PROTOCOL TITLE

A Multicenter, Open-label Study of SI-6603 in Patients with Lumbar Disc Herniation (Phase III)

Sponsor:	Seikagaku Corporation 6-1, Marunouchi 1-chome, Chiyoda-ku, Tokyo 100-0005, Japan
Clinical Research Organization:	PAREXEL International 195 West Street Waltham, MA 02451, USA
Principal Investigator:	To be assigned
Sponsor Protocol No.:	6603/1132
IND No.:	100,398
EudraCT No.:	2014-001449-26
Study Drug Name:	SI-6603
Development Phase:	Phase III Study
Date of Protocol:	24 June 2016
Version Number	4.0
Date of Previous Protocol:	9 September 2015

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki[1] and with other applicable regulatory requirements.

SIGNATURE PAGE

Declaration of Sponsor

Title: A Multicenter, Open-label study of SI-6603 in Patients with Lumbar Disc Herniation (Phase III)

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, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, [2013][1], and the guidelines on Good Clinical Practice.

_____ _____

[redacted] Date

General Manager, Clinical Development Department
Research and Development Division
Seikagaku Corporation

Declaration of the Principal Investigator

Title: A Multicenter, Open-label study of SI-6603 in Patients with Lumbar Disc Herniation (Phase III)

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in [2013][1] and the guidelines on Good Clinical Practice.

Principal Investigator

_____ _____

Name
Title
Institution

Date

Declaration of the National Coordinating Investigator

Title: A Multicenter, Open-label study of SI-6603 in Patients with Lumbar Disc Herniation (Phase III)

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in [2013][1] and the guidelines on Good Clinical Practice.

National Coordinating Investigator

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

Declaration of the Investigator

Title: A Multicenter, Open-label study of SI-6603 in Patients 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. This documentation includes this study protocol, Investigator's Brochure, electronic Case Report Form (eCRF) and other scientific data.

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

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

Responsible Investigator of the local study center

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

PROTOCOL SYNOPSIS

Title	A Multicenter, Open-label study of SI-6603 in Patients with Lumbar Disc Herniation (Phase III).
Sponsor Study No.	6603/1132
Phase	Phase III Study
Sponsor	Seikagaku Corporation
Principal Investigator	Not yet assigned
Study Center(s)	Approximately 80 centers located in the United States of America (USA) and European Union (EU).
Objective	The primary study objective is to evaluate the safety of a single-dose intervertebral disc injection of SI-6603 (a lyophilized injectable drug containing condoliase as the active ingredient) at a dose of 1.25 units (U) in patients with lumbar disc herniation, for a 26-week follow-up period.
Design	This is a multicenter, open-label study to monitor the safety and efficacy of SI-6603. The study duration for each patient will be approximately 30 weeks: a 4-week Screening period, a 1-day Treatment Administration Day, and a 26-week follow-up period.
Treatment	Patients will receive a single-dose injection of SI-6603 1.25 U into an intervertebral disc.
Number of Patients	Approximately 1000 patients are planned to be enrolled into this study.
Population	The study population will consist of male and female patients, 30 to 70 years of age at the time of informed consent, with lumbar disc herniation between adjacent lumbar vertebra (L1–L2, L2–L3, L3–L4, L4–L5), or between the 5th lumbar vertebra and the 1st sacral vertebra (L5–S1) "protrusion type" or "extrusion type" in the posterior lateral or central location as assessed by magnetic resonance imaging (MRI) and clinical symptoms corresponding to the level of the impaired nerve root.

Criteria for Evaluation of Safety	The following safety endpoints will be assessed:
	• Occurrence of adverse events (AEs)
	• Stability evaluation of vertebral bodies by X-ray
	  – Translation of vertebral body
	  – Vertebral body angle formed by flexion
	• Changes from baseline in disc height (disc index) assessed by X-ray
	• Changes of disc degeneration and vertebral body endplates, and adjacent bone marrow as assessed by MRI
	  – Modic classification
	  – Pfirrmann classification
	• Clinically significant changes in vital signs
	• Clinically significant changes in clinical laboratory tests
	• Serum anti-SI-6603 antibody
	• Occurrence of post-treatment lumbar surgery other than surgery for lumbar disc herniation at the same level of the investigational drug administration

Criteria for Evaluation of Efficacy	The following secondary efficacy endpoints will be assessed from baseline through Week 26: • Worst leg pain during the past 24 hours assessed by Visual Analog Scale (VAS). • Worst back pain during the past 24 hours assessed by VAS. • Functional disability measured by the Oswestry Disability Index (ODI). • Change of neurological status from baseline determined by neurological examinations (Femoral Nerve Stretching [FNS] test [for patients with lumbar disc herniation L1–L2, L2–L3, or L3–L4] or Straight Leg Raising [SLR] test [for patients with lumbar disc herniation L4–L5 or L5–S1], sensation, muscle strength, and deep tendon reflex). • Occurrence of post-treatment surgery for lumbar disc herniation at the same level of administration of the investigational drug up to Week 26 including patients who discontinued from the study.
Statistical Methods	All statistical tests will be performed 2-sided with a significance level of 5%, unless otherwise stated. The following populations will be assessed: • Safety: All patients who were treated with the investigational drug • Intent-to-Treat (ITT): All patients who were treated with the investigational drug The primary objective is the assessment of safety by evaluating the above listed safety endpoints. Safety analyses will be performed on the safety population. The incidence of AEs and associated 95% confidence interval (CI) will be determined and presented. Similar analyses will be conducted for other safety endpoints with categorical outcomes. Safety outcomes with continuous variables will be summarized descriptively. The research hypothesis is that the treatment of 1.25 U of SI-6603 followed for 26 weeks after administration of a single dose is a safe treatment. The total of 1000 patients are to be enrolled in order to further characterize the frequency and outcome of the treatment-related AE. Categorical variables will be summarized by the number and percentage of patients in each category. Continuous variables will be summarized by number of observations, mean, standard deviation, median, inter-quartile range, minimum, and maximum. Where data are collected over time, both the observed data and change from the Screening period (baseline) will be summarized at each time point. All electronic Case Report Forms (eCRF) collected and derived data will be listed.
Schedule of Procedures	The schedule of procedures and assessments is detailed in *Table 3* and located in Section 7.1.

