Clinical Study Protocol

Protocol Title:	A Multicenter, Randomized, Double-blind, Sham-controlled, Comparative Study of SI-6603 in Subjects with Lumbar Disc Herniation (Phase 3)
Protocol Number:	6603/1133
Study Phase:	Phase 3
Investigational Product:	SI-6603
IND Number:	100,398
Sponsor:	Seikagaku Corporation 6-1, Marunouchi 1-chome Chiyoda-ku, Tokyo 100-0005, Japan
Date of Protocol:	14, February 2020
Version Number:	7.0
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LIST OF STUDY PERSONNEL

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SIGNATURE PAGE

Declaration of Sponsor

Title: A Multicenter, Randomized, Double-blind, Sham-controlled, Comparative Study of SI-6603 in Subjects with Lumbar Disc Herniation (Phase 3)

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product (SI-6603 or control [sham injection]), as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the guidelines on Good Clinical Practice.

_____ _____

Yosuke Funakoshi Date
Executive Vice President, Clinical Development Department
Research and Development Division
Seikagaku Corporation

Declaration of the Principal Investigator

Title: A Multicenter, Randomized, Double-blind, Sham-controlled, Comparative Study of SI-6603 in Subjects with Lumbar Disc Herniation (Phase III)

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. Documentation includes this study protocol, investigator's brochure, case report form, and other scientific documents or data.

The study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB, except where necessary to eliminate an immediate hazard to the subjects.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Principal Investigator

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

SYNOPSIS

Protocol Title:	A Multicenter, Randomized, Double-blind, Sham-controlled, Comparative Study of SI-6603 in Subjects with Lumbar Disc Herniation (Phase 3)
Protocol Number:	6603/1133
Investigational Product:	SI-6603
Study Phase:	Phase 3
Objectives	
Primary Objective:	The primary objective is to evaluate the effectiveness of a single-dose intervertebral disc injection of SI-6603 at a dose of 1.25 units (U) compared to control in subjects with lumbar disc herniation (LDH) by comparing the change in worst leg pain during the past 24 hours, as assessed by visual analogue scale (VAS), from baseline to Week 13 after injection of the investigational product.
Secondary Objectives:	The secondary objectives are to evaluate the efficacy of SI-6603 1.25 U for key secondary endpoints, and to demonstrate whether SI-6603 1.25 U is safe and well tolerated.
Overall Study Design	
Study Design:	This is a multicenter, randomized, double-blind, sham-controlled, comparative study. The study duration for each subject will be approximately 56 weeks: a 4-week screening period, a 1-day treatment administration day, and a 52-week follow-up period.
Dosage/Dose Regimen:	Subjects randomized to the SI-6603 treatment group will receive a single-dose injection of SI-6603 1.25 U into an intervertebral disc. Subjects randomized to the control group will receive a sham injection (the needle will not be placed in the disc).
Duration of Treatment:	Single injection
Planned Number of Subjects:	It is planned to enroll approximately 320 subjects, 160 in the SI-6603 group and 160 in the control group.

Study Population	
Summary:	The study population will consist of male and female subjects, 30 to 70 years of age (inclusive) at the time of informed consent, with single-level LDH (L4-L5 or L5-S1 (or L5-L6)) with clear, demonstrable nerve root impingement as assessed by magnetic resonance imaging (MRI) and clinical symptoms corresponding to position of the impaired nerve root.
Criteria for Evaluation	
Efficacy Assessments:	**Primary:** The primary endpoint is the change from baseline to Week 13 in average worst leg pain score during the past 24 hours over the previous 7 days, as assessed by 100 mm VAS. **Key Secondary:** The key secondary endpoints include the following: 1) Change from baseline to Week 13 in herniation volume 2) Change from baseline to Week 13 in Oswestry Disability Index (ODI) score 3) Change from baseline to Week 52 in average worst leg pain score during the past 24 hours over the previous 7 days, as assessed by 100 mm VAS. **Secondary:** Additional secondary endpoints are described in the full protocol.
Safety Assessments:	The following safety endpoints will be assessed after investigational product administration: • Adverse events • Laboratory tests • Vital signs • Imaging assessment by X-ray and MRI - Disc height (disc index) - Vertebral body translation - Vertebral body angle formed by flexion

	- Modic classification • Occurrence of post-treatment lumbar surgery - Surgery for treatment of LDH at a different level than administration of the investigational product - Lumbar surgery not for treatment of LDH
Statistical Methods:	The change from baseline in the worst leg pain scores will be analyzed by a mixed model for repeated measures (MMRM) analysis for Week 1 through Week 52 in the modified intention-to-treat (mITT) population. The average worst leg pain scores over the previous 7 days will be analyzed at Week 1, 2, 4, 6, 13, 26, 39, 52. The primary comparison will be the mean change from baseline of the SI-6603 group at Week 13 compared with the control group, estimated using this model. The model will include the baseline worst leg pain score, treatment, time, treatment-by-time interaction, and duration of leg pain as fixed effects. An unstructured covariance will be used to model the covariance structure among repeated measures. Should the model fail to converge with the type = UN option, a compound symmetry structure will be used. Kenward-Roger method will be used for computing the denominator degrees of freedom. The missing data will be implicitly handled via a mixed-effect model, without explicit imputation. Statistical methods for key secondary endpoints and adjustment for multiplicity are described in the full protocol.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CTCAE	Common Terminology Criteria for Adverse Events
EQ-5D-5L	EuroQol Group 5-Dimension Quality of Life instrument, 5-level version
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference for Harmonisation
IWRS	Interactive Web Response System
IRB	Institutional Review Board
mITT	modified Intention-to-treat
LDH	Lumbar Disc Herniation
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures

MRI	Magnetic Resonance Imaging
NF	National Formulary
NIAID/FAAN	National Institute of Allergy and Infectious Disease Food Allergy and Anaphylaxis Network
NSAID	Non-steroidal Anti-inflammatory Drug
ODI	Oswestry Disability Index
PGIC	Patient Global Impression of Change
PP	Per-Protocol
QOL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-36	36-item Short Form Health Survey
SLR	Straight Leg Raise
TEAE	Treatment-emergent Adverse Event
TEAESI	Treatment-emergent Adverse Events of Special Interest
ULN	Upper Limit of Normal
USP	United States Pharmacopoeia
VAS	Visual Analogue Scale
WPAI	Work Productivity and Activity Impairment Questionnaire

1 INTRODUCTION

1.1 Background

Lumbar disc herniation (LDH) occurs as a result of a protrusion or prolapse of the nucleus pulposus of an intervertebral disc into the spinal canal following partial or complete perforation and destruction of the posterior annulus fibrosus. The nucleus pulposus compresses the spinal and nerve root, causing symptoms including leg pain, low back pain, and numbness.[1] The principal treatment for LDH is conservative, resulting in a response in approximately 90% of patients.[2, 3] Conservative treatment includes rest, bed rest, medication (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], steroids, and muscle relaxants), corset, traction therapy, thermotherapy, epidural block, nerve root block, and physical therapy. Surgical treatment is an option for approximately 20% to 50% of the patients who do not respond to conservative treatment.[4, 5] To minimize the invasiveness of surgical procedures, new treatment approaches have become available, including chemonucleolysis, percutaneous nucleotomy, percutaneous laser disc decompression, and microendoscopic discectomy.

Chemonucleolysis alleviates the symptoms of LDH using an enzyme, which is injected into the relevant intervertebral disc to reduce nerve root compression through lysis of the nucleus pulposus and reduction of disc pressure.[1] Chemonucleolysis is a valuable treatment for patients who do not respond to other conservative treatments, those with severe disorders, and those who are candidates for surgery, and it is currently positioned as a minimally invasive option after conservative treatment has failed and as an alternative to invasive surgery.[6, 7] Although chymodiactin (chymopapain) is approved in the United States (US) as a drug for chemonucleolysis, the neurological adverse events (AEs) due to its protease activity have been problematic.[1, 8] Therefore, development of drugs that are highly specific to the nucleus pulposus alone and that do not influence nerve tissue surrounding the disc is needed for safe and effective chemonucleolysis.

Condoliase is a glycosaminoglycan-decomposing enzyme isolated and purified from a gram-negative rod, *Proteus vulgaris*.[9] In LDH, Condoliase is thought to decompose glycosaminoglycan chains, thereby relieving disc pressure and compression on the spinal nerve root. In addition, Condoliase has the potential advantage of minimizing AEs, such as nerve tissue injuries in the area surrounding intervertebral discs, due to its substrate specificity[10] and lack of protease activity when compared with chymopapain. Seikagaku Corporation (SKK) is developing SI-6603, a lyophilized injectable drug containing Condoliase as the active ingredient for treating LDH. The phase 1/2 study (Study Number: SKK6603J01), phase 2/3 study (Study Number: 6603/1021), and phase 3 study (Study Number: 6603/1031) and a follow-up study after completion of the phase 2/3 and phase 3

studies (Study Number: 6603/10R2) have been completed in Japan, and a phase 2 study (Study Number: 6603/1121) and a phase 3 double blind study (Study Number: 6603/1131) have been completed in the US, and also a phase 3 open label study (Study Number: 6603/1132) has been completed in the US and EU.

1.1.1 Summary of Clinically Significant Findings Obtained in Nonclinical Studies and Clinical Studies

A summary of nonclinical studies and prior clinical studies of SI-6603 can be found in Section 1 in the current edition of the investigator's brochure (IB), which contains comprehensive information about SI-6603.

1.1.2 Current Study

The current study is a Phase 3, multicenter, randomized, double-blind, sham-controlled, comparative study of SI-6603 in subjects with LDH. Subjects will receive a single intradiscal dose of SI-6603 1.25 U or a sham injection as control. Safety will be followed for 12 months after investigational product administration.

1.2 Risk and Benefit

1.2.1 Possible Risks

1.2.1.1 Allergic Reactions

SI-6603 is a foreign protein, so it has the potential to cause anaphylaxis or severe allergic reaction. AEs such as asthma, dermatitis, drug eruption, drug hypersensitivity, eosinophil count increased, erythema, flushing, hand dermatitis, hypersensitivity, injection site rash, pruritus, pruritus generalized, rash, rash erythematous, rash generalized, rash pruritic, and swelling face were observed in previous clinical studies. Anaphylaxis has been reported in post-marketing use of SI-6603.

1.2.1.2 Back Pain

The most frequently reported treatment-related AE in previous studies was back pain. Occurrence of back pain is likely to be influenced by the primary disease; however, back pain occurring soon after administration of SI-6603 may be attributable to nucleus pulposus degradation. There are 2 potential mechanisms for this: 1) an increase in intervertebral disc pressure immediately after injection of SI-6603, and 2) pain associated with changes in disc height leading to pain from associated vertebral end plates and facet joints.

1.2.1.3 Decrease of Lumbar Disc Height and Change in Bone Marrow Adjacent to Vertebral Endplates

In past studies with SI-6603 administration, treatment-related AEs of nuclear magnetic resonance imaging (MRI) abnormal (change in bone marrow adjacent to vertebral endplates; Modic change), spinal X-ray abnormal (such as intervertebral posterior angle dilation), and 30% decrease of disc height were observed. The clinical significance of Modic changes remains unclear, and past SI-6603 studies did not reveal any increase in leg pain or back pain in conjunction with Modic changes.

1.2.1.4 Radiation

Risks associated with radiological imaging are well quantified.[11] The effective radiation dose from each radiograph performed in this study is as follows:

During screening or follow-up visits:

- lateral lumbar spine: 0.290 millisievert (mSv)
- anteroposterior lumbar spine: 0.690 mSv

The total radiation dose for each screening or follow-up visit is 1.560 mSv, for a total of 4.7 mSv for 3 of these visits during the study.

During the injection procedure:

- 1.25 mSv (varies depending on procedure of each site)

X-ray imaging and the use of fluoroscopy may cause burns ranging in severity from skin reddening to ulcers, loss of hair in the procedural area, and delayed development of neoplasia. The overall radiation dose for this study is within the reasonable amount, so the risks associated with study-related radiation for this study are acceptable.

1.2.1.5 Intradiscal Injection

Temporary discomfort, injection site pain, bleeding, vascular damage, bruising, vagal reaction, nerve damage, disc damage, and/or infection at the injection site may occur due to the injection procedure. These events may also occur for the sham injection procedure even if the needle is not be inserted into the disc space and no placebo is injected.

1.2.1.6 Opioid Dependence

There is a risk that subjects who are prescribed opioid rescue could become dependent on the study-provided opioid, which could lead to cravings for or seeking opioids beyond those required during the study. The study minimizes this risk in several ways. First, only subjects

who were previously on opioids will be prescribed hydrocodone/acetaminophen as a rescue medication. Second, the subject will be limited to 60 tablets across 52 weeks. Third, investigators will be monitoring labs and having discussions with subjects to identify signs of addiction or abuse.

1.2.2 Possible Benefits

Nonclinical data suggest SI-6603 appears to decrease pressure in the intervertebral disc by reducing the high water-holding capacity of proteoglycans, leading to a volume reduction of the herniated disc material and a consequent reduction of pressure on the nerve root. Clinical data suggest that a single administration of 1.0 mL of the 1.25 U/mL, 2.5 U/mL, or 5.0 U/mL formulations of SI-6603 injected into the intervertebral disc relieved leg pain, the major complaint of patients with LDH. In the Japanese phase 2/3 and phase 3 studies, administration of SI-6603 1.25 U/mL demonstrated clinically significant improvement of leg pain and favorable improvement of back pain in LDH patients with contained-type hernia (unruptured posterior longitudinal ligament) who failed to improve after undergoing conservative treatment for a period of more than 6 weeks.

