 – Days 2, 3, 4, and 5

[redacted]

[redacted]

3.5.2.5 Visit 8 (Treatment 1, Day 8 ± 2 days)

[redacted]

3.5.2.6 Visit 9 (Treatment 1, Day 15 ± 2 days)

[redacted]

3.5.2.7 Visit 10 (Treatment 1, Day 28 ± 2 days)

[redacted]

3.5.2.8 Telephone Contact

The subject is to be contacted by telephone weekly to determine the need for the repeat injection (T2). If after 4 weeks from Visit 10, the subject does not need T2, schedule Visit 19/EOS/ET.

3.5.2.9 Visit 11 (Treatment 2 Baseline)

[redacted]

[redacted]

3.5.2.10 Treatment 2

3.5.2.10.1 Visit 12 (Treatment 2 – Day 1, Day of SP-102 Injection)

[redacted]

[redacted]

3.5.2.10.2 Visit 13 through Visit 16 – Days 2, 3, 4, and 5

[redacted]

3.5.2.11 Visit 17 (Treatment 2, Day 8 ± 2 days)

[redacted]

3.5.2.12 Visit 18 (Treatment 2, Day 15 ± 2 days)

[redacted]

3.5.2.13 Visit 19/End of Study/Early Termination (Treatment 2, Day 28 ± 2 days)

[redacted]

3.5.3 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 Visit 19/EOS/ET procedures should be performed. If the ET occurs prior to Visit 10, the subject should be encouraged to continue in the study until Visit 10, if possible. Subjects who do not receive both T1 and T2 will be discontinued from the study and the Visit 19/EOS/ET procedures should be performed. In case of ET, the subject should be encouraged to return to the site for ET procedures, or failing a return visit, a telephone visit should be arranged to encourage the subject to complete the Visit 19/EOS/ET procedures (Section 3.5.2.13).

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 3.3.4.

3.5.4 Pharmacodynamic Assessments

3.5.4.1 Cortisol

Blood is collected to measure the level of the hormone cortisol in the blood, which may indicate problems with the adrenal glands or pituitary gland. Ideally, this test should be performed at 8 am after at least a 10-hour fast; this is not required at Screening. Cortisol will be measured from blood samples collected at Screening, Visit 3 through Visit 10, and Visit 12 through Visit 19. NOTE: The Screening test result is to be compared to the local laboratory normal range for cortisol daily variation.

3.5.4.2 Glucose

A glucose level measures the amount of sugar circulating in the blood. Accurate levels of glucose are measured from blood obtained in a fasting state; therefore, the subject will undergo at least a 10-hour fast prior to this being tested at 8 am; this is not required at Screening. Glucose will be measured at Screening, Visit 3 through Visit 10, and Visit 12 through Visit 19. NOTE: The Screening test result is to be compared to the local laboratory normal range for non-fasted glucose.

3.5.4.3 White Blood Cell Count

The WBC count tabulated the number of WBC circulating in the blood. WBC will be measured at Screening, Visit 3 through Visit 10, and Visit 12 through Visit 19.

3.5.4.4 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). The subject will use the NPRS to record their current pain, average pain in the past 24 hours, and worst pain in the past 24 hours for both their affected leg(s) and back pain. The NPRS will be collected at each study visit.

3.5.4.5 Brief Pain Inventory - Short Form

The BPI-SF (Appendix F) 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 all study visits except Screening.

3.5.5 Safety Assessments

3.5.5.1 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. The Screening physical examination will also include an assessment of lumbosacral radiculopathy. 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. A physical examination will be done at Screening, T1 – Day 0, T1 – Day 28, and T2 – Day 28 (Visit 19/EOS/ET).

3.5.5.2 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 focusing on signs and symptoms of lumbosacral radiculopathy, including straight leg raise test, will be performed according to the checklist (see Appendix G). 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 pre-dose and post dose on T1 – Day 1, pre-dose and post dose on T2 – Day 1, and on T2 – Day 28 (Visit 19/EOS/ET).

3.5.5.3 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 min 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. Vital signs will be recorded at each clinic visit and will be monitored within 15 min prior to the procedure, approximately every 5 min during the procedure (prior to syringe removal), and approximately every 15 min after for 60 min after the procedure. Height (in inches without shoes) and weight (in pounds) will be recorded at Screening. Weight will also be recorded at T1 – Day 0, T1 – Day 28, and T2 – Day 28 (Visit 19/EOS/ET).

3.5.5.4 Electrocardiogram

Standard 12-lead ECGs will be measured in triplicate on the site machines after the subject has been supine for at least 5 min at Screening, Baseline, T1 – Day 28, and T2 – Day 28 (Visit 19/EOS/ET). The ECG results will be documented in the eCRF.