LIST OF STUDY PERSONNEL

Sponsor	[redacted] General Manager, Clinical Development Department Research and Development Division Seikagaku Corporation [redacted] Assistant Manager, Clinical Development Department Research and Development Division Seikagaku Corporation 6-1, Marunouchi 1-chome, Chiyoda-ku, Tokyo 100-0005, Japan Telephone number: +81-(0)-3-5220-8593 Fax number: +81-(0)-3-5220-8594.
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Principal Investigator	Not assigned yet
Contract Research Organization	PAREXEL International 195 West Street Waltham, MA 02451, USA Telephone number: +1-781-487-9900 Fax number: +1-781-487-0525
Serious Adverse Event Reporting	PAREXEL North American Medical Services One Federal Street Billerica, MA 01821, USA Serious adverse event (SAE) fax number: +1-781-434-5957 SAE hotline: +1-781-434-5010
Central Laboratory	Eurofins Global Central Laboratory 2430 New Holland Pike 17601 Lancaster PA – USA Tel: +1 717 556 7350

Anti-SI-6603-Antibodies	Envigo CRS, Inc. Princeton Research Center (PRC) Biomarkers, Bioanalysis and Clinical Sciences (BBC) 100 Mettlers Road East Millstone, NJ 08875-2360, USA Tel: +1 732 873 2550
Central X-ray and Magnetic Resonance Imagining Reader	BioClinica 7707 Gateway Boulevard, 3rd Floor Newark, CA 94560, USA Telephone number: +1-415-817-8900 Fax number: +1-415-817-8960
Drug Packaging Vendor	Catalent Pharma Solutions 14 Schoolhouse Road Somerset, NJ 08873, USA

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
DRL	Drug Reference List
eCRF	Electronic Case Report Form
EU	European Union
FNS	Femoral Nerve Stretching
HEK	Human embryonic kidney
hERG	human Ether-à-go-go-related gene
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethic Committee
Ig	Immunoglobulin
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat (population)
L1–L2	The disc between the 1st and 2nd lumbar vertebra
L2–L3	The disc between the 2nd and 3rd lumbar vertebra
L3–L4	The disc between the 3rd and 4th lumbar vertebra

L4–L5	The disc between the 4th and 5th lumbar vertebra
L5–S1	The disc between the 5th lumbar vertebra and 1st sacral vertebra
LSM	Least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
mSv	Millisievert
mU	Milliunit
NOAEL	No-observed-adverse-effect level
ODI	Oswestry Disability Index
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviations
SI-6603	Condoliase, an active ingredient of SI-6603 injectable solution
SKK	Seikagaku Corporation
SLR	Straight Leg Raising (test)
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
U	Units
ULN	Upper limit of normal
USA	United States of America
VAS	Visual Analog Scale
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

Seikagaku Corporation (SKK) is developing SI-6603, a lyophilized injectable drug containing condoliase as the active ingredient. In 1991, SKK started investigations into the safety and efficacy of SI-6603 as a chemonucleolysis drug for the treatment of lumbar disc herniation. The Phase I/II, Phase II/III, Phase III clinical studies in Japan, and Phase II clinical study in the United States of America (USA) have been completed, and a Phase III clinical study in the USA is currently being conducted.

Lumbar disc herniation occurs as a result of a protrusion or prolapse of the nucleus pulposus of a disc into the spinal canal following partial or complete perforation and destruction of the posterior annulus fibrosus. When this occurs, the nerve root is compressed by the nucleus pulposus, causing various symptoms including leg pain, back pain, and numbness.[2] The principal treatment for lumbar disc herniation is conservative, resulting in an approximately 90% response.[3,4] Conservative treatment includes rest, bed-rest, medication (e.g., nonsteroidal anti-inflammatory drugs, steroids, and muscle relaxants), corset, traction therapy, thermotherapy, epidural block, nerve root block, and physical therapy. Approximately 20% to 50% of the patients are eligible for surgical treatment when no improvement is observed following conservative treatment.[5] To reduce 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 lumbar disc herniation using the enzyme chymopapain (a protease), which is injected into an intervertebral disc to reduce nerve root compression through lysis of the nucleus pulposus and reduction of disc pressure.[2] 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 is currently positioned as the final step in conservative treatment as minimally invasive and effective treatment.[6,7]

Although chymopapain has been approved and used in the USA, Europe, Canada, and Korea as a drug for chemonucleolysis, the use is limited due to its non-specific protease activity.[8,9] Although it is rare, serious neurological complications (e.g., paraplegia, transverse myelitis, cerebral hemorrhage, subarachnoid hemorrhage, and quadriplegia) were reported.[8] Therefore, drugs that are highly specific to the nucleus pulposus alone and that do not influence nerve tissue surrounding the disc are needed for safe and effective chemonucleolysis.[10]

Condoliase is a glycosaminoglycan-decomposing enzyme isolated and purified from a gram-negative rod, *Proteus vulgaris*.[11] Condoliase has substrate specificity for chondroitin sulfate, dermatan sulfate, and hyaluronic acid which are components of glycosaminoglycan chains that exists in proteoglycans in nucleus pulposus, but not for

keratan sulfate, heparin, or heparan sulfate.[12] In addition, unlike chymopapain, condoliase lacks protease activity. In lumbar disc herniation, condoliase is thought to decompose glycosaminoglycan chains, such as chondroitin sulfate in the proteoglycans of the nucleus pulposus and to reduce the high water retention attributable to proteoglycans, thereby relieving disc pressure and compression on the spinal nerve root caused by lumbar disc herniation. Due to its substrate specificity and lack of protease activity when compared with chymopapain, with condoliase chemonucleolysis, the risk of adverse effects such as nerve tissue injuries in the area surrounding intervertebral discs can be minimized with condoliase chemonucleolysis.