1.2.2.1 Improvement of LDH Symptoms

In the Japanese Phase 3 study, statistically significant differences were observed in the Least Squares (LS) mean change from baseline in worst leg pain at Week 13 in the 1.25 U dose group compared with the placebo group (-49.5 mm in 1.25 U group and -34.3 mm in placebo group on a 100 mm visual analogue scale [VAS]). This finding demonstrated the superiority of SI-6603 over placebo for the treatment of LDH in this study. The decrease in mean worst leg pain in the treatment groups also continued beyond Week 13; at the final observation at Week 52, the values were 30.9 mm in the placebo group and 18.5 mm in the 1.25 U dose group on a 100 mm VAS. These results indicated that SI-6603 treatment led to long-term improvement of leg pain due to LDH.

In addition, the LS mean change from baseline in worst low back pain at Week 13 was -28.5 mm in 1.25 U dose group and -21.4 mm in the placebo group. The LS mean change from baseline in worst low back pain at Week 52 was -34.0 mm in 1.25 U dose group and -24.5 mm in placebo group. This difference between treatment groups was not statistically significant, but a similar study by McGirt et al. assessing the VAS scores of 108 lumbar discectomy patients showed that low back pain improved from 4.6 cm before surgery to 2.1 cm at 6 weeks after surgery, which means the change from baseline was -25.0 mm.[(12)] These results indicated that the observed improvement in low back pain with SI-6603 injection would be considered clinically beneficial.

1.2.3 Rationale for Study Design, Administration Route, Dosage (Regimen), and Treatment Period Selection

The result of the Japanese phase 3 study suggests that SI-6603 intradiscal injection is safe and effective for improving the signs and symptoms of LDH. Therefore, we plan to conduct a clinical study intended to evaluate the efficacy of SI-6603 1.25 U compared with control for the treatment of LDH. The intradiscal route was selected as the route of SI-6603 administration for this study. The dose selected for this study is 1.25 U administered as a single injection into the intervertebral disc as a result of the Japanese phase 2/3 and phase 3 study results, in which the 1.25 U dose was shown to be safe and effective. Single dose administration was selected for SI-6603 rather than repeat dose administration due to the risk of allergic reaction with multiple injections that is unlikely, but possible, to occur due to the heterologous protein preparation of *Proteus vulgaris*. Additionally, it is preferable to obtain a long-term effect with a single dose administration.

LDH is treated primarily with conservative non-operative therapy; in patients who fail to respond to this therapy, surgery remains one of the only remaining options. Thus, the target population of the current study is patients who have failed conservative therapy and who have not received surgery.

2 OBJECTIVES

2.1 Primary Objective

The primary objective is to evaluate the effectiveness of a single-dose intervertebral disc injection of SI-6603 at a dose of 1.25 U compared to control in subjects with LDH by comparing the change in worst leg pain during the past 24 hours, as assessed by VAS, from baseline to Week 13 after injection of the investigational product.

2.2 Secondary Objectives

The secondary objectives are to evaluate the efficacy of SI-6603 1.25 U for key secondary endpoints, and to demonstrate whether SI-6603 1.25 U is safe and well tolerated.

3 STUDY DESIGN AND PLAN

3.1 Study Design

This is a multicenter, randomized, double-blind, sham-controlled, comparative study.

3.2 Dosage/Dose Regimen

Subjects randomized to the SI-6603 treatment group will receive a single dose injection of SI-6603 1.25 U into an intervertebral disc. Subjects randomized to the control group will receive a sham injection (the needle will not be placed in the disc).

3.3 Study Population

The subjects enrolled in the current study are those who have LDH and who have shown inadequate improvement with conservative treatment prior to screening. See Section 4 for additional details on the study population.

3.4 Duration of Study

The study duration for each subject will be approximately 56 weeks in total. There is a screening period of up to 4 weeks, 1 day for treatment administration, and a follow-up period of 52 weeks. Screening period starts from time of informed consent and ends at time of randomization.

3.5 Study Assessments

The primary endpoint is the change from baseline to Week 13 in average worst leg pain score during the past 24 hours over the previous 7 days, as assessed by 100 mm VAS. The key secondary endpoints are the change from baseline to Week 13 in herniation volume, change from baseline to Week 13 in Oswestry Disability Index (ODI) score, and change from baseline to Week 52 in average worst leg pain score during the past 24 hours over the previous 7 days, as assessed by 100 mm VAS. The incidence of treatment-emergent adverse events (TEAEs) and the imaging assessments for X-ray and MRI will be used to assess safety. Study assessments are also listed in Section 9.

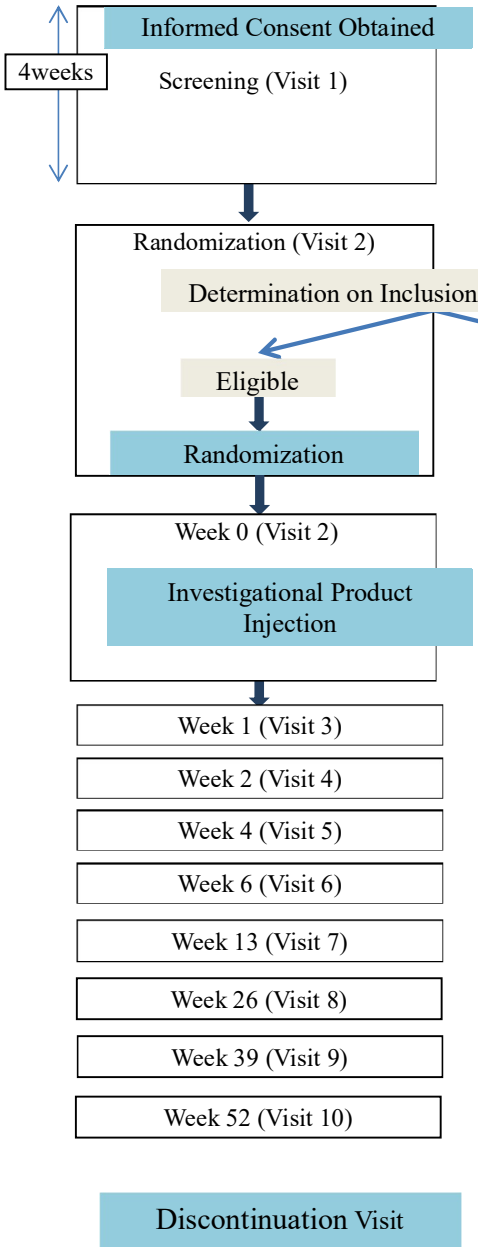
3.6 Planned Number of Subjects

It is planned to enroll approximately 320 subjects, 160 in the SI-6603 group and 160 in the control group.

3.7 Randomization

All eligible subjects will be randomized on a 1:1 basis to SI-6603 or control based on a computer-generated randomization schedule. The randomization will be balanced by randomly permuted blocks and stratified by site.

3.8 Study Design Schematic



Informed Consent Section 6.1

Screening period (Day -28 to Day -1) Section 9.2.1

Screening Section 6.2

Visit 2: Randomization (Day -1 or Day 1) Section 9.2.2
Subject Study Entry Section 6.3

Visit 2: Study Drug Treatment (Day 1) Section 9.2.3

Investigational Product Injection Section 6.4

Visit 3: Week 1 (Day 8±1 day) Section 9.2.4

Visits 4 and 5: Week 2 (Day 15 ±3 days) and Week 4 (Day 29 ±3 days) Section 9.2.5

Visit 6: Week 6 (Day 43 ±7 days) Section 9.2.6

Visit 7: Week 13 (Day 92 -7, +14 days) Section 9.2.7

Visit 8: Week 26 (Day 183 ±14 days) Section 9.2.8

Visit 9: Week 39 (Day 274 ±14 days) Section 9.2.9

Visit 10: Week 52 (Day 365 ±14 days) Section 9.2.10

Discontinuation visit Section 9.2.11

4 STUDY POPULATION

4.1 Inclusion Criteria

Subjects will be allowed to participate in this study only if they meet all of the following criteria:

1. Subjects who have given their written informed consent to participate in the clinical study based on voluntary agreement after a thorough explanation of subject participation is provided to them. Subjects should be willing and able to provide written informed consent, adhere to the study visit schedule, and answer the questions on subject-completed assessments.
2. Male or female subjects 30 to 70 years of age, inclusive, at the time of informed consent.
3. Subjects with contained posterolateral LDH at either L4-L5 or L5-S1 (or L5-L6):
    a. with the presence of demonstrable nerve root impingement,* as assessed by MRI;
    b. chief complaint of unilateral radiculopathy** and/or radicular leg pain corresponding to the ipsilateral leg and distribution of the affected nerve root; and
    c. positive result of Straight Leg Raise (SLR) test (≤70°) on the ipsilateral leg corresponding to the pain and distribution of the affected nerve root. The SLR should be performed with the subject lying flat on his/her back, and the angle measured relative to the horizontal plane of the examining table.

    *Judged first by the investigator, then confirmed by assessment of independent central image readers.

    **Defined as a condition characterized by pain radiating to some or all portions of the ipsilateral L5 or S1 dermatomes, which may be accompanied by corresponding ipsilateral weakness, sensory loss, and/or (for S1 compression) decreased or absent ankle (Achilles) reflex.
4. Subjects with a current episode of radiculopathy that:
    a. is symptomatic only in the unilateral leg and with a distribution corresponding to that of the affected nerve root, and
    b. has been present for 6 weeks or more but 12 months or less, and
    c. which is still ongoing at the time of informed consent.

Note: Subjects may have had similar past episodes involving the same nerve root; in this case, however, the most recent past episode must have ended at least 3 months prior to the onset of the current episode.

5. Subjects with inadequate improvement in pain caused by LDH despite 6 weeks or more of conservative treatment,* which is still ongoing at the time of informed consent.

   *Conservative treatment is pharmacotherapy (e.g., steroids, NSAIDs, or non-opioid analgesics), physical therapy, chiropractic, acupuncture, spinal injection, epidural injection, or nerve block. For spinal injection, an inadequate response over a 4-week period can be counted toward the required ≥ 6 weeks of conservative treatment.

6. Subjects whose worst leg pain (100 mm VAS) for the 7 consecutive days up to the day before randomization meets following conditions:

   a. worst leg pain scores have been recorded for at least 5 out of the 7 days;

   b. the mean of the worst leg pain scores is 50 to 90 mm; and

   c. the range of fluctuation in worst leg pain scores over the 7 days (difference between minimum and maximum scores) is ≤ 25 mm.

7. Subjects who can comply with the rules of concomitant medications (See Section 6.6) and therapies (See Section 6.7) usage as defined in the protocol.

8. Subjects who can comply with the rules of rescue medication usage as defined in the protocol (See Section 6.6.4) and, for those who qualify to receive rescue medication 2 (hydrocodone/acetaminophen), are not at high risk of opioid abuse, as determined by the investigator.

9. Subjects with ≥30% on the ODI at the time of randomization.

4.2 Exclusion Criteria

Subjects will not be allowed to participate in this study if they meet any of the following criteria:

1. Subjects who have LDHs demonstrating clear impingement to the nerve root* at 2 or more levels as assessed by MRI and possessing symptoms corresponding to the distribution of the affected nerve root.

   *Judged first by the investigator, then confirmed by assessment of independent central image readers.

2. Subjects with a contraindication to receive MRIs (e.g., pacemaker or other metallic implants not compatible with MRI).

3. Subjects demonstrating LDH as described below in the disc to be treated, as assessed by MRI*:
    a. rupture into the posterior longitudinal ligament (those with transligamentous extrusion or sequestration [free fragment]-type LDH);
    b. isolated central herniation;
    c. anterolateral herniation; and/or
    d. extraforaminal herniation.

    *Judged first by the investigator, then confirmed by assessment of independent central image readers.
4. Subjects demonstrating clinical symptoms of radiculopathy (e.g., sciatica, weakness, sensory loss, or positive result of SLR test [≤70°]) caused by LDH on the contralateral leg.
5. Subjects who, within 28 days prior to randomization, have:
    a. received a block procedure (e.g., spinal injection, epidural injection or nerve block) for treatment of LDH; and/or
    b. received oral or injectable corticosteroids to the back, buttock, or posterior/lateral aspects of the affected leg.

    Note: Inhaled, nasal, or topical steroids used over small areas of skin (e.g., < 100 cm^2) is permitted.
6. Subjects who, within 7 days prior to randomization, have:
    a. taken opioids (including tramadol, tapentadol, meperidine, or opioid-containing combination products) by any route of administration;
    b. taken cannabis by any route of administration; and/or

    Note: Use of CBD oil that contains regulated quantities of tetrahydrocannabinol (i.e., psychoactive CBD oil preparations) is prohibited; amounts of THC resulting in a positive drug test will be disqualifying.
    c. received local anesthesia to the back, buttock, or posterior/lateral aspects of the affected leg (local anesthesia to the back during SI-6603 injection procedure is permitted). If the local anesthesia was part of a block procedure, exclusion criterion 5 applies.

Note: The protocol permits enrollment of otherwise qualifying subjects who are on opioids immediately prior to screening and who are willing to switch to hydrocodone/acetaminophen as an on-study rescue medication. However, it is possible and permissible that some sites may elect not to enroll such subjects for logistical or other reasons.

7. Subjects who currently have any of the following conditions:

    1) low back pain caused by disorders other than LDH;

    2) mean of worst low back pain assessed by VAS for 7 consecutive days up to the day before randomization is > 90 mm; or;

    3) mean of worst low back pain assessed by VAS for 7 consecutive days up to the day before randomization is > 10 mm higher than the mean of worst leg pain.

        Note: For low back pain assessment by VAS for 7 consecutive days up to the day before randomization, at least 5 out of 7 days need to be entered.