3.5.5.5 Laboratory Parameters

The following clinical laboratory tests are to be performed at Screening, Baseline, T1 – Day 5, T1 – Day 28, T2 – Day 5, and T2 – Day 28 (Visit 19/EOS/ET) unless noted below:

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

Serum 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 or Baseline: 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, and T1 – Day 28. A urine drug screen may be repeated if deemed necessary by the Investigator.

WOCBP: Serum pregnancy test at Screening. Urine pregnancy test at Baseline and at Visit 11 (T2 – Day 0). A urine pregnancy test may be repeated if deemed necessary by the Investigator.

Laboratory samples will be analyzed by the local laboratory. 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.

3.5.5.6 Adverse Events

All AEs occurring after the subject signs the ICF through EOS/ET (Visit 19) will be recorded.

See Section 4 for additional information.

3.5.6 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-1994). 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-2017). 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 H) 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 H.

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 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 AEs occur at a time after the procedure that are attributable (ie, possibly related or related) to IP should be reported in the eCRF and Medical Monitor is to be contacted immediately and the reporting procedures for SAEs is to be followed (Section 4.2.3):

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

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 Institutional Review Board (IRB) according to its standard operating procedures.

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]
- [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 Semnur confirming that the subject is lost to follow-up. SAEs that are ongoing at EOS 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.

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 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. 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

In an effort to streamline and modernize this clinical investigation in accordance with FDA's Electronic Source Data in Clinical Investigations Guidance for Industry (Food and Drug Administration), this trial promotes capturing source data in electronic form via DDE into eCRFs. This real-time electronic data capture is intended to eliminate unnecessary duplication of data, reduce the possibility for transcription errors, encourage entering source data during subject visits, eliminate transcription of source data into an eCRF, facilitate remote monitoring of data, promote real-time access for data review, and facilitate the collection of accurate and complete data.

For data entered directly into eCRFs, the eCRF is source. If a paper transcription or separate electronic source step is used such as for subject-facing rating scales, then the paper or other electronic documentation should be retained and made available for monitoring. Study data in this protocol will be source verified only if paper transcription or separate electronic source precede eCRF DDE.

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 Analysis Methods

No formal statistical hypothesis testing will be performed in this study, however descriptive statistics will be presented.

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to treatments T1 or T2 (reference start date). This includes screening or unscheduled assessments that would have been performed no earlier than 21 days before the reference start date.

In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-reference, but AEs and medications commencing on the reference start date will be considered post-reference.

For vital signs parameters, an assessment performed on reference start date with time point marked as "pre-dose" will be considered as baseline.

For cortisol suppression, glucose, and white blood cell counts, baseline is defined as the last non-missing value obtained prior to T1 or T2, which is T1/T2 Day 1 pre-dose measurement.

For NPRS, baseline is defined as the last non-missing value obtained prior to T1 or T2, which is T1/T2 Day 0 measurement.

Details on definition of baseline and calculations for the change and percent change in PD values will be defined in detail in the SAP.

5.2.4 Analysis Populations

The Safety Analysis population is defined as all enrolled subjects who receive at least one SP-102 injection.

The PD Analysis population is defined as all enrolled subjects who have a T1 period baseline PD result and at least 1 postdose PD assessment result without any protocol deviations available in either T1 or T2.

The Complete Analysis population is defined as all enrolled subjects who receive only one SP-102 injection who complete T1 – Day 28 plus those subjects who receive two SP-102 injections who complete T2 – Day 28.

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

- Entered the study even though they did not satisfy the entry criteria;
- Developed withdrawal criteria during the study but were not withdrawn;
- Received the incorrect dose;
- Received an excluded concomitant treatment.

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

5.2.5 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.

5.2.6 Pharmacodynamic Endpoints

- Dexamethasone-induced HPA suppression as measured by:
    - Observed total blood cortisol levels, change from baseline cortisol levels, and percent change from baseline cortisol levels
    - Observed glucose levels, change from baseline glucose levels, and percent change from baseline glucose levels
    - Observed white blood cell counts, change from baseline white blood cell counts, and percent change from baseline white blood cell counts
- NPRS (average leg pain and back pain) and BPI-SF
- Change from T1 Day 0 and T2 Day 0 through Day 28 in NPRS (average leg pain and back pain) and BPI-SF over time following the index (T1) and repeat (T2) epidural injections, respectively
- Percent change from T1 Day 0 and T2 Day 0 through Day 28 in NPRS (average leg pain and back pain) and BPI-SF following the index (T1) and repeat (T2) epidural injections, respectively

5.2.7 Pharmacodynamic Analyses

All PD analyses will use the PD population as the primary analysis population.

Cortisol levels, WBC counts, and fasting blood glucose levels (observed, change from baseline, and percent change from baseline) will be summarized by treatment and measurement time using descriptive statistics. Dexamethasone-induced HPA suppression will be evaluated by using the observed total plasma cortisol level, blood glucose levels, and WBC count. Other PD analyses may be performed as appropriate. For these PD endpoints, the pre-dose morning values will be determined for each subject as a Baseline for each treatment and the data will be presented as observed value, change from baseline, and as a percent of Baseline value.