1.1.1 Summary of Clinically Significant Findings Obtained in Non-Clinical Studies

1.1.1.1 Pharmacology

In the primary pharmacology studies of SI-6603, the following effects have been investigated: the inhibitory effect on nucleus pulposus swelling and the effect of releasing nucleus pulposus components *in vitro*, the effect of decreasing intradiscal pressure, and the disc height reducing effect which is observed as an event accompanied with regression of the nucleus pulposus *in vivo*. The efficacy of SI-6603 for intervertebral disc herniation was investigated by the improvement of disc hernia syndrome after intradiscal injection of SI-6603 in dogs with disc herniation.

1.1.1.2 Safety Pharmacology

In safety pharmacology studies, no effects on the central nervous system or respiratory system in rats, or cardiovascular system in dogs were observed after single subcutaneous administration of SI-6603 at 0.2, 2 or 20 units (U)/kg. At concentrations up to 4.36 milliunit (mU)/mL, SI-6603 had no effects on human Ether-à-go-go-related gene (hERG) current in a patch-clamp assay using hERG-transfected human embryonic kidney (HEK) 293 cells *in vitro*.

1.1.1.3 Pharmacokinetics and Metabolism

When ^{125}I-SI-6603 was injected intradiscally in beagle dogs at a single-dose of 50 U/disc, the radioactivity concentration was nearly constant for 14 days with a level ranging from 0.2 to 0.5 mU equivalent per milliliter (mU eq/mL). Furthermore, the plasma SI-6603 concentrations were below the lower limit of quantification at all-time points of measurement, and the concentration in major tissues was low, suggesting that SI-6603 could be slowly distributed in the systemic circulation after a single intradiscal injection. The enzyme activity in the injected intervertebral discs remained up to 14 days after the administration, and the radioactivity showed that SI-6603 remained in the injected intervertebral disc for a long time while preserving its substantial enzyme activity. When the study was repeated in beagle dogs by injecting ^{125}I-SI-6603 intradiscally at a reduced single-dose of 2 U/disc, the SI-6603 enzyme activity was

detected even up to 30 days in the injection site. A similar result was found in cynomolgus monkeys when ^{125}I-SI-6603 was injected intradiscally at a single-dose of 2 U/disc.

1.1.1.4 Toxicology

In consideration of the clinical administration route, the potential for tissue injury on or surrounding the intervertebral disc following intradiscal administration of SI-6603 was evaluated. The potential for systemic toxicity was evaluated in studies using the intravenous, subcutaneous and intramuscular routes of administration.

In the long-term (3-month to 3-years) observation studies following a single-dose intradiscal injection of SI-6603, histological changes related to pharmacological effects of SI-6603 were observed in cynomolgus monkeys, rabbits and dogs, i.e., degenerative changes of the nucleus pulposus and annulus fibrosus. In addition to these common changes, in cynomolgus monkeys, other changes were observed from 1 week after administration including cellular degeneration and necrosis, and decreased staining in both the cartilaginous endplate and epiphysial growth plate. In the vertebral body, decrease and necrosis of bone marrow cells and changes associated with new bone formation were observed. In addition, cellular regeneration, vascular invasion and ossification in the cartilaginous endplate, and focal disappearance of the epiphysial growth plate were observed from 4 weeks after administration. At 13 weeks after administration, some histological changes showed a clear tendency of recovery, and at 26 weeks after administration, no necrotic changes were observed in sites ranging from the cartilaginous endplate to the vertebral body. The histological features of the cartilaginous endplate and epiphysial growth plate at 26 weeks after administration are qualitatively similar to those reported in humans, who exhibit aging-related thinning, ossification or disappearance of the cartilaginous endplate and epiphysial growth plate. In rabbits, no remarkable changes except for osteocyte necrosis in vertebral body adjacent to the cartilaginous endplates were observed. In dogs, protrusion of nucleus pulposus tissues into the bone marrow cavity of the vertebral body (Schmorl's nodes-like lesions) was observed, associated with degeneration of cartilaginous endplates.

It is considered that the intervertebral disc structure in the cynomolgus monkey is most similar to that in humans among the laboratory animals used. Therefore the cynomolgus monkey would be the most relevant species to predict the effects of SI-6603 in humans. In cynomolgus monkeys, adverse effects were noted in sites ranging from the cartilaginous endplate to a part of the vertebral body from 1 to 13 weeks after administration. But these effects were not severe, and some histological changes showed a clear tendency of recovery. At 26 weeks after administration, the histological changes subsided and the histological features were indicative of recovery, even at a dose just below 500 times the recommended clinical dose which was calculated based on the ratio of the nucleus pulposus volume. This result suggests that SI-6603 is unlikely to cause serious histological changes in the clinical setting.

In the short-term (within 7-days) observation studies following a single-dose intradiscal injection of SI-6603 in rabbits, which were conducted as local tolerance studies, only nucleus pulposus was affected and no changes were seen in the annulus fibrosus, cartilaginous endplate, vertebral body, and their surrounding tissues at 0.075 U/disc (20 times the recommended clinical dose). At 2 U/disc (534 times the recommended clinical dose), pharmacological and its related effects extended to the annulus fibrosus. In addition, changes in bone tissues surrounding the intervertebral disc were seen. SI-6603 was also administered to the spinal subarachnoid space, spinal nerve root or muscle of rabbits. The nerve tissues exhibited good tolerance but transient and mild irritation was observed in muscle tissues.