8. Subjects who are pregnant or breast-feeding, or women of childbearing potential with a positive serum or urine pregnancy test(s).
   Pregnancy tests will not be required for female subjects who have undergone a hysterectomy and/or bilateral tubal ligation, or who are postmenopausal (have not menstruated within the past 2 years).

9. Sexually active female subjects of childbearing potential who have a male partner and are not willing to use adequate contraceptive measures to avoid pregnancy until the end of the study. Sexually active male subjects with female partners who are not willing to use adequate contraceptive measures until Week 13 of the study.

   Adequate methods of birth control include the following:

    a. Hormonal contraception (female subjects) or use of at least one acceptable double-barrier method. Acceptable double barrier methods include the following:

        i. diaphragm plus a spermicidal agent; or

        ii. condoms (male or female) plus a spermicidal agent.

    b. Vasectomy, hysterectomy, bilateral tubal ligation, intrauterine device, and/or an exclusive sexual partner for whom one of these methods applies.

   Female subjects who have undergone hysterectomy and/or bilateral tubal ligation, or are postmenopausal (have not menstruated within past 2 years) do not need to practice birth control.

10. Subjects who have undergone a lumbar operation, lumbar percutaneous nucleotomy, or lumbar intradiscal therapies (e.g., chemonucleolysis or intradiscal electrothermal treatment) at the affected level of lumbar spine, or surgery at any other lumbar spine level with persistent symptom(s) including failed back surgery syndrome.
11. Subjects with any of the following:
    a. X-ray imaging findings of vertebral body angle formed by flexion ≥5°, and/or spondylolisthesis (vertebral body translation ≥3 mm)* in the disc to be treated;
    b. Any of the following spinal related disorders*: spondylosis deformans, degenerative spondylolisthesis, spinal deformity (scoliosis: Cobb angle >20° or lordosis [L1-S1]: Cobb angle <20°), spinal tumor, diskitis, vertebral fracture adjacent to the disc to be treated, bony stenosis with nerve root impingement at L3-L4, L4-L5 or L5-S1, or severe lumbar degenerative disc disease in the disc to be treated;
    c. Any of the following spinal related disorders* associated with low back pain that would interfere with safety or efficacy evaluations: spinal canal stenosis (except for stenosis caused by LDH), spondyloarthritis, ankylosing spondylitis, vertebral fracture in the lumbar spine, significant degenerative disease of the facet joints, or other disorders of the lumbar spine;
    d. Presence of osteophytes in the lumbar spine (Nathan's classification ≥3rd degree).*

    *Judged first by the investigator, then confirmed by assessment of independent central image readers.
12. Subjects with history, diagnosis, signs or symptoms of disorders that, in the investigator's opinion, is likely to interfere with pain efficacy assessments.
    Examples may include: chronic pain disorders (e.g., fibromyalgia, restless legs syndrome), peripheral neuropathy caused by certain disorders (e.g., diabetes), Parkinson's disease, complex regional pain syndrome, osteoarthritis (unless symptoms are only in the upper extremities), osteoporosis, spondyloarthritis, ankylosing spondylitis, rheumatoid arthritis, or gout.
13. Subjects with any history of any psychosis or psychotic disorder (includes schizophrenia and bipolar I disorder), or subjects with any nonpsychotic psychiatric disorder, including known personality disorders, that has been sufficiently severe to cause functional impairment within 6 months prior to screening. This latter exclusion is not intended to exclude subjects with depression or anxiety that does not cause functional impairment or

who are adequately treated with antidepressant or anxiolytic medication at doses that are not expected to change during the course of the trial.

14. Subjects with history within the last 5 years of substance abuse or dependency, including, but not limited to, alcohol, opioids, cannabis (even where legal), and prescribed Central Nervous System (CNS) stimulants or depressants.
15. Subjects with alcohol consumption in excess of an average of 2 drinks per day (1 unit = 12 ounces of beer, 5 ounces of non-fortified wine, or 1.5 ounces of 80-proof liquor).
16. Subjects who meet either of the following conditions:
    a. Subjects who cannot wash-out opioids or cannabis for relief of pain, and cannot remain free of these prohibited medications during the course of the trial;
    b. or subjects who have opioid withdrawal symptoms.
17. Subjects who test positive at screening or randomization for drugs of abuse, including (but not limited to) opioids, amphetamines (even when prescribed), cocaine, and cannabinoids (even where legal, prescribed, or possibly due to use of CBD oil). A positive result for benzodiazepine may be permissible if, in the investigator's opinion, is the result of appropriate use of a prescribed medication. A positive result for opioids or cannabinoids at screening, but not baseline, is permissible if, in the investigator's opinion, the result is from opioids or cannabinoids taken before screening and which have since been stopped and will not be resumed during the study, except as specified for rescue medication (See Section 6.6.4). Exclusionary urine drug tests are considered conclusive and may not be repeated.

    Note: Subjects should be advised that they should *not* submit for urine drug testing if they have taken any opioids in the preceding 3 days or are using any of the prohibited drugs. Subjects should not be urine drug tested if there is any reported or known prohibited drug use or opioid use within the preceding 3 days.
18. Subjects who test positive for alcohol on the blood alcohol test at screening. Subjects should be informed that they must not drink alcohol within 12 hours of the screening blood test, and should not take the test if they have done so. A positive blood alcohol test cannot be repeated.

19. Subjects who have cancer or a past history of any cancer within 5 years prior to the time of informed consent, with the exception of basal cell or squamous cell carcinoma of the skin curatively treated or localized gynecologic cancer treated by total hysterectomy.
20. Subjects with neurological disorders, including cauda equina syndrome that is severe or that demonstrates rapid progression, and subjects who have had a seizure in the past 5 years or who are taking anticonvulsant medications for any reason other than neuropathic pain.
21. Subjects with motor weakness graded less than 4 (Medical Research Council Scale <4).
22. Subjects with human immunodeficiency virus (HIV), or a current, active, clinically significant systemic infection requiring treatment with antibiotics, antivirals, or antifungals.
23. Subjects with the following medical conditions or diseases:
    a. clinically significant disorders such as uncontrolled pulmonary disease (e.g., asthma, chronic obstructive pulmonary disease [COPD]), uncontrolled hypertension, type I or uncontrolled type II diabetes, or other serious heart, liver, kidney, or blood disease or immunodeficiency.
    b. clinically evident cerebrovascular disease, pulmonary infarction, congestive heart failure, or arrhythmia (e.g., excludes normal sinus rate variations and atrial or ventricular ectopy ≤2/min).
    c. history or signs of coronary artery disease with or without angina pectoris or myocardial infarction within the last 6 months.
24. Subjects who have difficulty receiving injection of investigational product, or subjects with a tendency to bleed or with bleeding disorders such as (but not limited to) hemophilia, aplastic anemia, cirrhosis of the liver, leukemia, thrombocytopenia, and vitamin K deficiency. Subjects using medication for the purpose of anticoagulation, including heparin and warfarin, which cannot be reversed preoperatively will also be excluded.
25. Subjects with medical conditions and/or diseases that the investigator believes could affect the study results or interfere with safe conduct of the study.
26. Subjects who meet any of the following criteria:
    a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5x upper limit of normal (ULN)

b. Total bilirubin ≥1.5 x ULN, unless isolated Gilbert's syndrome

c. Serum creatinine ≥1.5 x ULN

d. Hepatitis C virus antibody or hepatitis B surface antigen positive. Subjects who have been successfully treated for hepatitis C and currently have undetectable HCV RNA are eligible for study participation.

27. Subjects with a body mass index (BMI) ≥40.
28. Subjects who have difficulties securing an investigational product injection route by the investigator for anatomical reasons.
29. Subjects who are currently hospitalized or have a planned hospitalization during the life of the study.
30. Subjects who have a planned move that may result in difficulty visiting a clinical site(s) during the life of the study.
31. Subjects who previously participated in a clinical study of SI-6603.
32. Subjects who are receiving compensation according to the Workers' Compensation Act or are involved in personal injury litigation due to a lumbar-related injury.
33. Subjects who participated in another interventional clinical study within 30 days prior to the time of informed consent, or who are expected to participate in another study during the period of this study.

5 SUBJECT WITHDRAWAL FROM THE STUDY

5.1 Criteria for Subject Withdrawal

The investigator will withdraw a subject from the clinical study if any of the following situations occur:

1. When the occurrence of an AE or other safety concern leads the investigator to judge it inadvisable for the subject to continue the clinical study;
2. When a poor response to the investigational product leads the investigator to judge it difficult or inadvisable for the subject to continue the clinical study, such as using the prohibited block procedure for treating LDH before Week 13 or receiving surgery to treat LDH at any time over the course of the study;
3. Subjects who test positive for drugs of abuse, including (but not limited to) opioids [other than hydrocodone or its metabolites (hydromorphone, nor hydrocodone) when

hydrocodone is being prescribed within this study], amphetamines (even when prescribed), cocaine, and cannabinoids (even where legal, prescribed, or possibly due to use of CBD oil). A positive result for benzodiazepine may be permissible if, in the investigator's opinion, is the result of appropriate use of a prescribed medication. Truly equivocal urine drug screen results, should they occur, must be discussed with the medical monitor for a decision on subject disposition.

Subjects who are withdrawn from the study as a result of testing positive for drugs of abuse (other than allowed hydrocodone) will be offered a referral for follow up at a drug treatment facility.

4. When a protocol deviation or pattern of deviations lead the investigator to judge it difficult or inadvisable for the subject to continue the clinical study or is likely to significantly confound the study safety or efficacy results;
5. When the subject chooses to discontinue from the clinical study;
6. When the subject is lost to follow-up; or
7. Any other reason that, in the documented opinion of the investigator, makes continued study participation unfavorable for the subject or for study integrity.

5.2 Procedures for Subject Withdrawal

Subjects may withdraw from the entire study, including follow-up, at any time without penalty and for any reason without prejudice to his or her future medical care. In all cases, the reason(s) for withdrawal, including the primary reason, must be recorded on the electronic case report form (eCRF). If a subject is prematurely withdrawn from the study for any reason, the investigator must make every effort to perform the evaluations described for the appropriate discontinuation visit. If a subject withdraws consent and still agrees to undergo a final examination, this will be documented in the eCRF. A subject may also be withdrawn from the study by the investigator, sponsor, regulatory authority(ies), or an Institutional Review Board (IRB). Subjects will also be withdrawn if the entire study is terminated prematurely. Withdrawn subjects will not be replaced.

5.3 Post-treatment Surgery Follow-up for Withdrawn Subjects

Subjects withdrawn from the study will be followed by investigators until 52 weeks after injection to gather data about post-treatment surgery. Information about post-treatment

surgery will be collected for following surgery types:

- Post-treatment surgery for treatment of LDH at the same level of administration of the investigational product;
- Post-treatment surgery for treatment of LDH at a different level than administration of the investigational product; and
- Post-treatment lumbar surgery not for treatment of LDH.

6 STUDY METHOD AND PROCEDURES

6.1 Informed Consent

Before each subject is admitted to the study, informed consent will be obtained from the subject according to the regulatory and legal requirements of the participating country/state. This consent form must be signed, dated, and retained by the investigator as part of the study records. The investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. When consent is obtained must also be documented in the subject source record and eCRF.

If a protocol amendment is required, the informed consent form (ICF) may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IRB and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study, except for when the change is administrative or resigning is not required per the IRB.

[Pre-screening Visit]

Before each subject is screened for the study, a pre-screen informed consent can be obtained from the subject for the purpose of conducting a detailed assessment of subject eligibility on an as-needed basis. This consent form must be signed, dated, and retained by the investigator as part of the study records and a copy must be provided to the subject. When a subject has signed a pre-screen consent form, the investigator can conduct pre-screening for procedures and assessments considered necessary for the subject's eligibility assessment (e.g., neurological examination, pain assessment, imaging assessment). These procedures and assessments can be set based on the investigator's decision. During the pre-screening period, the investigator or delegated site staff can collect X-ray and MR images and transmit them to the central imaging facility according to a separate procedural manual. MRI and X-ray images are not required to be repeated as long as these images were previously acquired within 56 days prior to the randomization date.

6.1.1 Subject Identification

At the screening visit, a unique subject number will be assigned consecutively for each subject after he or she signs the ICF. For subjects going through pre-screening, such subjects will be assigned with unique subject number for purpose of pre-screening.

6.2 Screening

6.2.1 Central Imaging Eligibility Assessment

The investigator will confirm the subject's eligibility based on the X-ray and MR images and clinical symptoms at screening. When the investigator judges that the subject is eligible, the investigator will submit the images to the central imaging facility. The central imaging facility will perform the central eligibility assessment and issue a report including the results. The investigator will comply with the central imaging facility result in judging the subject's eligibility. The detailed method for central imaging eligibility assessment will be provided in a separately distributed manual.

6.2.2 Handling of Concomitant Medications

The investigator will confirm all medications being taken by the subject (including those for treatment of LDH) during the screening visit. If a subject is taking any prohibited medication(s) described in Section 6.6.1, the medication should be washed out at screening. Subjects are permitted to switch their medications to other restricted concomitant medications described in Section 6.6.2 if washout is necessary. The investigator should record the names, doses, and dosing regimens of all medications the subject is taking at screening, noting whether these medications will be taken through the course of the study (only if allowable) or whether they will be discontinued at screening. For medications that will be discontinued, the date of the last dose must be recorded.

6.2.3 Subject Daily Diary

For each subject, site staff will set up an electronic subject diary, give an explanation of the diary to the subject, and confirm that the subject is able to operate the electronic subject diary adequately, according to a separately distributed manual. Site staff will remind the subject to record entries in their diary every day basically before going to bed and will confirm subject eligibility based on the pain intensity recorded during the screening period.