The following pain-score endpoints will be summarized over time by treatment using descriptive statistics:

- NPRS (average leg pain and back pain) and BPI-SF
- Change from T1 Day 0 and T2 Day 0 through Day 28 in NPRS (average leg pain and back pain) and BPI-SF over time following the index (T1) and repeat (T2) epidural injections, respectively
- Percent change from T1 Day 0 and T2 Day 0 through Day 28 in NPRS (average leg pain and back pain) and BPI-SF following the index (T1) and repeat (T2) epidural injections, respectively

For blood cortisol and glucose levels, and WBC counts (change-from-baseline), PD parameters, ie, area under the effect curve over 28 days ($AUEC_{28\ days}$) and maximum effect (E_{max}) following the T1 (index) and T2 (repeat) injections will be calculated.

$AUEC_{28\ days}$ is defined as the change from baseline (for cortisol, glucose, and WBC) and calculated using linear trapezoidal summation from pre-dose to Day 28 in each treatment period. E_{max} is the baseline-adjusted maximum increase in glucose level and WBC count or the maximum decrease in cortisol levels over the 28 days post dose in each treatment period.

The PD parameters will be analyzed using a mixed model analysis of variance using PROC MIXED with a fixed effect for treatment and a random effect for subject. Estimates and 90% confidence intervals (CIs) will be first constructed in the logarithmic scale. By taking anti-logarithms, estimates and CIs for the geometric means and ratios of geometric means will be calculated. All CIs will be 2-sided.

A lack of effect of repeat injection on the PD will be concluded if the 90% CIs for the ratio of T2 (repeat injection; Test) to T1 (index; Reference) for both $AUEC_{28\ days}$ and E_{max} are completely contained within the range of 80 to125%.

5.2.8 Safety Analyses

Safety endpoints are as follows:

- Incidence of treatment-emergent adverse events (TEAEs) and SAEs
- Change from baseline in clinical laboratory parameters, vital sign measurements, ECG findings, physical examination, general neurological examination findings, and targeted neurological examination findings following each treatment

5.2.8.1 Adverse Events

All AEs will be coded using the most current version of MedDRA. TEAEs and SAEs will be summarized descriptively for each treatment.

5.2.8.2 Laboratory Data

Mean changes from Baseline 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.

5.2.8.3 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

5.2.8.4 Electrocardiographic Data

A listing of 12-lead ECG parameter results will be presented. Shifts in ECG parameters will be summarized by treatment group from Screening to each post dose visit at which ECG assessments are obtained.

5.2.8.5 Physical Examination Findings

Shifts in physical examination findings will be summarized by treatment group from Screening to each post dose visit at which a physical examination was performed.

5.2.9 Interim Analyses

No interim analysis is planned for this study.

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) (ICH-E6-1996), 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 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

As a multicenter trial, the sponsor intends to publish clinical data from all centers participating in the investigation. A publication committee selected by the sponsor will submit draft manuscripts to all participating investigators for their comments. In conformity with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals published by the International Committee of Medical Journal Editors, investigators whose contribution consists solely in the collection of data will not be named individually as authors (Kassirer-1991). Rather, those investigators will receive a collective authorship and will be identified in a note.

Individual investigators and/or their associates subsequently may publish additional findings of this study in scientific journals or present them at scientific meetings, if the sponsor is given ample opportunity to review any proposed abstract, manuscript, or slide presentation before its submission. This review is required to ensure that the sponsor is aware of all written and oral presentations of the data and does not imply any editorial review or restriction of the contents of the presentation or use.