In the single-dose toxicity studies (intravenous, intramuscular, and subcutaneous administrations) in mice, rats and dogs, no remarkable findings were observed except for sluggishness, whining, ataxia, paralysis and hunching which were transiently observed in dogs. Approximate lethal doses were over 2000 U/kg in these species. In the repeated-dose (1 month) toxicity studies in rats and dogs, no marked abnormalities were found, although the appearance of anti-SI-6603 antibodies and subsequent increases in the antibody titer were found. No-observed-adverse-effect levels (NOAELs) were considered to be 200 U/kg or greater for both species.

No potential genotoxicity was noted for SI-6603. For the reproductive and developmental toxicity studies in rats and rabbits, no abnormalities were seen in early embryonic development to implantation, fetal organogenesis, pre- and postnatal development, including maternal function in all reproductive and developmental toxicity studies. In the dermal irritation studies in guinea pigs, no primary irritative effects on the skin were noted after the intradermal administration of SI-6603, although the white discoloration around the injection area was observed. The antigenicity studies in guinea pigs showed positive results because SI-6603 is a foreign protein derived from the bacterium *Proteus vulgaris*.

1.1.2 Summary of Important Findings Obtained in Prior Clinical Studies

1.1.2.1 Phase I/II Clinical Study in Patients with Lumbar Disc Herniation (Study Number: SKK0197) (Sweden)

A Phase I/II study was conducted in patients with lumbar disc herniation of the disc between the 4th and 5th lumbar vertebra or between the 5th lumbar and 1st sacral vertebra (L4–L5 or L5–S1), with the intention of administering SI-6603 at doses of 0.25 U/mL (0.5 U dose group), 1.25 U/mL (2.5 U dose group) and 5 U/mL (10 U dose group) with a maximum volume of 2 mL. A decision was made to discontinue the study for non-safety-related reasons and data were compiled for the 0.5 U dose group to the time of termination.

In the 0.5 U dose group (single-dose injections with an upper limit of 0.5 U), 9 adverse events (AEs) in 3 patients included back pain (5 events/2 patients), lumbar fatigability

(3 events/1 patient), and vomiting (1 event/1 patient). Back pain occurred as a serious adverse event (SAE) (1 event/1 patient) and was assessed as being unrelated to SI-6603. No AEs involving the cartilage endplates, annulus fibrosus, or adjacent discs were recorded.

1.1.2.2 Phase I/II Clinical Study in Patients with Lumbar Disc Herniation (Study Number: SKK6603J01) (Japan)

This was a single-dose study in patients with lumbar disc herniation (L4–L5 or L5–S1). Eighteen patients who were administered SI-6603 at 0.5 U, 2.5 U, or 10 U reported a total of 67 AEs. The AEs occurring at a high frequency and within each dosage group included back pain (66.7%) and puncture site reactions (55.6%). The SAEs (seriousness criterion: prolonged existing hospitalization) comprised 5 events in 2 patients in the 0.5 U dose group: back pain in 1 patient and pruritus, exanthem, skin warm and dermatitis bullous in another patient. Anti-SI-6603 antibodies (immunoglobulin [Ig] E and IgG) were negative in all groups throughout the study. All patients in the 2.5 U and 10 U dose groups were negative on prick test. In the 10 U dose group, abnormal spinal X-rays were detected in 33.3% of cases (2 of 6).

The 10 U/mL/disc dose was associated with tolerance problems; therefore, the planned dose escalation to 40 U was terminated. The safety of SI-6603 at doses up to 2.5 U/mL by intervertebral disc administration was established for the treatment of patients with lumbar disc herniation.

Plasma concentrations of SI-6603 determined in each dosage group during 12 weeks following administration were all below the lower limit of quantification (100 μU/mL). Additionally, the time-course of plasma chondroitin sulfate concentration exhibited a slight decrease 2 and 6 hours after administration in the 2.5 U dose group, however, no changes were observed at other time points in all dosage groups. Conversely, serum keratan sulfate concentrations tended to increase within 24 hours after administration in each dosage group and then decreased to roughly baseline values by 12 weeks after administration. Analysis of the area under the serum concentration-time curve of keratan sulfate in each dosage group revealed a statistically significant dose-response relationship.

1.1.2.3 Prognostic Study of Patients with Lumbar Disc Herniation Administered with SI-6603 in Japanese Phase I/II Clinical Study (Japan)

A retrospective follow-up study was conducted 6 years after the initial study to confirm the long-term effects of SI-6603 on the degeneration of nucleus pulposus and vertebral stability of intradiscal administration.

Ten of the total 18 patients who participated in the initial Phase I/II clinical study consented to participate in this study. The observation period was 3.2 to 77.8 months after administration.

No patients had progressive disc height decrease, worsening of clinical symptoms, or lumbar surgery after the administration of SI-6603.

There were no clinically problematic events such as progressive decrease of disc height and worsening of clinical symptoms, and the findings were unchanged from the final observation time of the initial Phase I/II study (SKK6603J01). In patients who had changes in imaging findings, no clinical symptoms accompanied the changes. The results of this study supported the long-term safety of the disc and its surrounding tissue after administration of SI-6603.

1.1.2.4 Prick test of SI-6603-P in Healthy Adult Volunteers (Study Number: SKK6603J02) (Japan)

This study in 20 healthy volunteers was to evaluate skin irritation and safety of SI-6603-P (lyophilized injectable drug preparation with condoliase as the ingredient). The prick test was performed at doses of 5 U/mL, 10 U/mL, 20 U/mL, 40 U/mL, and 80 U/mL using a prick lancet. None of the patients tested positive and all AEs were assessed as unrelated to SI-6603 administration.

No skin irritation was observed and SI-6603 was confirmed to be safe for clinical application.