6.2.4 Re-screening

Re-screening of subjects may be allowed in circumstances where both of the following conditions are met:

1) In the investigator's opinion, the subject is likely to fully qualify for study participation, despite the previous screen failure, because either "a" or "b" below applies:
    a. The evaluation(s) being repeated initially yielded an equivocal or uninterpretable result and repeating the evaluation is likely to give more definitive results *OR* the evaluation(s) being repeated initially yielded a result that is likely to be transient and inconsequential (e.g., subject is actively losing weight on a diet but today has a BMI of 40.1 [≥ 40.0 is exclusionary]).
       Note: Exclusionary urine drug tests may not be repeated.
    b. Previous MRI and X-ray images were deemed eligible, needing clinical correlation, or not read by central imaging facility during the initial screening attempt *OR* required images were deemed of unacceptable quality but could not be repeated within the screening window.
2) Approval in writing (email) is obtained from the medical monitor after medical monitor is fully apprised of the screening findings and reason(s) for the re-screening request.

During the re-screening period, MRI and X-ray images are not required to be repeated as long as these evaluations were previously performed within 28 days prior to the re-screening informed consent (Visit 1) date.

6.3 Subject Study Entry

At the time of each subject's entry into the study, the investigator will perform all the examinations described in Section 9.2.1 and confirm that the subject is eligible for the study. Each subject who is judged as eligible for the study by the investigator will be enrolled into the study.

6.3.1 Allocation/Randomization of Subjects to Treatment

Randomization of a subject to treatment will occur after all screening procedures have been performed and the subject's eligibility for the study has been confirmed. Each randomized subject will receive a unique randomization number. Randomized subjects who terminate their study participation for any reason, regardless of whether investigational product was taken or not, will retain their randomization numbers. The Interactive Web Response System (IWRS) will assign subjects to treatment groups based on the predefined randomization list.

6.4 Investigational Product or Sham Injection Procedure

At Visit 2 (Week 0), randomized study subjects will receive either a single injection of SI-6603 or a sham injection by an unblinded injector. For subjects in the active treatment group, a vial of SI-6603 for injection will be reconstituted with 1.2 mL of saline to prepare a 1.25 U/mL solution of SI-6603. A volume of 1.0 mL will be injected into the intervertebral disc in a single dose. For subjects in the control group, a solution will not be prepared and the needle will not be placed in the intervertebral disc. The sham injection procedure should be comparable to that of the active treatment procedure. The unblinded investigator who injected the investigational product must save the images taken during injection that specifically show needle placement during the procedure. The detailed method for administration will be provided in a separately distributed manual.

6.5 Treatment Blinding

The study will be performed in a double-blind manner. The investigator will develop a procedure for maintenance of blinding at the site in accordance with the criteria outlined in a separately distributed manual and documented in the site's blinding plan. Only the physician who performs the injection and the unblinded study coordinator will be unblinded and will not discuss any aspects of the procedure with the subject or other blinded study site personnel. Additionally, the physician performing the injection will not be involved in any other study procedure except for imaging assessment before injection or have any additional subject contact.

The study blind should not be broken except in a medical emergency (where knowledge of the investigational product received would affect the treatment of the emergency) or regulatory requirement. Blinding will be maintained in accordance with a separately distributed manual.

6.6 Concomitant Medications

6.6.1 Prohibited Medications

Use of the following medications are prohibited after wash-out. Prohibited concomitant medications include the following:

[Prohibited in any forms]

- Opioids (including tramadol, tapentadol, meperidine, and opioid-containing combination products) except as described in rescue medication Section 6.6.4)
- Cannabis (even where legal)

  Note: Use of CBD oil that contains regulated quantities of tetrahydrocannabinol (i.e., psychoactive CBD oil preparations) is prohibited; amounts of THC resulting in a positive drug test will be disqualifying.

[Prohibited in specific forms]

- Oral and injectable corticosteroids to the back, buttock, or posterior/lateral aspects of the affected leg.

  Note: Inhaled, nasal, or topical steroids used over small areas of skin (e.g., < 100 cm^2) is permitted.
- Local anesthesia to the back, buttock, or posterior/lateral aspects of the affected leg.

  Note: Local anesthesia to the back during the investigational product injection procedure is permitted.

Subjects should also suspend the use of over-the-counter medications that may contain any active ingredient(s) described above.

For further details, see medication listings that will be separately distributed.

6.6.2 Restricted Concomitant Medications

Subjects who had been taking restricted concomitant medications to treat LDH at stable dose and regimen for at least 7 days prior to randomization may be enrolled in the study. These restricted concomitant medications include NSAIDs, acetaminophen, muscle relaxants, medicines for neuropathic pain (e.g., pregabalin, gabapentin), and medicines for depression used to treat LDH. Medications stated as restricted concomitant medications for purpose of use other than to treat LDH should also remain in stable dose.

Throughout the follow-up period, subjects are allowed to reduce the amount of their restricted medication drug after injection by consultation with investigators, but they must not add a medication or increase a dose once it is decreased.

All restricted concomitant medications used on an as-needed basis (except for rescue medications) are prohibited.

For further details, see medication listings that will be separately distributed.

6.6.3 Medication Use Before, After or During the Injection Procedure

If subjects are required to stop use of any restricted concomitant medications temporarily prior to injection, such restricted concomitant medication can be resumed with same dose/dosage after the injection. However, such subjects can only stop medication within 2 days prior to date of randomization.

Conscious sedation with non-opioid medications is permitted for the injection procedure and/or imaging procedure when necessary for subject comfort or safety. Use of prohibited medication (e.g. inhalational anesthetics, opioids including fentanyl or morphine) before, after or during the injection procedure is not allowed. Use of rescue medication 2 (hydrocodone/acetaminophen) after the injection procedure is allowed.

For the purpose of managing post-injection pain and if the use of rescue medication 1 (acetaminophen) is not sufficient for pain control, it is permissible to add or increase the dose of an NSAID for pain or a muscle relaxant for muscle spasm during the 3-day post-injection period.

6.6.4 Rescue Medications

[Acetaminophen (rescue medication 1)]

Subjects will be provided with acetaminophen at each clinic visit to use as a rescue medication 1 for breakthrough pain resulting from LDH or for treatment of AEs. Subjects will be instructed to use the acetaminophen only if the pain has sufficient severity to require use of the rescue medication.

Subjects will be advised to limit their total acetaminophen use to 3,000 mg/day. Subjects will also be reminded not to use other medications that contain acetaminophen, such as cold or allergy medications, as this may cause them to consume more than 3,000 mg of acetaminophen in 1 day.

Subjects will also be asked to bring the acetaminophen container(s) with any remaining tablets every visit. If a subject has enough remaining acetaminophen, additional medication will not be provided.

[Hydrocodone/acetaminophen (rescue medication 2): limited to opioid users at study start]

Hydrocodone/acetaminophen will be prescribed as rescue medication 2 only for subjects who are using prescribed opioids at the time of informed consent (or documented within the past 2 months). Further, in order to participate, these subjects must be willing to wash-out of their current opioid therapy (See Section 4.2) and, when not already prescribed hydrocodone/acetaminophen, switch to hydrocodone/acetaminophen for the duration of the study. These subjects may be prescribed up to 60 hydrocodone/acetaminophen (5mg/300-325mg) tablets to use as a rescue medication 2 through the end of the study.

Subjects will be instructed that the hydrocodone/acetaminophen should be used on a limited basis and only when acetaminophen alone fails to adequately relieve pain. Further they will be instructed that they should wait at least 4 hours after using acetaminophen before they dose with hydrocodone/acetaminophen.

Subjects will be allowed to take hydrocodone/acetaminophen at 1 - 2 tablets every 4 to 6 hours as needed for severe pain, but not to exceed 4 tablets per day. Subjects will be advised to limit their total acetaminophen use to 3,000 mg/day. As such, subjects will be reminded not to use other medications that contain acetaminophen, such as cold or allergy medications, as this may cause them to consume more than 3,000 mg of acetaminophen in 1 day.

During each of the consecutive 7 days prior to Visit 6 (Week 6), Visit 7 (Week 13), Visit 8 (Week 26), Visit 9 (Week 39), and Visit 10 (Week 52), the use of hydrocodone/acetaminophen is prohibited. For Visit 7 (Week 13) and Visit 10 (Week 52), subjects will be instructed to suspend use of hydrocodone/acetaminophen 10 days prior to those visits. As noted in the exclusion criteria, no opioid use of any kind is allowed within the 7 days prior to Visit 2 (Week 1) (See Section 4.2).

Hydrocodone/acetaminophen will be prescribed at a maximum of 28 tablets per prescription and not to exceed total of 60 tablets during the study. Subjects will also be asked to bring the hydrocodone/acetaminophen container(s) with any remaining tablets to every visit. If a subject has enough remaining hydrocodone/acetaminophen to last until the next scheduled visit, additional medication will not be provided.

6.7 Concomitant Therapies

6.7.1 Prohibited Concomitant Therapies

Lumbar operation, lumbar percutaneous nucleotomy, or lumbar intradiscal therapies (e.g., chemonucleolysis, intradiscal electrothermal treatment) for treatment of symptoms caused by

LDH, such as low back pain and leg pain, are prohibited throughout the study. Block procedures (e.g., nerve block, epidural block, or facet block) for treatment of symptoms caused by LDH is prohibited before Week 13. If a subject is to receive a prohibited concomitant therapy during the study, they should return to the site for a discontinuation visit and be discontinued from the study.

6.7.2 Restricted Concomitant Therapies

Subjects who had been receiving physical therapy (e.g., exercise therapy, thermotherapy, braces, acupuncture, manipulative treatment, transcutaneous electrical nerve stimulation) to treat LDH beginning 7 days or more prior to randomization may continue with that therapy during the study only if the frequency and intensity will not be changed. Subjects are allowed to reduce the frequency or intensity after injection by consultation with investigators, but they must not add new therapy or increase a frequency or intensity once it is reduced.

6.7.3 Lifestyle Restrictions

Subjects will be instructed by the site about any lifestyle or activity restrictions following the injection procedure, such as avoiding strenuous activities. Specific instructions will be provided in a separately distributed manual.

7 INVESTIGATIONAL PRODUCT

7.1 Identity of Investigational Products

7.1.1 SI-6603

SI-6603 will be administered as a lyophilized injection that, when reconstituted with 1.2 mL of saline, provides 1.0 mL of solution containing the ingredients listed below:

Ingredient	
Active ingredient	SI-6603
Inactive ingredients	Monosodium phosphate dihydrate (United States Pharmacopoeia [USP])
	Disodium hydrogen phosphate, dodecahydrate (USP)
	Sucrose (National Formulary [NF])
	Polyethylene glycol 3350 (NF)

SI-6603 for injection (1.25 U [1.5 U/vial]) will be manufactured for reconstitution with 1.2 mL of saline for delivery of 1.25 U in 1.0 mL.

7.1.2 Control

The control group subjects will receive a sham injection. Boxes including empty vials with an identical label to boxes containing SI-6603 will be shipped as investigational products for use in the sham injections.

7.2 Packaging and Labeling

Investigational product will be packaged by the vendor according to all local legal requirements and applicable regulatory requirements.

7.3 Preparation, Handling, Storage, and Accountability

All investigational product supplies must be stored in the original boxes in accordance with the manufacturer's instructions (2 to 8°C and shielded from light). Investigational product must be stored in a securely locked area, accessible to authorized personnel only. The investigator is responsible for maintaining accurate investigational product accountability records throughout the study. Individual subject dispensing of investigational product must be documented in the subject source record and eCRF. The investigator is responsible for returning all used or unused investigational product in the original boxes to the sponsor or designee and must verify that no remaining supplies are in the investigator's possession.

8 ENDPOINTS

8.1 Efficacy Endpoints

8.1.1 Primary

The primary endpoint is the change from baseline to Week 13 in average worst leg pain score during the past 24 hours over the previous 7 days, as assessed by 100 mm VAS.

8.1.2 Key Secondary

The key secondary efficacy endpoints for this study are as follows:

- Change from baseline to Week 13 in herniation volume
- Change from baseline to Week 13 in ODI score
- Change from baseline to Week 52 in average worst leg pain score during the past 24 hours over the previous 7 days, as assessed by 100 mm VAS.