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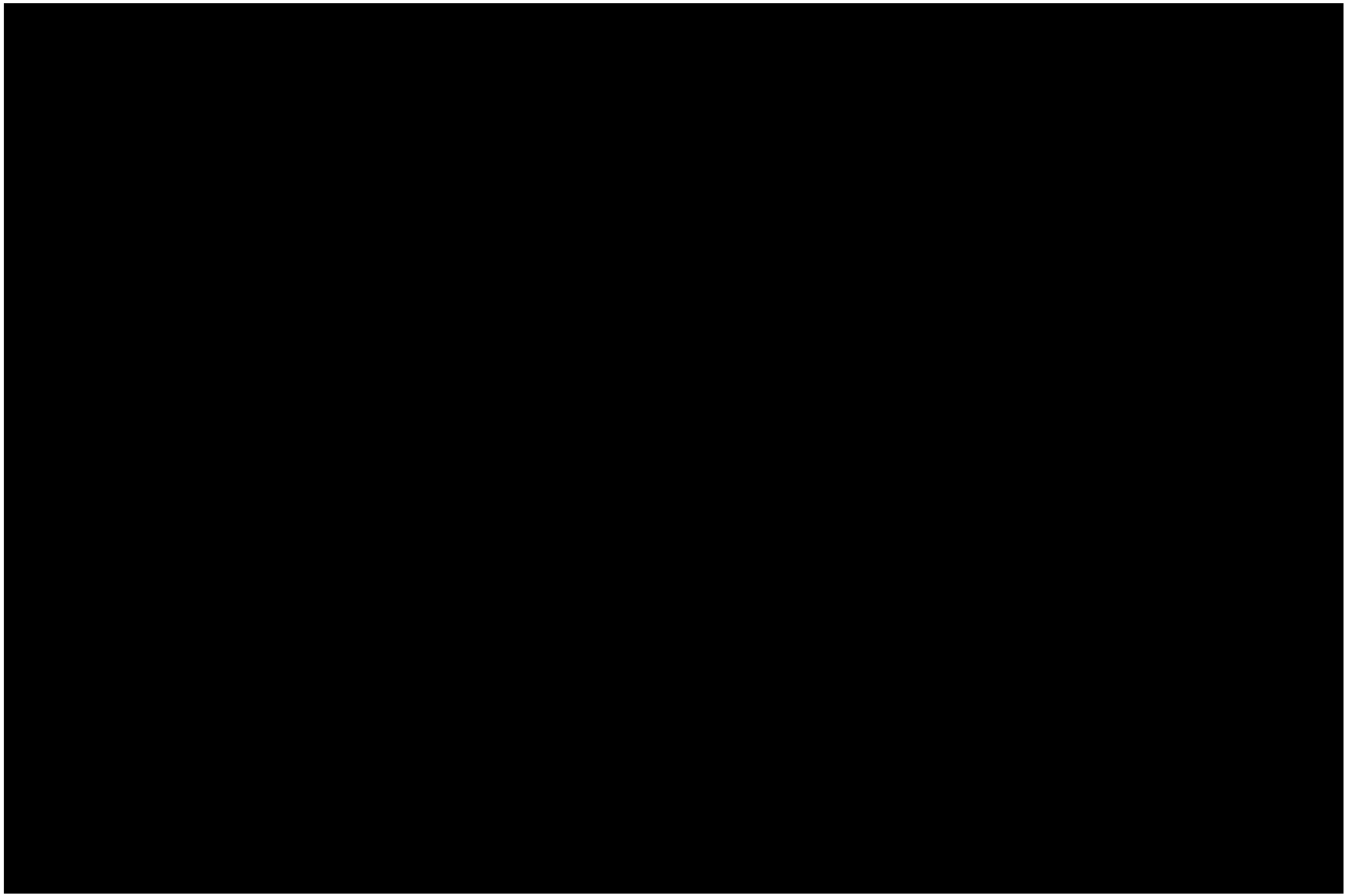
8 APPENDICES

Appendix A BMI Table



Appendix B Cockcroft-Gault Equation

[redacted]

Appendix C Morphine Equivalents

Appendix D Instructions for Study Drug Injection

You should follow CDC communications III.A.1.c. Infection Control Practices for Special Lumbar Puncture Procedures. In general, the procedure should be sterile and face masks should be used.

[redacted]

2. **Collect vital signs.** [redacted]
3. **Prepare study subject for injection.** [redacted]
4. **Obtain IP kit.** [redacted]
5. **Prepare for injection.** [redacted]
6. **Inject IP.** [redacted]