1.1.2.5 Phase II/III Clinical Study in Patients with Lumbar Disc Herniation (Study Number: 6603/1021) (Japan)

This was a multicenter, randomized, double-blind, placebo-controlled, comparative study that sought to verify the superiority of SI-6603 versus a placebo at 13 weeks after single-dose administration of 1.25 U, 2.5 U, or 5 U of SI-6603 or placebo into the nucleus pulposus of an intervertebral disc of patients with lumbar disc herniation (L4–L5 or L5–S1). An additional objective of this study was to determine a recommended dose for SI-6603 by monitoring the stability of the intervertebral disc and surrounding tissue for up to 52 weeks after administration.

The least squares mean (LSM) of the primary endpoint of change from baseline in worst leg pain over the past 24 hours at Week 13 was –31.7 mm in the placebo group, –46.7 mm in the 1.25 U dose group, –41.1 mm in the 2.5 U dose group, and –47.6 mm in the 5 U dose group. There were significant differences for all SI-6603 groups compared to the placebo group.

The LSM change from baseline in worst leg pain at the final observation in Week 52 was about the same in all SI-6603 groups: –46.1 mm in the placebo group, –60.7 mm in the1.25 U dose group, –59.3 mm in the 2.5 U dose group, and –62.6 mm in the 5 U dose group. There were significant differences for all SI-6603 groups compared to the placebo group.

SAEs were reported in 5 of the 194 patients treated with SI-6603 or placebo, but no causal relationship with SI-6603 or placebo was established for any of these events.

Severe AEs occurred in 10 of the 147 patients in the SI-6603 groups. A causal relationship with SI-6603 or placebo could not be ruled out for 2 patients in the 2.5 U dose group (neutrophil count decreased and lymphadenitis).

The incidence of treatment-related AEs was found to be dose responsive at 14.9% in the placebo group, 46.9% in the 1.25 U dose group, 44.9% in the 2.5 U dose group, and 61.2% in the 5 U dose group.

Treatment-related AEs with a high incidence in the SI-6603 groups were nuclear magnetic resonance imaging (MRI) abnormal, back pain, and spinal X-ray abnormal. Incidences of back pain, nuclear MRI abnormal, and spinal X-ray abnormal were high in each of the SI-6603 groups compared to the placebo group, with the latter treatment-related AE occurring most frequently in the 5 U dose group. All AEs were classified as mild or moderate by the Investigators. There was no observed increase in the AE incidence of leg and low back pain accompanying the occurrence of AEs relating to stability of the intervertebral disc and surrounding tissues.

No patients were found to have a definitely elevated serum anti-SI-6603 IgE antibody titer. At Week 13, one patient each from the 2.5 U and 5 U dose groups exhibited a definitely elevated serum anti-SI-6603 IgG antibody titer, but neither experienced any AEs characterized by allergy-like symptoms.

Plasma SI-6603 concentration was below the limit of quantification in all patients at all time points (<100 μU/mL).

1.1.2.6 Phase II Clinical Study in Patients with Lumbar Disc Herniation (Study Number: 6603/1121) (USA)

This study was an open-label, multicenter, sequential dose-escalation study. The objective of this study was to evaluate the safety of SI-6603 in lumbar disc herniation patients (L4–L5 or L5–S1) followed for 52 weeks after administration of SI-6603 into an intervertebral disc. Exploratory efficacy endpoints were investigated. Patients received a single 1.0 mL injection of SI-6603 (0.5 U, 1.25 U, or 2.0 U) into the nucleus pulposus of an intervertebral disc of each patient. A Data Safety Monitoring Board (DSMB) evaluated safety and tolerability once the Week 13 data were available for each cohort. On the basis of the recommendation of the DSMB, the Sponsor proceeded to the next higher dose for the second (1.25 U) and third cohorts (2.0 U).

A total of 17 patients (94.4%) in the safety population experienced 39 AEs. Two patients (11.1%) discontinued the study due to an AE and no patient discontinued due to a treatment-related AE. No patient experienced a SAE or died during the study.

The most frequently observed treatment-related AE with an incidence of ≥3 patients in the total safety population was nuclear MRI abnormal (4 patients, 22.2%). The event was all mild in intensity and did not require intervention in all patients. The following 3 treatment-related AEs (each reported for a different patient) were not resolved before the end of the study: nuclear MRI abnormal, spinal X-ray abnormal, and dysesthesia.

Clinical observations of the patients with these treatment-related AEs were terminated after each patient's condition was determined to be stable.

Evaluation of translation and angulation of vertebral bodies did not raise safety concerns. One patient had a decrease in disc height ≥30%. Overall, 6 patients (33.3%) in the safety population had a change to Modic classification Type I or II, which included 1 patient (20.0%) in the 0.5 U dose group, 3 patients (50.0%) in the 1.25 U dose group, and 2 patients (33.3%) in the 2.0 U dose group.

No patient had an increase in serum anti-SI-6603 IgE antibody titer. At Week 13, one patient each from the 0.5 U, 1.25 U and 2.0 U dose groups had an IgG antibody titer that was increased by one grade from baseline, but with unclear SI-6603 specificity.

Efficacy evaluations showed improvement from baseline in leg pain Visual Analog Scale (VAS). At Week 13, the mean worst leg pain values that were assessed during the 7 days prior to the Week 13 visit were 9.1 mm in the 0.5 U dose group, 38.4 mm in the 1.25 U dose group, and 5.1 mm in the 2.0 U dose group. Improvement of the worst leg pain in the treatment groups also continued beyond Week 13. At screening (baseline), the values were 65.9 mm in the 0.5 U, 70.8mm in the 1.25 U, and 81.7mm in the 2.0 U, at the final observation at Week 52 the values were 24.0 mm in the 0.5 U dose group, 39.0 mm in the 1.25 U dose group, and 13.2 mm in the 2.0 U dose group. Mean worst back pain values at Week 52 that were assessed during the 7 days prior to Week 52 visit were lowest in the 2.0 U dose group (11 mm) and highest in the 1.25 U dose group (45 mm).