8.1.3 Other Secondary

The other secondary efficacy endpoints for this study are as follows:

- Change from baseline in worst leg pain score at each time point
- Change from baseline in worst low back pain score at each time point
- Change from baseline in ODI score at each time point
- Percentage of subjects with negative SLR test
- Percentage of subjects without hypoesthesia, muscle weakness or hyporeflexia
- Patient Global Impression of Change (PGIC) score at each time point
- Clinical Global Impression of Change (CGIC) score at each time point
- Change from baseline in 36-item Short Form Health Survey (SF-36) scores at each time point
- EuroQol Group 5-Dimension Quality of Life instrument, 5-level version (EQ-5D-5L) quality of life (QOL) score and VAS score at Week 13 and Week 52
- Work Productivity and Activity Impairment Questionnaire (WPAI) score at Week 13 and Week 52
- Incidence and amount of rescue medication use over 13 weeks
- Change from baseline in amount of rescue medication use at each time point
- Cumulative distribution of percentage change from baseline in worst leg pain score at Week 13 and Week 52

- Cumulative distribution of percentage change from baseline in ODI score at Week 13 and Week 52
- Responder rate by composite definition[*1] at Week 13
- Change from baseline in intervertebral disc volume at Week 13 and Week 52
- Change from baseline in herniation volume at Week 13 and Week 52
- Incidence of post-treatment surgery for LDH at the same level of investigational product injection
- Number of subjects with recurrence of LDH[*2] at Week 52

*1 A subject who meets all 4 criteria below (A, B, C, and D) as assessed at Week 13:

A. A reduction of 30% in worst leg pain score during the past 24 hours assessed by VAS from baseline to Week 13;

B. Improvement of 30% in ODI score from baseline to Week 13;

C. Maintenance or improvement of neurologic status (motor, sensory, reflexes) from baseline to Week 13; and

D. No "Treatment Failure"

"Treatment Failure" is defined as a subject to whom any of the conditions shown below become applicable until Week 13 after investigational product injection:

i. Use of additional medication/therapy to treat TEAEs or complications associated with LDH

- New prohibited medications used for more than 7 days;
- Increase of restricted medications used for more than 7 days;
- Use of new prohibited therapies; or
- Increase in frequency or intensity of restricted therapies.

ii. Poor response to investigational product that leads the investigator to judge it necessary to perform a surgical intervention for back pain/leg pain or withdraw from the study

iii. Increase of measurement value on either vertebral body angle formed by flexion or vertebral body translation from baseline to values:

- Vertebral body angle formed by flexion of ≥5º, or

- Vertebral body translation of ≥3 mm

iv. Occurrence of treatment-related AEs that lead the investigator to judge it necessary for the subject to have surgical intervention or withdraw from the study

*2 Recurrence of LDH is defined as below:

A subject who has all of the following conditions:

a. The subject shows improvement according to all of the following clinical symptoms at Week 13:
   - Reduction of 30% in worst leg pain score from baseline,
   - Improvement of 30% in ODI score from baseline, and
   - Maintenance or improvement of neurologic status (motor, sensory, reflexes) from baseline;

b. The subject does not show with any improvement of worst leg pain score, ODI score, or neurologic status at Week 52 or discontinuation visit; and

c. The subject has been judged by the investigator as a "Treatment Failure" for efficacy reason(ii), as described above.

8.2 Safety Endpoints

The following safety endpoints will be assessed after investigational product administration:

- Adverse events
- Laboratory tests
- Vital signs
- Imaging assessments by X-ray and MRI
  - Disc height (disc index)
  - Vertebral body translation
  - Vertebral body angle formed by flexion
  - Modic classification
- Occurrence of post-treatment lumbar surgery
  - Surgery for treatment of LDH at a different level than administration of the investigational product
  - Lumbar surgery not for treatment of LDH

9 STUDY SCHEDULE AND VARIABLES

9.1 Schedule of Activities

The schedule of study activities is provided in Table 1.

Table 1 Schedule of Study Activities

	Pre-screening	Screening			Follow up									
Visit		1	2		3	4	5	6	7	8	9	10	DC	
Week		-4	0		1	2	4	6	13	26	39	52	≤ 13	>13
Day		-28	1		8	15	29	43	92	183	274	365		
			Before Injection	After Injection										
Window (days)			-1		±1	±3	±3	±7	-7, +14	±14	±14	±14		
Informed consent	X[k]	X												
Inclusion/exclusion criteria	X[k]	X	X											
Demographics, medical history	X[k]	X												
Concomitant medications/ rescue medication use		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X		X	X	X	X	X	X	X	X	X	X
Adverse events		→	→	→	→	→	→	→	→	→	→	→	→	→
Urine drug test		X	X			X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]		
Neurological examination	X[k]	X	X			X	X	X	X	X	X	X	X	X
Laboratory tests[a]		X				X			X	X			X	
Pregnancy test[b]		X	X											
Imaging (X-ray, MRI)	X[k]	X[c]								X[d]			X[d]	X[d]	X[d]
Central eligibility assessment for imaging	X[k]	X												
Confirmation of washout			X											
Daily diary (VAS pain assessment and rescue medication use)		→	→	→	→	→	→	→	→	→	→	→	→	→
Subject education[e]		X		X				X			X			
Distribution of rescue medication (acetaminophen)[f]		X		X	X	X	X	X	X	X	X			
Distribution of rescue medication (hydrocodone/ acetaminophen)[f]				X	X	X	X	X	X	X	X			
ODI			X			X	X	X	X	X	X	X	X	X
SF-36			X					X	X	X	X	X	X	X
EQ-5D-5L			X						X			X	X	X
WPAI			X						X			X	X	X
Randomization[g]			X											
Injection[h]				X										
PGIC							X	X	X	X	X	X	X	X
CGIC							X	X	X	X	X	X	X	X
Telephone call before visit[i]									X	X	X	X		
Determine treatment failure									X			X	X	X
Occurrence of lumbar surgery[j]												X	X	X
Collect remaining rescue medication												X	X	X

X = Essential examination.
CGIC = Clinical Global Impression of Change; DC = Discontinuation; EQ-5D-5L = EuroQol Group 5-Dimension Quality of Life instrument, 5-level version; LDH = Lumbar Disc Herniation; MRI = Magnetic Resonance Imaging; ODI = Oswestry Disability Index; PGIC = Patient Global Impression of Change; SF-36 = 36-Item Short-Form Health Survey; VAS = Visual Analogue Scale; WPAI = Work Productivity and Activity Impairment Questionnaire.

a Laboratory tests are provided as listed in Table 2.
b Women of childbearing potential only. Blood test will be performed at Visit 1, and urine test will be performed at Visit 2.
c If subject is re-screened, the imaging is not required to be repeated as long as the imaging was performed within 28 days prior to the re-screening informed consent (Visit 1) date or within 56 days of the planned randomization date, whichever is longer.
d If repeat imaging is needed during follow-up visits, the window for imaging will be extended by a maximum of an additional 7 days.
e Subjects will be educated on appropriate expectations around their participation in a clinical study and the importance of reliably, consistently and accurately reporting their pain throughout the study.
f If a subject has enough remaining acetaminophen (rescue medication 1) or hydrocodone/acetaminophen (rescue medication 2), additional medication will not be provided. Not to exceed a maximum of 60 tablets of hydrocodone/acetaminophen throughout the study.
g Subjects may be randomized on the day before (Day -1) or the day of (Day 1) investigational product administration.
h Treatment should be administered within 4 weeks after informed consent.
i Site staff should contact a subject by telephone call and/or other method by a minimum of 14 days before scheduled visit.
j Subjects who discontinued the study will be followed until the Week 52 Visit.
k Before each subject is screened for the study, a pre-screen informed consent can be obtained from the subject for the purpose of conducting a detailed assessment of subject eligibility on an as-needed basis. Investigator can conduct pre-screening for procedures and assessments considered necessary for the subject's eligibility assessment (e.g., neurological examination, pain assessment, imaging assessment) and these procedures and assessments can be set based on the investigator's decision.
l Urine drug tests at these visits are required only for subjects receiving hydrocodone/acetaminophen rescue.

9.2 Procedures by Visit

Each subject will be asked to complete 10 study visits:

- Screening period (Visit 1)
- Randomization at Week 0, Day -1 or Day 1 (Visit 2)
- Investigational product treatment at Week 0, Day 1 (Visit 2)
- Follow-up visits at Week 1, Week 2, Week 4, Week 6, Week 13, Week 26, Week 39, and Week 52 (Visit 3 through Visit 10)

Subjects who discontinued the study in mid-course will be asked to complete a discontinuation visit. Before each subject is screened for the study, a pre-screen informed consent can be obtained from the subject for the purpose of conducting a detailed assessment of subject eligibility on an as-needed basis.

9.2.1 Visit 1: Screening Period (Day -28 to Day -1)

The following activities will be performed at screening (Visit 1) or during the screening period (Day -28 to -1).

Before performing any screening procedures:

- Obtain written informed consent.

After informed consent obtained:

- Collect demographics and baseline characteristics, including diagnosis and history of LDH.
- Collect medical history.
- Collect concomitant medication and therapy information, including for the treatment of LDH.
- Collect vital signs.
- Record baseline signs and symptoms as baseline conditions to assess future potential AEs.
- Perform neurological examination.
- Perform urine drug test.
- Collect blood sample for laboratory tests (hepatitis test; pregnancy test [for women of childbearing potential]; hematology, hepatic, serology and chemistry panels; and blood alcohol test).

- Collect concomitant medication and therapy information.
    - Confirm use and amount of concomitant medication(s)/therapy(ies).
    - Assess use of restricted medication(s)/therapy(ies) for LDH.
    - Assess washout of prohibited medication(s)/therapy(ies) (washout of prohibited medication(s)/therapy(ies) to be completed before subject performs 7 days of VAS assessment).
- Perform imaging tests (X-ray and MRI), assess the images, and transmit the images to the central independent image readers for assessment of eligibility.

At least by 14 days prior to randomization date, sites should:

- Provide instructions for recording daily pain assessment and rescue medication use.
- Provide subject education and materials on accurate pain reporting and appropriate expectations of personal benefit in a clinical trial.
- Distribute subject daily diary.
- Distribute acetaminophen as a rescue medication.

After subject performs 7 days of VAS assessment:

- Record AEs.
- Verify conformance with inclusion/exclusion criteria.

9.2.2 Visit 2: Randomization (Day -1 or Day 1)

The following activities will be performed on the day before (Day -1) or the day of (Day 1) investigational product administration.

Before randomization:

- Complete the ODI, SF-36, EQ-5D-5L, and WPAI assessments.
- Collect concomitant medication and therapy information.
    - Confirm use and amount of concomitant medication(s)/therapy(ies).
    - Assess use of restricted medication(s)/therapy(ies) for LDH.
    - Confirm washout of prohibited medications.
    - Confirm rescue medication use.
- Collect vital signs.
- Record AEs.
- Perform neurological examination.

- Perform urine drug test.
- Perform urine pregnancy test (for women of childbearing potential).
- Confirm that the subject meets all of the inclusion criteria and none of the exclusion criteria and is therefore eligible to participate in the study.

Randomization:

Randomization must occur within screening period or on the day of investigational product administration (Day 1).

- Randomize subject to SI-6603 or sham injection once all screening assessments are complete.

9.2.3 Visit 2: Investigational Product Treatment (Day 1)

The following activities will be performed at Visit 2 (Day 1).

Before investigational product administration:

- Monitor vital signs.
- Record AEs, if randomization was performed on Day -1.

During and after investigational product administration:

The following activities will be performed by an unblinded site staff:

- Administer SI-6603 or sham injection as described in Section 6.4.
- Take and store the views of the target level with the needle placed within the disc or on the periphery.
- Record concomitant medication and therapy information at investigational product administration.
- Record AEs.

After investigational product administration:

Require subjects to rest for at least 4 hours. During this resting period, the investigator will monitor the subject's vital signs and general health status. After subject monitoring, the investigator will judge if the subject is ready for discharge based on observation and verification there are no findings that negatively influence discharging the subject.

- Monitor vital signs (approximately 2 and 4 hours after investigational product administration) and general health status.
- Record AEs that occurred after investigational product administration.

- Record concomitant medication and therapy information following investigational product administration.
- Provide instructions for recording daily pain assessment and rescue medication use.
- Provide subject education on accurate pain reporting and appropriate expectations of personal benefit in a clinical trial.
- Distribute acetaminophen rescue, as described in Section 6.6.4.
- As applicable per Section 6.6.4, distribute hydrocodone/acetaminophen rescue medication.
- Provide instructions to avoid any strenuous activities.

9.2.4 Visit 3: Week 1 (Day 8 ±1 day)

The following activities will be performed at Visit 3 (Week 1).

- Complete ODI assessment.
- Collect concomitant medication and therapy information.
    - Confirm use and amount of concomitant medication(s)/therapy(ies).
    - Assess use of restricted medication(s)/therapy(ies) for LDH.
- Review the subject daily diary and assess compliance.
- Collect vital signs.
- Record AEs.
- Perform neurological examination.
- Perform urine drug test for subjects prescribed hydrocodone/acetaminophen rescue.
- Collect blood sample for laboratory tests (hematology and chemistry panels).
- Provide instructions for recording daily pain assessment and rescue medication use.
- Distribute acetaminophen rescue, as described in Section 6.6.4.
- As applicable per Section 6.6.4, distribute hydrocodone/acetaminophen rescue medication. Discuss usage and counsel, as appropriate.
- Remind subject to avoid any strenuous activities.

9.2.5 Visits 4 and 5: Week 2 (Day 15 ±3 days) and Week 4 (Day 29 ±3 days)

The following activities will be performed at Visit 4 (Week 2) and Visit 5 (Week 4):

- Complete the ODI, SF-36, and PGIC assessments (SF-36 will not be performed at Visit 4).
- Collect concomitant medication and therapy information.

- Confirm use and amount of concomitant medication(s)/therapy(ies).
- Assess use of restricted medication(s)/therapy(ies) for LDH.

- Collect vital signs.
- Record AEs.
- Perform neurological examination.
- Perform urine drug test for subjects prescribed hydrocodone/acetaminophen rescue.
- Complete the CGIC assessment.
- Provide instructions for recording daily pain assessment and rescue medication use.
- Distribute acetaminophen rescue, as described in Section 6.6.4.
- As applicable per Section 6.6.4, distribute hydrocodone/acetaminophen rescue medication. Discuss usage and counsel, as appropriate.
- Remind subject to avoid any strenuous activities.