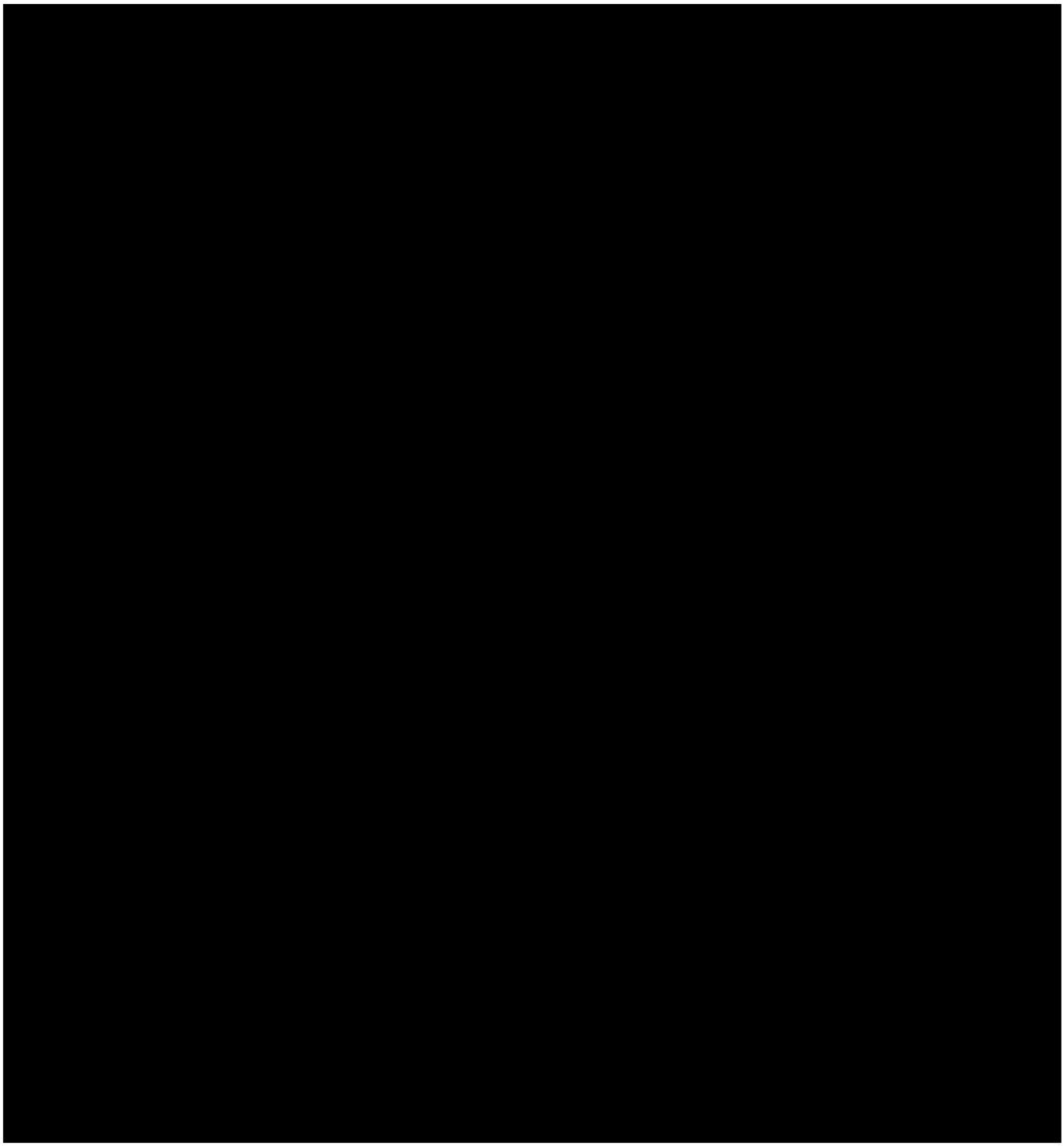
a. **Confirm correct positioning of the needle** [redacted]

b. **Capture and save fluoroscopic images of:** [redacted]

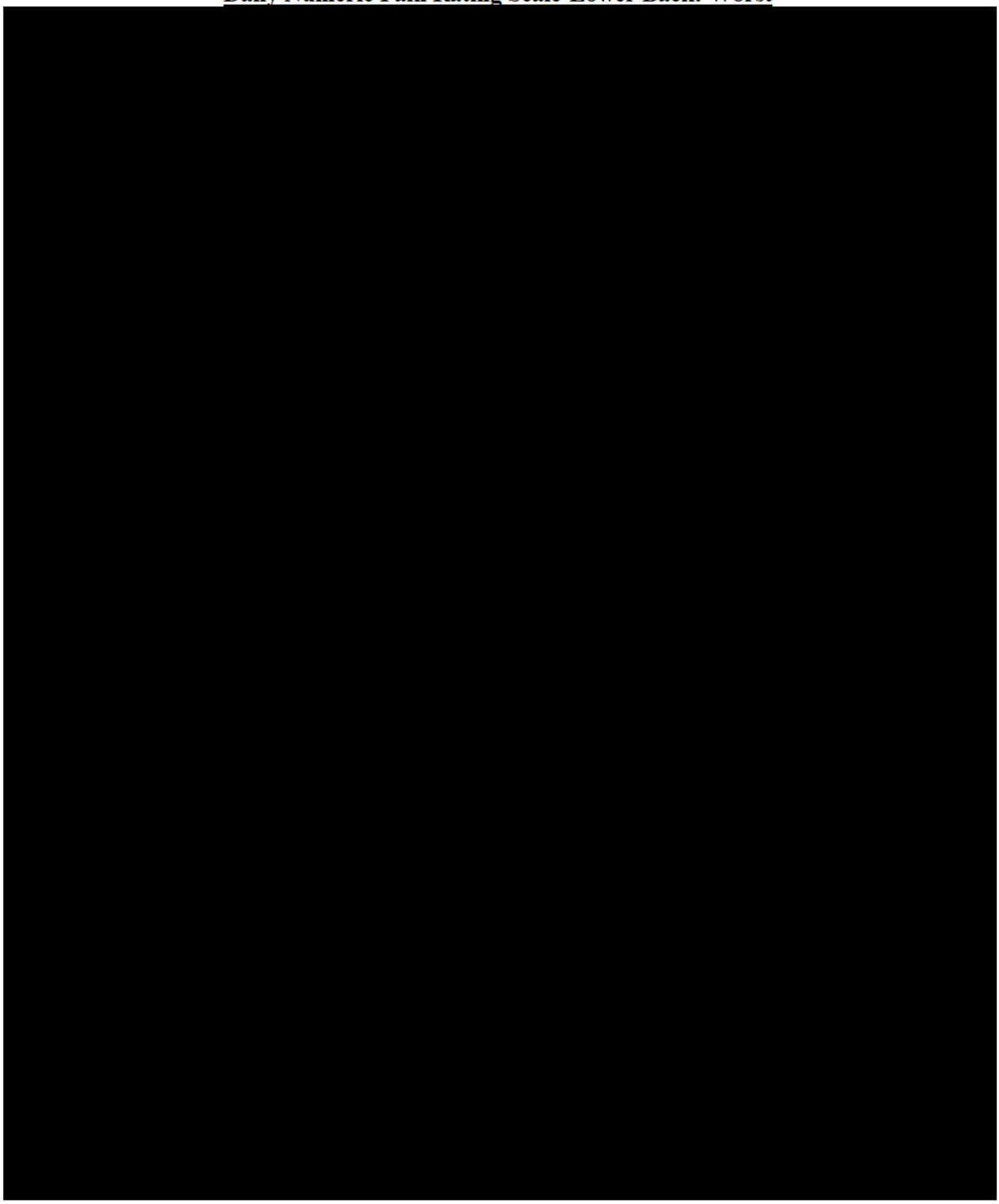
7. **Label study materials.** [redacted]