The plasma SI-6603 concentration was below the limit of quantification in all patients at all time points (<100 μU/mL).

In conclusion, SI-6603 was well tolerated for up to 52 weeks after administration with no major safety concerns. SI-6603 improved leg pain and underlying symptoms of lumbar disc herniation.

1.1.2.7 Phase III Clinical Study in Patients with Lumbar Disc Herniation (Study Number: 6603/1031) (Japan)

This study was a multicenter, randomized, double-blind, placebo-controlled, comparative study that sought to verify the superiority of SI-6603 versus a placebo at 13 weeks after single-dose administration of 1.25 U of SI-6603 or the placebo into the nucleus pulposus of an intervertebral disc of patients with lumbar disc herniation (L4–L5 or L5–S1). A further objective of this study was to monitor the stability of the intervertebral disc and surrounding tissue up to 52 weeks after administration.

The LSM of the primary endpoint of change from baseline in worst leg pain over the past 24 hours at Week 13 was –34.3 mm in the placebo group and –49.5 mm in the 1.25 U group showing significant difference for the 1.25 U group compared to the placebo group.

The LSM change from baseline in worst leg pain at the final observation in Week 52 was −42.3 mm in placebo group and −54.2 mm in 1.25 U group; showing significant difference for SI-6603 group compared to the placebo group.

In the safety evaluation, SAEs were seen in 10 of the 163 patients treated with the investigational drugs (placebo group: 6 patients and 1.25 U group: 4 patients). In 10 patients with SAEs, a causal relationship with the investigational drug could not be ruled out for 1 patient in the 1.25 U group with back pain. Five patients in the placebo group discontinued the study due to an AE but no causal relationship with investigational drug was established for any of these events. Severe AEs occurred in 13 of the 163 patients treated with the investigational drug (placebo group: 7 patients and 1.25 U group: 6 patients). A causal relationship with the investigational drug could not be ruled out for 1 patient in the 1.25 U group with toxic skin eruption.

The incidence of treatment-related AEs was 33.3% in the placebo group and 57.3% in the 1.25 U group, with a significant difference between the 1.25 U group and the placebo group.

In the 1.25 U group, treatment-related AEs with a high incidence were back pain (placebo group: 4.9%; 1.25 U group: 24.4%), nuclear MRI abnormal (placebo group: 12.3%; SI-6603 group: 24.4%), and spinal X-ray abnormal (placebo group: 3.7%; SI-6603 group: 23.2%). Treatment-related AEs in the1.25 U group with an incidence that is higher by10% or more than placebo were back pain, nuclear MRI abnormal, and spinal X-ray abnormal. The severity of all treatment-related AEs with high incidence was mild or moderate. Patients in the 1.25 U group with AEs relating to the stability of the intervertebral disc (decrease in disc height of ≥30% and intervertebral posterior angle of ≥5°) showed a trend towards a high incidence of the treatment-related AE of low back pain.

No patients were found to have an elevated serum anti-SI-6603 IgE antibody titer. One patient each from the placebo group and the 1.25 U group exhibited an elevated serum anti-SI-6603 IgG antibody titer but neither experienced any AEs characterized by allergy-like symptoms.

1.1.3 Additional Information

Further details can be found in the current Investigator's Brochure (IB), which contains comprehensive information on SI-6603[13].

1.1.4 Current Study

The current study is a Phase III, multicenter, open-label, study of SI-6603 in patients with lumbar disc herniation. Patients will receive a single intradiscal dose of SI-6603 1.25 U injection. Safety and efficacy will be followed for 26 weeks after investigational drug administration. See Section 3.1 for details concerning the design of the current study and Section 3.3 for study design justification of this study.

1.2 Rationale

1.2.1 Study Rationale

Lumbar disc herniation is treated primarily with conservative non-operative therapy. However, in patients who fail to respond to this therapy, surgery is one of the only remaining options. The target population of this study is patients with signs and symptoms of lumbar disc herniation who failed conservative therapy and who have not received surgery at the target level or who qualify for surgery but wish to avoid it. Patients who require immediate surgical intervention such as those with significant neurologic deficit will be excluded.

The results of the Japanese Phase II/III clinical study (Study Number: 6603/1021) suggest that SI-6603 intradiscal injection is safe and effective in improving the signs and symptoms of lumbar disc herniation. In addition, the Japanese Phase III clinical study (Study Number: 6603/1031) verified that SI-6603 intradiscal injection is safe and effective in improving the signs and symptoms of lumbar disc herniation. Therefore, conducting a further clinical study intended to assess safety and efficacy of intradiscal SI-6603 at a dose of 1.25 U was proposed.

1.2.2 Rationale for Dose and Schedule Selection

The intradiscal route was selected as the route of SI-6603 administration for this study. SI-6603 acts by decreasing intradiscal pressure and ameliorating pressure on the spinal nerve root by decomposing glycosaminoglycan chains (e.g., chondroitin sulfate) of proteoglycan present in the nucleus pulposus of an intervertebral disc. This reduced the water retention by the proteoglycan.

The dose selected for this study was 1.25 U administered as a single injection into the intervertebral disc, based on the result of the Japanese Phase II/III clinical study (Study Number: 6603/1021) and the Japanese Phase III clinical study (Study Number: 6603/1031), where the 1.25 U dose was shown to be safe and effective.

A retrospective follow-up prognostic study of patients with lumbar disc herniation was conducted 6 years after the Japanese Phase I/II clinical study (Study Number: SKK6603J01). There were no occurrences of lumbar surgery or worsening of the clinical symptoms (see Section 1.1.2.3).

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*.