9.2.6 Visit 6: Week 6 (Day 43 ±7 days)

The following activities will be performed at Visit 6 (Week 6):

- Complete the ODI, SF-36, and PGIC assessments.
- Collect concomitant medication and therapy information.
  - Confirm use and amount of concomitant medication(s)/therapy(ies).
  - Assess use of restricted medication(s)/therapy(ies) for LDH.
- Collect vital signs.
- Record AEs.
- Perform neurological examination.
- Perform urine drug test for subjects prescribed hydrocodone/acetaminophen rescue.
- Complete the CGIC assessment.
- Collect blood sample for laboratory tests (hematology and chemistry panels).
- Provide instructions for recording daily pain assessment and rescue medication use.
- Provide subject education on accurate pain reporting and appropriate expectations of personal benefit in a clinical trial.
- Distribute acetaminophen rescue, as described in Section 6.6.4.
- As applicable per Section 6.6.4, distribute hydrocodone/acetaminophen rescue medication. Discuss usage and counsel, as appropriate.
- Remind subject to avoid any strenuous activities.

9.2.7 Visit 7: Week 13 (Day 92 -7, +14 days)

Contact will be made with the subject by telephone call (and/or other method) by a minimum of 14 days before this visit. The following activities will be performed at Visit 7 (Week 13):

- Complete the ODI, SF-36, PGIC, EQ-5D-5L, and WPAI assessments.
- Collect concomitant medication and therapy information.
    - Confirm use and amount of concomitant medication(s)/therapy(ies).
    - Assess use of restricted medication(s)/therapy(ies) for LDH.
- Collect vital signs.
- Record AEs.
- Perform neurological examination.
- Perform urine drug test for subjects prescribed hydrocodone/acetaminophen rescue.
- Complete the CGIC assessment.
- Collect blood sample for laboratory tests (hematology and chemistry panels).
- Determine whether there is treatment failure.
- Provide instructions for recording daily pain assessment and rescue medication use.
- Distribute acetaminophen rescue, as described in Section 6.6.4.
- As applicable per Section 6.6.4, distribute hydrocodone/acetaminophen rescue medication. Discuss usage and counsel, as appropriate.
- Remind subject to avoid any strenuous activities.
- Perform imaging tests (X-ray and MRI)*, assess the images, and transmit the images to the central independent image readers.

  * If repeat imaging is needed, the window for imaging only will be extended by a maximum of an additional 7 days.

9.2.8 Visit 8: Week 26 (Day 183 ±14 days)

Contact will be made with the subject by telephone call (and/or other ways) by a minimum of 14 days before these visits. The following activities will be performed at Visit 8 (Week 26):

- Complete the ODI, SF-36, and PGIC assessments.
- Collect concomitant medication and therapy information.
    - Confirm use and amount of concomitant medication(s)/therapy(ies).
    - Assess use of restricted medication(s)/therapy(ies) for LDH.
- Collect vital signs.

- Record AEs.
- Perform neurological examination.
- Perform urine drug test for subjects prescribed hydrocodone/acetaminophen rescue.
- Complete the CGIC assessment.
- Provide instructions recording daily pain assessment and rescue medication use.
- Distribute acetaminophen rescue, as described in Section 6.6.4.
- As applicable per Section 6.6.4, distribute hydrocodone/acetaminophen rescue medication. Discuss usage and counsel, as appropriate.
- Remind subject to avoid any strenuous activities.

9.2.9 Visit 9: Week 39 (Day 274 ±14 days)

Contact will be made with the subject by telephone call (and/or other ways) by a minimum of 14 days before these visits. The following activities will be performed at Visit 9 (Week 39):

- Complete the ODI, SF-36, and PGIC assessments.
- Collect concomitant medication and therapy information.
    - Confirm use and amount of concomitant medication(s)/therapy(ies).
    - Assess use of restricted medication(s)/therapy(ies) for LDH.
- Collect vital signs.
- Record AEs.
- Perform neurological examination.
- Perform urine drug test for subjects prescribed hydrocodone/acetaminophen rescue.
- Complete the CGIC assessment.
- Provide instructions recording daily pain assessment and rescue medication use.
- Provide subject education on accurate pain reporting and appropriate expectations of personal benefit in a clinical trial.
- Distribute acetaminophen rescue, as described in Section 6.6.4.
- As applicable per Section 6.6.4, distribute hydrocodone/acetaminophen rescue medication. Discuss usage and counsel, as appropriate.
- Remind subject to avoid any strenuous activities.

9.2.10 Visit 10: Week 52 (Day 365 ±14 days)

Contact will be made with the subject by telephone call (and/or other ways) by a minimum of 14 days before these visits. The following activities will be performed at Visit 10 (Week 52):

- Complete the ODI, SF-36, PGIC, EQ-5D-5L, and WPAI assessments
- Collect concomitant medication and therapy information.
    - Confirm use and amount of concomitant medication(s)/therapy(ies).
    - Assess use of restricted medication(s)/therapy(ies) for LDH.
- Collect vital signs.
- Record AEs.
- Record occurrence of any lumbar surgery.
- Perform neurological examination.
- Complete the CGIC assessment.
- Determine whether there is treatment failure.
- Collect or account for any remaining rescue medication.
- Perform imaging tests (X-ray and MRI) *, assess the images, and transmit the images to the central independent image readers.

  * If repeat imaging is needed, the window for imaging will be extended by a maximum of an additional 7 days.

9.2.11 Discontinuation Visit

Subjects who discontinue early from the study will be asked to complete a discontinuation visit. The following activities will be performed at the discontinuation visit:

- Complete the ODI, SF-36, PGIC, EQ-5D-5L, and WPAI assessments
- Collect concomitant medication and therapy information.
    - Confirm use and amount of concomitant medication(s)/therapy(ies).
    - Assess use of restricted medication(s)/therapy(ies) for LDH.
- Collect vital signs.
- Record AEs.
- Record occurrence of any lumbar surgery.
- Perform neurological examination.
- Complete the CGIC assessment.
- Collect blood sample for laboratory tests (blood for hematology and chemistry panels)*.
- Determine whether there is treatment failure.
- Collect or account for any remaining rescue medication.

- Perform imaging tests (X-ray and MRI), assess the images, and transmit the images to the central independent image readers

  * If the subject discontinues prior to or within Week 13.

Subjects who discontinue early from the study will also be followed until Week 52 for the occurrence of any lumbar surgery.

9.2.12 Unscheduled Visit

In the event the investigator needs to conduct follow-up assessments to evaluate an AE, the following safety assessments may be performed on an unscheduled basis:

- Collect vital signs.
- Collect blood sample for laboratory tests (hematology and chemistry panels).
- Perform imaging tests (X-ray and MRI), assess the images, and transmit the images to the central independent image readers.

9.3 Background and Demographic Characteristics

9.3.1 Demographics

For subject demographics, the following information will be documented at the screening visit.

- Date of birth
- Sex [Male, Female]
- Race [American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other]
- Ethnicity [Hispanic or Latino, Not Hispanic or Latino]
- Height
- Weight
- Smoking history [Never smoked, Past smoker, Current smoker]
- Occupation [Heavy labor, Light labor]

9.3.2 History of Lumbar Disc Herniation

For disease history of LDH, the following information will be documented at the screening visit.

- Date of Diagnosis
- Herniation Site [L4-L5, L5-S1*]
- Location of Herniation [Left, Right]

- Location of Radicular Leg Pain [Left, Right]
- Date of Onset of Current Radicular Leg Pain
- Ongoing Low Back Pain Caused by Herniation [Yes, No]

  *including L5-L6

9.3.3 Medical History

For the documentation of medical history, any previous and concomitant diseases within the last 26 weeks and any significant medical history occurring before the time of informed consent will be investigated at the screening visit. The medical history will be obtained by interviewing the subject and/or by inspecting his/her medical records.

A brief history of the following treatments, if they have been used, will be recorded:

- Medications used for LDH in the 26 weeks before the time of informed consent: Name of medication, Usage, Frequency, Route, Start date, End date
- Physical therapies used for LDH in the 26 weeks before the time of informed consent: Name of therapy, Frequency, Start date, End date
- Block procedure used for LDH: Name of procedure, Date

9.4 Concomitant Medications/Therapies

9.4.1 Concomitant Medications

Investigators will record the following information for all medications used concomitantly during the period from 6 weeks prior to informed consent to 52 weeks after administration, or until the time of discontinuation.

- Name of medication
- Dose
- Route of administration
- Frequency
- Start date / End date
- Indication [LDH, Adverse event, Medical history, Other]

9.4.2 Concomitant Therapies

Investigators will record the following information for therapies used concomitantly for treatment of LDH during the period from time of informed consent to 52 weeks after administration, or until the time of discontinuation.

- Name of therapy

- Frequency
- Start date / End date

9.5 Efficacy Assessments

9.5.1 Pain Intensity

- Assessment Points: Daily from screening until Week 52
- Item: Worst leg pain and worst low back pain during the past 24 hours assessed by 100 mm VAS
- Method: The 100 mm VAS pain assessment tool will be used to measure pain intensity. At the screening visit, the investigator will provide a daily diary and instruct subjects to record daily the pain intensity from LDH over the last 24 hours basically before going to bed.

9.5.2 Oswestry Disability Index

- Assessment Points: Week 0, 1, 2, 4, 6, 13, 26, 39, and 52, and discontinuation visit
- Item: ODI, Version 2.1a
- Method: Investigator will have subjects answer the ODI questionnaire at each listed visit.

9.5.3 36-item Short Form Survey

- Assessment Points: Week 0, 4, 6, 13, 26, 39, and 52, and discontinuation visit
- Item: SF-36 v2 Standard, US Version 2.0
- Method: Investigator will have subjects answer the SF-36 questionnaire at each listed visit.

9.5.4 EuroQol Group 5-Dimension Quality of Life Instrument

- Assessment Points: Week 0, 13, and 52, and discontinuation visit
- Item: EQ-5D-5L
- Method: Investigators will have subjects answer the EQ-5D-5L questionnaire at each listed visit.

9.5.5 Patient Global Impression of Change

- Assessment Points: Week 2, 4, 6, 13, 26, 39, and 52, and discontinuation visit
- Item: PGIC questionnaire

- Method: Investigators will have subjects answer the PGIC questionnaire at each listed visit.

9.5.6 Clinical Global Impression of Change

- Assessment Points: Week 2, 4, 6, 13, 26, 39, and 52, and discontinuation visit
- Item: CGIC questionnaire
- Method: Investigators will answer the CGIC questionnaire based on subject's condition at each listed visit.

9.5.7 Work Productivity and Activity Impairment

- Assessment Points: Week 0, 13, and 52, and discontinuation visit
- Item: Work Productivity and Activity Impairment Questionnaire: Pain related to Lumbo-sacral Radiculopathy V1.0 (WPAI-PLR, referred to as WPAI)
- Method: Investigators will have subjects answer the WPAI questionnaire at each listed visit.

9.5.8 Rescue Medication Use

- Assessment Points: Daily from screening until Week 52
- Item: Amount of rescue medication used
- Method: At the screening visit, the investigator will provide a daily diary and instruct subjects to record daily the amount of rescue medication over the last 24 hours, basically before going to bed. The investigator will clarify the requirements for timing of opioid rescue as it relates to the other study assessments.

9.5.9 Neurologic Status

- Assessment Points: All Visits
- Item: SLR test [Positive (≤70°) or Negative (>70°)], sensation [Yes, No for existence of hypoesthesia], muscle strength [Yes, No for existence of muscle weakness], and deep tendon reflex [Yes, No for existence of hyporeflexia]
- Method: Neurological examinations will be performed by the investigator, and the results will be documented.

9.5.10 Treatment Failure

- Assessment Points: Week 13 and 52, and discontinuation visit

- Item: Treatment Failure [Yes, No], Reason [Concomitant medication use, Safety reason, Efficacy reason, Poor response, Increase of vertebral body angle, Increase of vertebral body translation]
- Method: Investigator will record the condition of and information about treatment failure. Treatment failure is defined in Section 8.1.3.

9.5.11 Disc and Herniation Volumes

- Assessment Points: Screening visit, Week 13, and 52, and discontinuation visit
- Item: Disc volume, Herniation volume
- Method: Disc and herniation volumes will be assessed with MRI by a central imaging facility. The investigator or site staff will collect the images and transmit them to the central imaging facility, according to a separately distributed manual.

9.5.12 Post-treatment Surgery for Lumbar Disc Herniation at Target Level

- Assessment Point: Week 52 (subjects who discontinued the study will be also followed until 52 weeks after injection)
- Item: Occurrence of lumbar disc surgery for LDH [Yes, No], Date of surgery
- Method: At 52 weeks after injection, investigators will collect information on the occurrence of post-treatment surgery for treatment of LDH at the same level of administration of the investigational product, including for subjects who discontinued from the study.

9.6 Safety Assessments

9.6.1 Adverse Events

Investigators should investigate any AEs occurring after the time of informed consent as follows and record them in the eCRF. Questions should be nonspecific, such as “How have you been feeling since the last visit?”

- AE Term
- Period AE occurred [Prior to injection, After injection]
- Start date
- End date
- Outcome [Recovered/Resolved, Recovering/Resolving, Not recovered/Not resolved, Recovered/Resolved with sequelae, Fatal, Unknown]
- Severity [Mild, Moderate, Severe]
- Causality [Related, Not related]

- Action Taken [None, Medication, Other]
- AE that caused study discontinuation [No, Yes]
- Serious Event [No, Yes]
- Special Interest [No, Yes]

9.6.2 Laboratory Tests

- Assessment Points for All Subjects: Screening visit, Weeks 0, 1, 6, and 13, and discontinuation visit prior to or within Week 13
- Additional Assessment Points for Subjects Receiving Hydrocodone/Acetaminophen Rescue: Week 1, 2, 4, 6, 13, 26 and 39
- Items:
    - Screening visit – urine drug test, serum pregnancy test, blood alcohol test, and hematology, serology markers, hepatic, and chemistry panels.
    - Week 0 – urine drug test, urine pregnancy test.
    - Week 1, Week 6, Week 13 and discontinuation visit (prior to or within Week 13) – hematology and chemistry panels
    - Week 1, 2, 4, 6, 13, 26 and 39 – urine drug test (only for subjects receiving hydrocodone/acetaminophen rescue)
- Method: Urine assessments will be performed at the study sites with provided kits. Blood assessments will be performed by a central laboratory. The investigator or site staff will collect blood samples according to a separately distributed manual. Laboratory variables from blood tests will be determined as listed in Table 2.