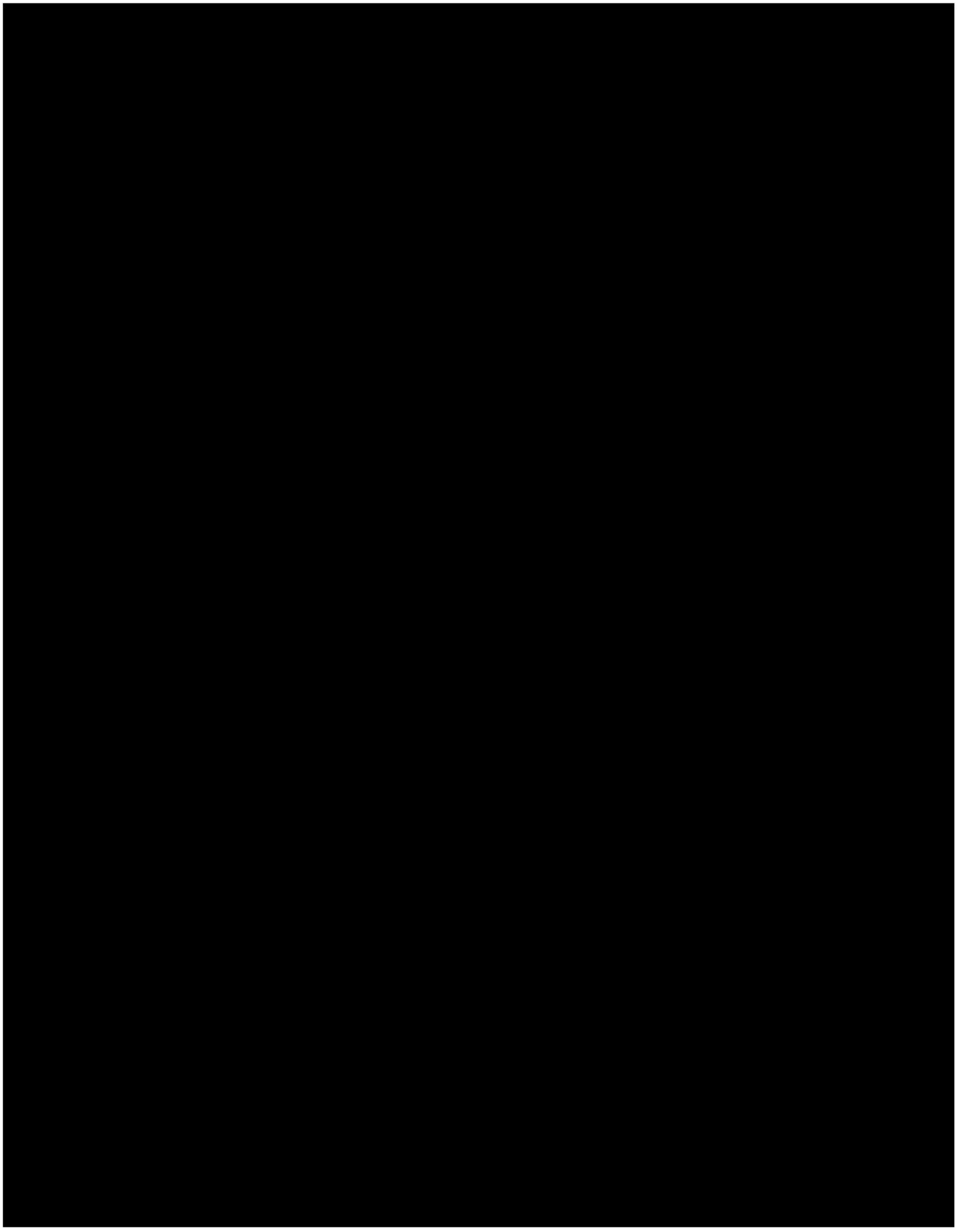
8. **Observe study subject post-injection and discharge.** [redacted]