1.3 Risk-Benefit Assessment

Lumbar disc herniation is treated primarily with conservative nonoperative therapy. However, in patients who fail to respond to this therapy, surgery is one of the only remaining options. This indicates an unmet medical need for a less invasive and safe

therapy that is effective in treating lumbar disc herniation in patients who fail to improve with nonoperative therapy.

The more common possible risks of injecting SI-6603 are back pain, nuclear MRI abnormal (Modic change), and spinal X-ray abnormal (decrease of disc height) Table 1. In past studies, the severity of back pain was mostly mild to moderate and symptoms recovered or resolved either without intervention or after appropriate treatment in most of the patients. Modic change and decrease of disc height were assessed as mild in severity in past studies and none of the affected patients exhibited any clinical symptoms posing safety concerns. Decrease of disc height in SI-6603 treated patients was assessed mild in severity in past studies and the degree of disc height decrease was considered comparable to or less than the lumbar discectomy.

In Japanese Phase II/III and Phase III studies, administration of SI-6603 1.25 U/mL demonstrated clinically significant improvement of leg pain and favorable improvement of back pain in lumbar disc herniation 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.

Taken together, it is considered that the risks of SI-6603 are manageable and the potential benefits outweigh those risks. During the study, X-ray and MRI assessments will be conducted to investigate the possibility of abnormalities. If any abnormalities occur, patients will be able to obtain immediate proper treatment. Detailed assessment of anticipated possible risks and benefits are stated below.

1.3.1 Possible Risks

1.3.1.1 Treatment-related Adverse Event

Information on major AEs and treatment-related AEs that were observed in SI-6603 clinical studies in patients with lumbar disc herniation are summarized below. The follow-up periods in the previous clinical studies were up to one year after the administration of a single-dose of SI-6603 into the intervertebral disc (Table 1).

1. The SAEs for which a causal relationship with SI-6603 could not be ruled out included: 4 events (pruritus, exanthema, skin warmth, and bullous dermatitis) in 1 patient in the 0.5 U dose group in the Japanese Phase I/II clinical study. All events were moderate in severity. However, they were processed as SAEs because of prolongation of an existing hospitalization.

   1 event (back pain) in 1 patient in the 1.25 U dose group in the Japanese Phase III clinical study. Although the event was moderate in severity, it was processed as SAE because inpatient hospitalization was required for nucleotomy.

2. The high incidence AEs for which a causal relationship with SI-6603 could not be ruled out:

back pain, nuclear MRI abnormal (change in bone marrow adjacent to vertebral endplates; Modic change), and spinal X-ray abnormal (30% decrease of disc height).

3. Severe AEs for which a causal relationship with SI-6603 could not be ruled out: 2 events (lymphadenitis and neutrophil count decreased) in 2 patients in the 2.5 U dose group in the Japanese Phase II/III study, 1 event (back pain) in 1 patient in the 2.0 U dose group in the USA Phase II study, and 1 event (toxic skin eruption) in 1 patient in the 1.25 U dose group in the Japanese Phase III study.
4. Abnormal laboratory values considered to be AEs for which a causal relationship with SI-6603 could not be ruled out:
neutrophil count decreased, C-reactive protein increased, blood triglycerides increased, white blood cell count decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood bilirubin increased, Lasegue's test positive, eosinophil count increased and platelet count decreased. Of these AEs, only neutrophil count decrease (1 patient in the 2.5 U dose group in the Japanese Phase II/III study) was determined to be severe.
5. In the non-clinical data of the SI-6603 long-term (3 months to 3 years) observation studies following a single-dose intradiscal administration, bulging of nucleus pulposus tissues into the bone marrow cavity of the vertebral body (Schmorl's nodes-like lesions) associated with degeneration of cartilaginous endplates was observed in dogs. However, similar findings were not observed in clinical studies in Sweden, Japan, and the USA, or in non-clinical studies using rabbits and cynomolgus monkeys.

A listing of the AEs that occurred in clinical studies to date in SI-6603 treatment groups (269 patients in total; 0.5 U, 1.25 U, 2.0 U, 2.5 U, 5 U, and 10 U dose groups) and placebo (128 patients) are shown in Table 1.

1.3.1.2 Allergic Reactions

As SI-6603 is a foreign protein, it has the potential to cause anaphylaxis or severe allergic reactions. Anaphylaxis or severe allergic reactions were not observed in the Phase I/II, Phase II/III, and Phase III studies in Japan, and the Phase II study in the USA.

In the Phase I/II study in Japan, 2 of the 18 patients exhibited AEs in the form of allergy-like symptoms for which a causal relationship with SI-6603 could not be ruled out. One of these patients developed a moderate case of pruritus, skin warm, exanthema, and dermatitis bullous, and the other patient developed a mild exanthema.

In the Phase II/III and Phase III studies in Japan, 6 of the 229 patients exhibited AEs in the form of allergy-like symptoms for which a causal relationship with SI-6603 could not be ruled out. One of these patients developed a severe toxic skin eruption.

All of these AEs in the form of allergy-like symptoms appeared 1 to 7 days after administration, but resolved after standard dermatological treatment.

No patients were found to have increased serum anti-SI-6603 IgE antibody titers.

1.3.1.3 Back Pain

Treatment-related AEs of back pain were the highest reported incidence in past studies (64/269 patients). Severity was mostly mild to moderate with 2 severe events from the Phase III study in Japan and Phase II study in the USA, respectively.

Occurrence of back pain is likely to be influenced by the primary disease. However, back pain that occurred soon after administration of SI-6603 may be attributable to nucleus pulposus degradation. Thus, it is assumed that nucleus pulposus degradation by SI-6603 administration will accompany the spine's architecture and create dynamic changes that lead to the occurrence of temporary back pain. It is also assumed that a 1 mL intervertebral injection of SI-6603 may lead to an occurrence of back pain, which is caused by a temporary increase on intervertebral disc inner pressure.