Table 2 Laboratory Assessments

Hematology:	hematocrit hemoglobin platelets red blood cell count white blood cell count with differential
Clinical chemistry:	creatinine C-reactive protein total protein total bilirubin direct bilirubin (determined if total bilirubin is elevated) total cholesterol urea nitrogen uric acid
Electrolytes:	calcium chloride magnesium potassium sodium
Liver enzymes:	alkaline phosphatase AST ALT lactic dehydrogenase γ-glutamyl transpeptidase albumin
Serological markers (at screening only)	Hepatitis B surface antigen Hepatitis C antibody; hepatitis C RNA only when required for documentation of sustained virologic response to reported effective treatment. HIV

AST = aspartate aminotransferase; ALT = alanine aminotransferase; HIV = human immunodeficiency virus

9.6.3 Vital Signs

- Assessment Points: All visits
- Items:
  - Blood pressure (systolic and diastolic; mmHg)
  - Heart rate (beats per minute)
  - Body temperature (°F or °C) - any route, but consistent for an individual subject
  - Respiration rate (breaths per minute)
- Method: Vital signs will be performed at study site.

9.6.4 Assessments by X-ray and MR Images

- Assessment Points: Screening visit, Week 13, 52, and discontinuation visit
- Item: Disc height (disc index), Vertebral body translation, Vertebral body angle formed by flexion, Modic classification
- Method: Imaging assessments of X-ray and MR images will be performed by a central imaging facility. The investigator or site staff will collect images and transmit them to the central imaging facility according to a separately distributed manual.

9.6.5 Post-treatment Surgery for LDH at Non-target Level

- Assessment Point: Week 52 (subjects who discontinued the study will also be followed until 52 weeks after injection)
- Item: Occurrence of lumbar disc surgery [Yes, No], Date of surgery, Target segment
- Method: At 52 weeks after injection, investigators will collect information on the occurrence of post-treatment lumbar disc surgery at levels other than where investigational product was administered, including for subjects who discontinued from the study.

9.6.6 Post-treatment Lumbar Surgery Not for LDH

- Assessment Point: Week 52 (subjects who discontinued the study will also be followed until 52 weeks after injection)
- Item: Occurrence of lumbar surgery [Yes, No], Date of surgery, Indication, Target segment, Surgical procedure
- Method: At 52 weeks after injection, investigators will collect information on the occurrence of post-treatment lumbar surgery not for LDH, including for subjects who discontinued from the study.

9.7 Other Assessments

9.7.1 Pregnancy Test

The sponsor has a responsibility to monitor the outcome of pregnancies where there has been maternal exposure to an investigational product.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the investigational product may have interfered with the effectiveness of a contraceptive medication.

Elective abortions without complications should not be handled as AEs, unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered a serious adverse event (SAE).

All pregnancies must be reported by the investigator via the eCRF. The investigator must follow up and document the course and outcome of all pregnancies, even if the subject was discontinued from the study or if the study has finished. Any SAE that occurs during pregnancy (e.g., serious maternal complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) must be reported within 24 hours in accordance with the procedure for reporting SAEs.

If a female partner of a male study subject who has been exposed to the investigational product becomes pregnant before the end of Week 13, the pregnancy and outcome of pregnancy should be monitored in the same fashion.

9.8 Subject Education

9.8.1 Accurate Pain Reporting Training

The Accurate Pain Reporting Program ("*Reporting Your Pain*," [redacted], Wayland, MA) consists of a set of subject and staff educational materials and instructions on how to accurately and reliably report pain scores and on the proper use of pain intensity scales, with the aim of increasing subjects' pain reporting accuracy. Staff training will be completed prior to performing any subject assessments. Subjects receive training at the screening visit.

9.8.2 Appropriate Expectations Training

The training "*Participating in a Research Study, What you need to know*" ([redacted], Wayland, MA) consists of a set of subject and staff educational materials for training on appropriate expectations of personal benefit while participating in a clinical trial. The purpose is to provide subjects with truthful information that will neutralize the typically excessive expectations that drive high placebo responses in clinical trials. Subjects receive initial training at the screening visit.

10 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

An AE is any untoward medical occurrence that occurs in a subject administered a investigational product, and that does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings and the imaging findings listed below), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

For this study, the following imaging findings will be recorded as AEs:

- Disc height (disc index): decrease in disc height ≥30% compared to baseline value
- Vertebral posterior angle: vertebral body angle formed by flexion of ≥5°
- Vertebral body translation: vertebral body translation of ≥3 mm
- Changes of vertebral body endplates and adjacent bone marrow as visible by MRI.
  The criteria are as follows: Modic Type 1, Type 2, or Type 3 change in vertebral body endplates and adjacent bone marrow.

Note: The above events are limited to the targeted level of the procedure and the adjacent vertebral bodies.

All AEs, including concurrent illnesses, occurring during the study will be documented in the subject source record and eCRF. Concomitant illnesses that existed before entry into the study will not be considered AEs unless they worsen after the investigational product administration. All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessments, imaging findings, subject reports) must be documented.

Pre-existing conditions will be recorded in the subject source record and eCRF on the Medical History or appropriate page.

A TEAE will be defined as an AE that begins or that worsens in severity after the investigational product has been administered.

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology.

10.1.2 Serious Adverse Events

An SAE is defined as any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening, meaning that the subject is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Results in a congenital anomaly or birth defect; or
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the above outcomes. 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.

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

AEs reported from clinical studies and associated with hospitalization or prolonged hospitalization are considered serious. Any hospitalization except observational admissions of less than 24 hours for logistical reasons meets these criteria. This category also includes transfer within the hospital to an acute/intensive care unit (e.g., from a standard-of-care unit to an acute/intensive care unit).

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities, or respite care (e.g., caregiver relief);
- Nursing homes or skilled nursing facilities;
- Emergency room visits;
- Same-day surgeries (such as outpatient/same day/ambulatory procedures); or
- <24-hour admissions for observation or evaluation for logistical reasons.

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include the following:

- Admission for treatment of a preexisting condition that did not worsen;

- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions; or
- Pre-planned treatments or surgical procedures, which should be noted in the baseline documentation for the individual subject.

10.1.3 Vital Signs and Laboratory Tests

If an abnormal laboratory finding or vital sign is observed, the investigator should judge whether it is an AE or not by referring to the following criteria:

- When any medical intervention such as pharmacotherapy or surgical care is performed in order to improve the abnormality, or
- Other than case above, when investigator judges that the abnormality is medically important and should be considered an AE.

10.1.4 Anaphylaxis

All AEs that meet the definition of anaphylaxis published by the National Institute of Allergy and Infectious Disease Food Allergy and Anaphylaxis Network (NIAID/FAAN) should be reported as SAEs throughout the study.[13]

Table 3 Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
- Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
- Reduced BP after exposure to known allergen for that patient (minutes to several hours): a. Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF = Peak expiratory flow; BP = Blood pressure

10.1.5 Adverse Events of Special Interest

For this study, the following events will be captured as Adverse Events of Special Interest (AESI) and recorded in the eCRF:

- Injection at wrong disc level

- Discitis
- Osteomyelitis
- Hematomas
- Hypersensitivity
- Imaging findings (See Section 10.1.1 for details)
  - Disc height (disc index)
  - Vertebral body translation
  - Vertebral body angle formed by flexion
  - New Modic change
- Leg pain*
- Back pain*

  *Defined as symptoms:
  - associated with primary disease;
  - caused by injection of investigational drug; or
  - related to injection procedure.

10.2 Assessment of Adverse Events

It is the responsibility of the investigator to collect all AEs, both serious and nonserious, derived by spontaneous, unsolicited reports of subjects, by observation, and by routine open questioning (e.g., "How have you felt since I last saw you?").

Adverse event recording will extend from the signing of the ICF until the AE resolves or stabilizes. If AEs are ongoing at the time of the last study visit, only treatment-related AEs will be followed beyond 12 months after investigational product administration. All AEs, regardless of the relationship to investigational product, will be recorded in the subject source record and eCRF.

All AE reports should contain a brief description of the event, date of onset, date of resolution, intensity, treatment required, timing and relationship to investigational product, action taken with the investigational product, outcome, and whether the event is classified as serious.

10.2.1 Intensity

The intensity of each AE must be assessed by the investigator using one of the following categories and recorded in the eCRF:

- Mild: No particular interference with the subject's activities of daily living or, despite slight interference, no particular intervention indicated (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1)
- Moderate: Interference with the subject's activities of daily living and minimal intervention indicated (CTCAE Grade 2)
- Severe: Disabling and almost complete interference with the subject's activities of daily living or systemic intervention indicated (CTCAE Grade 3/4)

10.2.2 Causality

The investigator will assess the causality/relationship between the investigational product and the AE and record the assessment in the eCRF. Causality will be recorded as related or not related.

The most likely cause of an SAE (e.g., disease under treatment, concomitant disease, concomitant medication, other) will be indicated in the eCRF with details of the concomitant disease or medication or other cause.

The causal relationship of the AE to investigational product will be described as:

- Not related: No temporal correlation or attributability to any other factor, such as the underlying disease, a complication, a concomitant drug, a predisposition, or concomitant intervention, can be explicitly explained.
- Related: There is a reasonable possibility that the relevant event can be judged to be due to the investigational product or a causal relationship cannot be ruled out.

10.3 Follow-up of Adverse Events

During the study, all AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until there is a reasonable explanation for the need not to follow up. If an AE is ongoing at the time of the last study visit, only treatment-related AEs will be followed beyond 12 months after investigational product administration.

10.4 Reporting Serious Adverse Events

The investigator must report any SAEs within 24 hours of becoming aware of the event. Reporting guidance will be provided separately.

The investigator and the sponsor or designee will review each SAE report and the sponsor or designee will evaluate the seriousness and the causal relationship of the event to study treatment. In addition, the sponsor or designee will evaluate the expectedness according to the reference document. Based on the investigator's and sponsor's assessment of the event, a decision will be made concerning the need for further action.

Serious adverse events occurring after the end of the study and coming to the attention of the investigator must be reported only if, in the opinion of the investigator, they are considered causally related to the investigational product.

10.5 Action Taken for Adverse Events

The investigator will treat participants experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes. If any medication is administered in response to the AE, this medication should be noted on the concomitant medication eCRF as a concomitant medication administered. The action taken and the outcome must be recorded. The term of AE resolution (e.g., Recovered/Resolved, Not recovered/Not resolved, Recovered/Resolved with sequelae, Recovering/Resolving, Fatal, Unknown) should also be recorded.

10.6 Action Taken for Serious Adverse Events

Serious adverse events will be recorded on the AE and SAE eCRFs. Sponsor or designee will provide safety reports to the Food and Drug Administration (FDA) and investigators in accordance with the regulations detailed in 21 Code of Federal Regulations (CFR) 312.32.

11 STATISICAL METHODS

The planned statistical analysis will be described in detail in a separately prepared statistical analysis plan (SAP).

11.1 Analysis Populations

The efficacy analyses will be performed on the modified intention-to-treat (mITT) population. Efficacy analyses of the per-protocol (PP) population will be supportive of the mITT analysis. The safety analyses will be performed on the safety population.

11.2 Modified Intention-to-Treat Population

The mITT population is defined as all randomized subjects who received the study injection, analyzed according to the assigned treatment.

11.3 Per Protocol Population

The PP population is defined as all mITT subjects who had no major protocol deviations that could affect the primary efficacy assessment. The details of major protocol deviations will be defined in the SAP, and included subjects will be determined prior to unblinding.

11.4 Safety Population

The safety population is defined as all randomized subjects who received the study injection, analyzed according to the treatments subjects received.

11.5 Demographics, Baseline Characteristics, Medical History, and Concomitant Medications

Baseline demographic and background variables will be summarized by treatment group and overall. For categorical variables, frequencies and percentages will be presented. For continuous variables, descriptive statistics be presented, including sample size, mean, median, standard deviation, minimum, maximum, Q1, and Q3.

11.6 Efficacy Analyses

11.6.1 Primary

The change from baseline in the worst leg pain scores will be analyzed by a mixed model for repeated measures (MMRM) analysis for Week 1 through Week 52 in the mITT population. The average worst leg pain scores over the previous 7 days will be analyzed at Week 1, 2, 4, 6, 13, 26, 39, 52 (See Section 11.8.1 for additional details). The primary comparison will be the mean change from baseline of the SI-6603 group at Week 13 compared with the control group, estimated using this model. The model will include the baseline worst leg pain score, treatment, time, treatment-by-time interaction, and duration of leg pain as fixed effects. An unstructured covariance will be used to model the covariance structure among repeated measures. Should the model fail to converge with the type = UN option, a compound symmetry structure will be used. Kenward-Roger method will be used for computing the denominator degrees of freedom. The missing data will be implicitly handled via a mixed-effect model, without explicit imputation.

11.6.2 Key Secondary

A longitudinal analysis model will be used as described in the primary efficacy analysis for the analyses of change from baseline in the herniation volume at Week 13, change from baseline in the worst leg pain score at Week 52, and change from baseline in the ODI at Week 13. The baseline value of each outcome will be included as a covariate in these models in place of the baseline worst leg pain score (from the primary analysis). Note that herniation

volume is collected only at Week 13 and 52; ODI assessment shares the same time points as the primary.