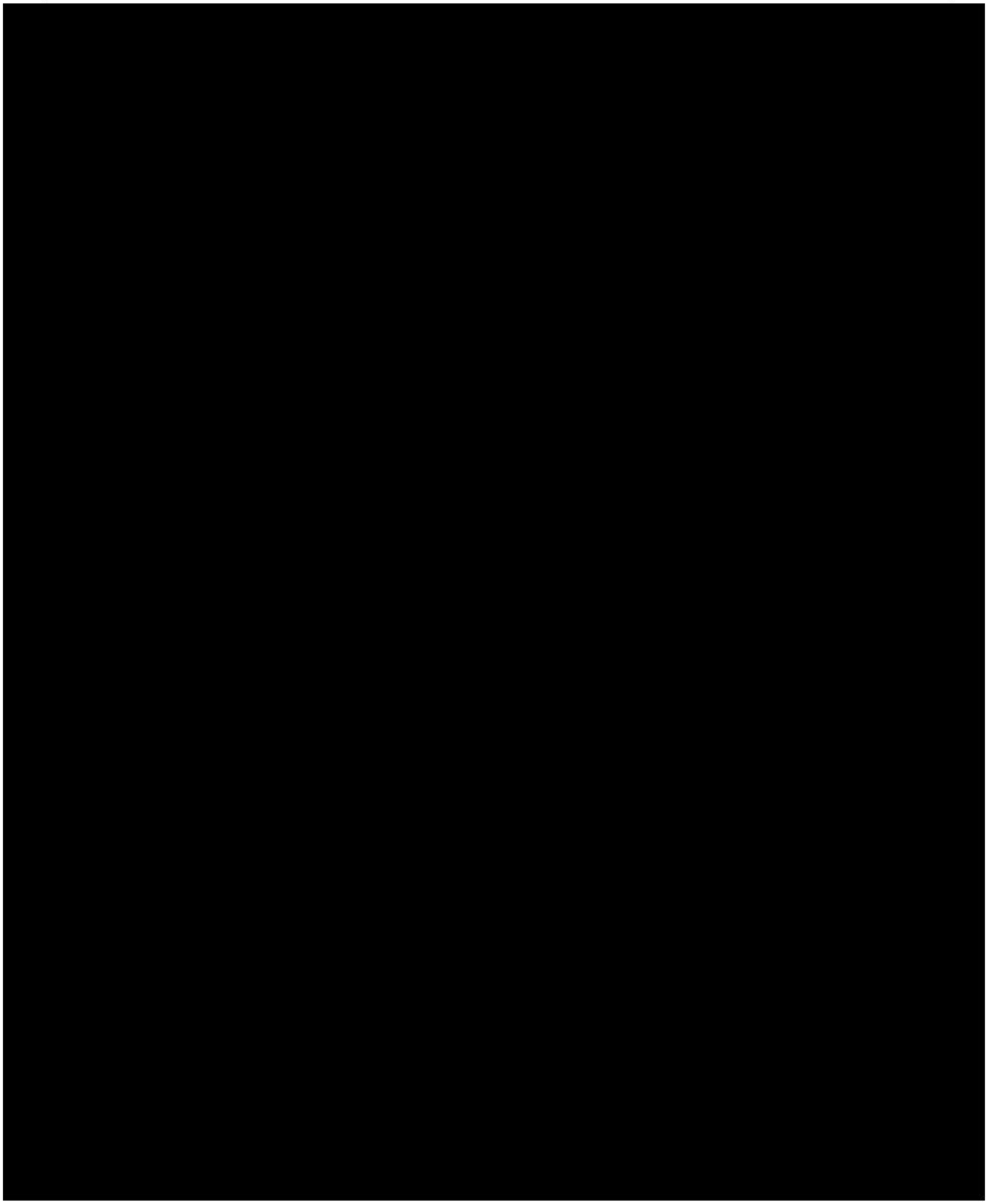
Appendix E Numeric Pain Rating Scale



Daily Numeric Pain Rating Scale-Lower Back: Worst







Appendix G Targeted Neurological Exam

Area of Assessment	Response		
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Appendix H Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review at 301-827-3070.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
September 2007

Contains Nonbinding Recommendations

Table of Contents

Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

Preventive vaccines are usually developed to prevent disease in a healthy population. The Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, regulates preventive vaccines under authority of section 351 of the Public Health Service Act (42 U.S.C. 262), as well as specific sections of the Federal Food, Drug, and Cosmetic Act, and reviews investigational new drug applications (INDs) and biologics license applications (BLAs). (See, for example, Title 21 Code of Federal Regulations (CFR) Parts 312, 600, and 601). Most of the clinical trials of preventive vaccines conducted to support INDs and BLAs enroll healthy volunteers in all phases of vaccine testing. The enrollment of healthy volunteers warrants a very low tolerance for risk in those clinical trials.