11.6.3 Other Secondary

All endpoints, including the primary and key secondary endpoints, will be summarized by treatment group and by time point. The differences of other secondary endpoints between the SI-6603 and control groups will be analyzed at each time point as below. In addition, weekly pain intensity scores will be summarized by treatment group.

- A similar longitudinal analysis model will be used as described in the primary efficacy analysis for the analysis of change from baseline in pain intensity scores, function scores, QOL scores, and volumes, by including the corresponding baseline value as the fixed effect instead of the baseline worst leg pain score.
- Neurologic status as determined by neurological examinations will be analyzed with a logistic regression model. Baseline neurologic status and duration of leg pain will be included as covariates.
- For the global assessments of PGIC score and CGIC score, responder analysis with the two best categories as “responder” will be analyzed with a logistic regression model. Baseline worst leg pain score and duration of leg pain will be included as covariates.
- Scores on the WPAI will be analyzed with the analysis of covariance model including the baseline value and duration of leg pain as covariates.
- The incidence of rescue medication use will be analyzed with Fisher’s exact test, and the amount of rescue medication use and usage of concomitant medications for LDH will be analyzed with the Wilcoxon rank sum test.
- Cumulative distribution of percentage change from baseline in worst leg pain and ODI will be generated, and differences between the SI-6603 and control groups in the percentages of subjects experiencing a >30% and >50% improvement in worst leg pain score will be analyzed with Fisher’s exact test.
- For the analysis of the percentages of responders by composite definition, differences between the SI-6603 and control groups in the percentages of positive responders will be analyzed with a logistic regression model. Baseline worst leg pain score and duration of leg pain will be included as covariates.
- Time to post-treatment surgery for LDH will be evaluated by survival analysis using the log-rank test.

11.7 Safety Analyses

Treatment-emergent AEs will be defined as any AEs that were recorded during or following the investigational product injection. Significant TEAEs will include TEAEs that result in study discontinuation.

The incidence and its exact 95% confidence intervals (CIs) will be calculated by treatment group for TEAEs, serious TEAEs, significant TEAEs, and Treatment-emergent Adverse Events of Special Interest (TEAESI). The incidences of TEAEs, serious TEAEs, significant TEAEs, and TEAESI will be tabulated according to system organ class and preferred term by treatment group. The incidences of TEAEs and TEAESI will be tabulated by severity or time of occurrence for each system organ class and preferred term. Treatment-related TEAEs will also be summarized separately.

If a subject has more than 1 occurrence of the same AE, he/she will be counted only once within that preferred term in the summary tables. The most severe occurrence of an AE, as well as the most extreme relationship of the AE to the study procedures and investigational product, will be indicated in cases of multiple occurrences of the same AE.

Vital signs, laboratory assessments, imaging findings, and occurrence of post-treatment lumbar surgery will be summarized by treatment group. In addition, association between imaging findings and clinical symptoms will be assessed.

11.8 General Considerations

11.8.1 Data Handling of Worst Leg Pain

The mean worst leg pain score from 7 consecutive days prior to each visit (the day of the visit will not be included) will be used as the worst leg pain score for each time point, after excluding the worst leg pain score on any of the following days:

- Days after prohibited concomitant therapies of lumbar operation, lumbar percutaneous nucleotomy, or lumbar intradiscal therapies occurred, and
- Days before the previous visit (for example, the Week 2 visit may fall just 5 days after Week 1; thus, the days prior to the Week 1 visit will not be considered as eligible for inclusion in the 7-day Week 2 average).

In addition, if less than 3 days of worst leg pain scores are available of the 7 consecutive days prior to a visit, the worst leg pain score will be handled as missing at the time point.

For the separate analysis of the weekly pain scores throughout the study, an average of the scores every 7 days will be calculated regardless of the visit date.

11.8.2 Visit Window and Unscheduled Assessments

All data collected during follow-up will be displayed and analyzed according to the actual visit date in the eCRF. Assessments taken outside of protocol-allowable windows will be displayed according to the eCRF assessment recorded by the investigator. Unscheduled assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in investigating or managing AEs) will be included in listings but not summaries of the data.

11.8.3 Significance Level and Confidence Coefficient

A two-sided 5% significance level for any hypothesis testing will be used, and the methodology for the adjustment of multiplicity is described in Section 11.8.5. A two-sided 95% confidence coefficient will be used for interval estimation unless otherwise specified.

11.8.4 Missing Data

For the efficacy analyses based on repeated-measures models of continuous endpoints, missing data will be implicitly handled via a mixed-effect model, without explicit imputation. Inferences based on this approach are unbiased under the assumption of missing at random, which is a weaker and more generally true assumption than missing completely at random. For the primary efficacy analysis, sensitivity analysis based on multiple imputation methods that changes imputation methods by missing pattern such as discontinuations due to AEs, lack of efficacy, and other will be performed for the mITT population.

For the analysis of percentages of positive responders by composite definition, subjects who discontinue the study because of AEs related to LDH or lack of efficacy and subsequently have missing efficacy data will be classified as non-responders.

No replacement of any missing data will be made for the safety analyses.

11.8.5 Adjustment for Multiplicity

To control family-wise error rate for multiple tests of the primary and key secondary endpoints, the following Holm-based testing algorithm will be used.

- The treatment effect on the primary endpoint will be evaluated at $\alpha = 0.05$.
- If the effect on the primary endpoint is significant, the treatment effect on the key secondary endpoints of herniation volume at Week 13 and worst leg pain score at Week 52 will be evaluated using the truncated Holm test at $\alpha = 0.05$. The truncation parameter will be set to 0.8.[14]
- If the effect on the key secondary endpoint of herniation volume at Week 13 is significant and/or the effect on the key secondary endpoint of worst leg pain score at

Week 52 is significant, the effect on the key secondary endpoint of ODI at Week 13 will be evaluated at a level that depends on the number of significant endpoints in the preceding step. If the key secondary endpoints of herniation volume at Week 13 and worst leg pain score at Week 52 are both significant, this level will be given by $\alpha = 0.05$; if only one of the two endpoints is significant, this level will be given by $\alpha = 0.005$.

11.8.6 Sample Size Determination

It is planned to enroll approximately 320 subjects, 160 in the SI-6603 group and 160 in the control group.

Sample size estimation is based on using the mean difference in the worst leg pain score change from baseline in the primary efficacy analysis. The following assumptions were made to compute the sample size:

- The 2-sample t-test comparing the group means of the change from baseline was used. (The 2-sample t-test approximates the test of the null hypothesis based on the repeated measures model that will be used in the primary efficacy analysis.)
- Treatment difference between SI-6603 and control groups of 12 mm
- Common standard deviation (SD) of 30 mm
- Dropout rate of 15%
- Power of 90%
- Two-sided significance level of 5%

12 ETHICAL CONSIDERATION

12.1 Good Clinical Practice Compliance

The procedures set out in this study protocol are designed to ensure that the sponsor, investigators, and other study participants abide by the principles of the Good Clinical Practice (GCP) guidelines of the International Conference for Harmonisation (ICH). The study also will be carried out in keeping with local legal requirements.

12.2 Institutional Review Board or Independent Ethics Committee Approval

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the sponsor will issue prompt notification to all parties, including regulatory authorities, investigators, and IRB(s). A significant safety issue is one that has a significant impact on the course of the clinical study or program (including the potential for

suspension of the development program or amendments to protocols) or warrants an immediate update of the ICF.

12.3 Data Protection

All study findings and documents will be regarded as confidential. The investigator and members of his/her research team must not disclose such information without prior written approval from the sponsor.

The anonymity of participating subjects must be maintained. Subjects will be identified on the eCRF and other documents submitted by their subject number, initials, and/or birth date, not by name. Documents not to be submitted that identify the subject (e.g., the signed ICF) must be maintained in confidence by the investigator.

12.4 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected (e.g. AE other than AEs listed in Table 6.1. in the current edition of the investigator brochure), significant, or unacceptable risk to the subjects enrolled in the study
- The occurrence of an AE considered at least possibly related to SI-6603, as noted below:
  a. Significant neurologic deficit; for example, progressive weakness or sudden loss of muscle strength, bowel or bladder dysfunction, or other signs and symptoms of cauda equine / conus medullaris involvement;
  b. Abnormal X-ray findings of instability, defined as vertebral body angle formed by flexion of ≥5° or vertebral body translation of ≥3 mm; or
  c. Abnormal X-ray or MRI findings which subjects exhibit correlating clinical symptoms posing safety concerns, leads the investigator to judge it necessary for the subject to have surgical intervention
- Failure to enroll subjects at an acceptable rate
- A decision on the part of the sponsor to suspend or discontinue development of the drug

13 PROTOCOL ADHERENCE AND INVESTIGATOR AGREEMENT

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB or competent authority, in accordance with local legal requirements.

The sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB approval prior to implementation (if appropriate). Following approval, the protocol amendment(s) will be submitted to the Investigational New Drug application under which the study is being conducted.

Administrative changes (not affecting the subject benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

14 PROCEDURE FOR COMPLETION AND CORRECTION OF THE CASE REPORT FORM

This study will use electronic data collection. Data obtained during this study should be entered in the eCRFs or collected by electronic subject diary promptly and correctly. All data entered into the eCRF should be accurate and attributable to the subject's source documents. Measurements for which source documents are usually available include laboratory assessments, MRIs, and X-rays. Some patient-reported outcomes will be completed on electronic devices by subjects and be stored in a database. These entries should not be changed by anyone except by the individual subject.

Data from external sources, such as laboratory data, MRIs, and X-rays, will be processed outside the clinical database according to the study data management plan.

15 DIRECT ACCESS TO SOURCE DATA

During the study, blinded and unblinded monitors will make site visits to review protocol compliance, compare eCRF entries and individual subject medical records, assess product accountability, and ensure that the study is being conducted according to pertinent regulatory requirements as applicable to their study role specified in the clinical monitoring plan. Entries in the eCRF will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained and the study blind is protected.

Checking of the eCRF entries and other study electronic systems for completeness and clarity and cross-checking with source documents will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, and/or the sponsor may wish to carry out such source data checks and/or on-site audit inspections. Direct access to

source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The investigator assures the sponsor or designee of the necessary support at all times.

16 DATA QUALITY ASSURANCE

The sponsor or designee will conduct a site visit to verify the qualifications of each investigator, inspect the site facilities, and inform the investigator of the responsibilities and procedures for ensuring adequate and correct documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded in the eCRF for this study must be consistent with the subjects' source documentation (e.g., medical records).

17 ARCHIVING OF SOURCE DATA AND OTHER RECORDS

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

18 LIABILITY AND INSURANCE

The sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The sponsor will arrange for subjects participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

19 PUBLICATION POLICY

By signing the study protocol, the investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, regulatory authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

An investigator shall not publish any data (e.g., poster, abstract, or paper) without having consulted with the sponsor in advance and having received written authorization.

20 REFERENCES

1. John A McCulloch ET. Macnab's Backache. 4th ed: *Williams & Wilkins*; 2006.

2. Saal JA, Saal JS. Nonoperative treatment of herniated lumbar intervertebral disc with radiculopathy. An outcome study. *Spine*. 1989 Apr;14(4):431-7.

3. Weber H. Lumbar disc herniation. A controlled, prospective study with ten years of observation. *Spine*. 1983 Mar;8(2):131-40.

4. Peul WC, van Houwelingen HC, van den Hout WB, Brand R, Eekhof JA, Tans JT, et al. Surgery versus prolonged conservative treatment for sciatica. *The New England journal of medicine*. 2007 May 31;356(22):2245-56.

5. Weinstein JN, Tosteson TD, Lurie JD, Tosteson AN, Hanscom B, Skinner JS, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial. *Jama*. 2006 Nov 22;296(20):2441-50.

6. Smith L. Enzyme Dissolution of the Nucleus Pulposus in Humans. *Jama*. 1964 Jan 11;187:137-40.

7. Gibson JN, Grant IC, Waddell G. The Cochrane review of surgery for lumbar disc prolapse and degenerative lumbar spondylosis. *Spine*. 1999 Sep 1;24(17):1820-32.

8. Agre K, Wilson RR, Brim M, McDermott DJ. Chymodiactin postmarketing surveillance. Demographic and adverse experience data in 29,075 patients. *Spine*. 1984 Jul-Aug;9(5):479-85.

9. Yamagata T, Saito H, Habuchi O, Suzuki S. Purification and properties of bacterial chondroitinases and chondrosulfatases. *The Journal of biological chemistry*. 1968 Apr 10;243(7):1523-35.

10. Hamai A, Hashimoto N, Mochizuki H, Kato F, Makiguchi Y, Horie K, et al. Two distinct chondroitin sulfate ABC lyases. An endoeliminase yielding tetrasaccharides and an exoeliminase preferentially acting on oligosaccharides. *The Journal of biological chemistry*. 1997 Apr 4;272(14):9123-30.

11. Shrimpton PC, Wall BF, Hart D. Diagnostic medical exposures in the U.K. *Applied radiation and isotopes* : including data, instrumentation and methods for use in agriculture, industry and medicine. 1999 Jan;50(1):261-9.

12. McGirt MJ, Eustacchio S, Varga P, Vilendecic M, Trummer M, Gorensek M, et al. A prospective cohort study of close interval computed tomography and magnetic resonance imaging after primary lumbar discectomy: factors associated with recurrent disc herniation and disc height loss. *Spine*. 2009 Sep 1;34(19):2044-51.

13. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *The Journal of allergy and clinical immunology*. 2006 Feb;117(2):391-7.

14. Dmitrienko A, Tamhane A. C, Wiens B. L General multistage gatekeeping procedures: *Biometrical Journal*. 2008 Oct 50(5):667-77.