This guidance provides you, sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials. The grading system described in the table can also be useful in defining a particular study's stopping rules (e.g., a certain number of adverse events, as defined in the table, may call for stopping the study). Less extreme observations (e.g., mild) may not require discontinuing the study vaccine but can still contribute to evaluating safety by identifying parameters to focus upon in subsequent product development. Uniform criteria for categorizing toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies. We, FDA, recommend using toxicity grading scale tables, provided below, as a guideline for selecting the assessment criteria to be used in a clinical trial of a preventive vaccine. We recommend incorporation of such appropriate, uniform, criteria into the investigational plan, case report forms, and study reports and correspondence with FDA, sponsors, monitors, investigators, and IRBs.

This guidance finalizes the draft guidance of the same title dated April 2005 (70 FR 22664, May 2, 2005).

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FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Standardized toxicity assessment scales have been widely used to evaluate products treating specific diseases. For example, the National Cancer Institute's Common Toxicity Criteria Scale and the Division of AIDS' Toxicity Grading Scale standardize the evaluation of adverse events among patients with cancer and HIV/AIDS, respectively (Refs. 1, 2). The defined toxicity parameters in those scales are designed for patients who may already experience mild, moderate, or severe adverse clinical or laboratory events due to the disease process, and may not be appropriate for healthy volunteers.

In the development of the toxicity grading scales for healthy volunteers, we chose parameter limit values based on published information, when such values were available (Refs. 1-6). For example, the Brighton Collaboration has developed case definitions and guidelines to evaluate some adverse events associated with administering vaccines (Ref. 3). In some cases, parameter limit values were based on clinical experience and experience reviewing vaccine clinical trials that enroll normal healthy subjects.

Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterization of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values.

III. TOXICITY GRADING SCALE TABLES

Adverse events in a clinical trial of an investigational vaccine must be recorded and monitored and, when appropriate, reported to FDA and others involved in an investigation (sponsors, IRBs, and investigators). (See, for example, 21 CFR 312.32, 312.33, 312.50, 312.55, 312.56, 312.60, 312.62, 312.64, 312.66). Although the use of a toxicity grading scale for adverse events would not replace these regulatory requirements, using a scale to categorize adverse events observed during a clinical trial may assist you in monitoring safety and making required reports. Nonetheless, we believe that categorization or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis.

These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers. The parameters in the tables below are not necessarily applicable to every clinical trial of healthy volunteers. The parameters monitored should be appropriate for the specific study vaccine. For some preventive vaccines under development, it may be appropriate

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to include additional parameters to be monitored during a clinical trial or to alter the choice of values in the toxicity table. For example, additional parameters might be added based on one or more of the following: safety signals observed in pre-clinical toxicology studies, the biological plausibility of the occurrence of certain adverse events, or previous experience with a similar licensed product.

As discussed above, the tables do not represent a recommendation to monitor all the listed parameters in all clinical trials of healthy volunteers, nor do the tables represent all possible parameters to be monitored. In addition, these tables do not represent study inclusion or exclusion criteria. We recommend that the parameters monitored be appropriate for the study vaccine administered to healthy volunteers participating in the clinical trial.

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

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Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

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Systemic Illnes	Mild (Grade 1)	(Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

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B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Contains Nonbinding Recommendations

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

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** "ULN" is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Contains Nonbinding Recommendations

IV. REFERENCES

1. National Cancer Institute Common Toxicity Criteria, April 30, 1999. (http://ctep.cancer.gov/reporting/CTC-3.html)

2. Division of AIDS Table for Grading Severity of Adult Adverse Experiences; August 1992. (http://rcc.tech-res-intl.com/tox_tables.htm)

3. The Brighton Collaboration. Finalized Case Definitions and Guidelines. (http://brightoncollaboration.org/internet/en/index/definition___guidelines.html)

4. HIV Vaccine Trials Network Table for Grading Severity of Adverse Experiences; September 18, 2002. (http://rcc.tech-res-intl.com/tox_tables.htm)

5. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, December 2004. (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/Safety/DAIDSAEGradingTable.pdf)

6. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory Reference Values. New England Journal of Medicine. 2004;351:1548-1563.