1.3.1.4 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 MRI abnormal (change in bone marrow adjacent to vertebral endplates; Modic change) were reported in 22.3% (60/269 patients) and spinal X-ray abnormal were reported in 14.1% (38/269 patients). Among 38 patients reporting spinal X-ray abnormal, AEs included intervertebral posterior angle dilation (7 events) and 30 % decrease of disc height (34 events). However, none of the affected patients exhibited any clinical symptoms posing safety concerns. Furthermore, there was no leg pain or back pain accompanying the occurrence of instability of the intervertebral disc and surrounding tissues. The clinical significance of Modic changes remains unclear and past SI-6603 studies did not reveal any increase of leg pain or back pain in conjunction with Modic changes.

Spinal imaging changes following lumbar discectomy were reported by McGirt, et al. as 18%, 21%, and 26% decreases of disc height at 3 months, 6 months, and 2 years post surgery, respectively.[14] In a follow-up study until 2 years after lumbar discectomy patients, Ohtori, et al. reported Modic changes in 7 (15.6%) of the 45 patients, with 1 of the 22 patients exhibiting a change from Modic Type 0 to Type 1, 3 of the 22 patients changing from Modic Type 0 to Type 2, and 3 of the 23 patients changing from Modic Type 1 to Type 2.[15] In a Phase II/III study in Japan, percent decrease in disc heights was highest in the 5 U dose group at 17.4% at Week 13, 18.9% at Week 26, and 21.8% at Week 52. The reductions in disc height in the SI-6603 groups were equal to or milder than those of the above-mentioned lumbar discectomy patients. The incidence of treatment-related Modic changes was slightly higher in the SI-6603 groups than in the lumbar discectomy patients at 22.3%.

There is a possibility that changes in the bone marrow adjacent to vertebral endplates and decreases of lumbar disc height may occur as the result of SI-6603 administration in the

same degree as seen in lumbar discectomy. In addition, there is a possibility of vertebral body instability (intervertebral posterior angle and vertebral body translation).

1.3.1.5 Radiation

The effective radiation dose from each radiograph is:

- During Screening or Follow-up visits
  - Lateral lumbar spine: 0.290 millisievert (mSv)
  - Anteroposterior lumbar spine: 0.690 mSv
- During the injection procedure: 1.1 mSv (varies depending on the procedure of each site or Investigator)

In this study, the total radiation dose for each Screening or Follow-up visit will be 1.56 mSv and the total for 5 visits of the study will be 7.8 mSv. In addition, during the injection, the radiation dose will be 1.1 mSv, which may vary depending on the procedure of each site or Investigator.

1.3.1.6 Intradiscal Injection

Due to the procedure itself, temporary discomfort, injection-site pain, bleeding, vascular damage, bruising vagal reaction, nerve damage, disc damage and/or infection at the injection site may occur.

Table 1: Adverse Events That Occurred in Clinical Studies to Date

Adverse event SOC/PT	SI-6603 Group (N=269)		Placebo Group (N=128)	
	AE Subjects (%)	Drug related AE Subjects (%)	AE Subjects (%)	Drug related AE Subjects (%)
Infections and infestations				
Nasopharyngitis	41 (15.2)		14 (10.9)	
Influenza	5 (1.9)		2 (1.6)	
Pharyngitis	3 (1.1)		1 (0.8)	
Gingivitis	3 (1.1)		1 (0.8)	
Tonsillitis	2 (0.7)		1 (0.8)	
Mastitis	1 (0.4)			
Otitis media	1 (0.4)			
Periodontitis	1 (0.4)		1 (0.8)	
Hordeolum	1 (0.4)			
Bronchitis	1 (0.4)			
Rhinitis	1 (0.4)		1 (0.8)	
Urinary tract infection	1 (0.4)			
Oral herpes			1 (0.8)	
Gastroenteritis			1 (0.8)	
Infected dermal cyst			1 (0.8)	
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
Uterine leiomyoma	2 (0.7)			
Blood and lymphatic system disorders				
Lymphadenitis	1 (0.4)	1 (0.4)		
Immune system disorders				
Allergy to arthropod sting			1 (0.8)	
Metabolism and nutrition disorders				
Hyperlipidaemia	2 (0.7)			
Dyslipidaemia	1 (0.4)			
Hyperkalaemia			1 (0.8)	1 (0.8)
Psychiatric disorders				
Insomnia	2 (0.7)			
Panic disorder	1 (0.4)			
Anxiety disorder	1 (0.4)			
Nervous system disorders				
Hypoaesthesia	8 (3.0)	1 (0.4)	7 (5.5)	1 (0.8)
Headache	6 (2.2)	3 (1.1)	5 (3.9)	
Dizziness	3 (1.1)		1 (0.8)	
Sensory disturbance	2 (0.7)	1 (0.4)	1 (0.8)	
Dysaesthesia	1 (0.4)	1 (0.4)		
Lumbar radiculopathy	1 (0.4)		1 (0.8)	
Cervicobrachial syndrome	1 (0.4)			
Migraine	1 (0.4)			
Convulsion			1 (0.8)	
Hyporeflexia			1 (0.8)	
Presyncope			2 (1.6)	
Radial nerve palsy			1 (0.8)	

Adverse event SOC/PT	SI-6603 Group (N=269)		Placebo Group (N=128)	
	AE Subjects (%)	Drug related AE Subjects (%)	AE Subjects (%)	Drug related AE Subjects (%)
Sciatica			1 (0.8)	
Somnolence			1 (0.8)	
Tremor			1 (0.8)	
Piriformis syndrome			1 (0.8)	
Vagus nerve disorder			1 (0.8)	1 (0.8)
Eye disorders				
Conjunctivitis allergic	1 (0.4)			
Dry eye	1 (0.4)			
Ear and labyrinth disorders				
Vertigo positional	1 (0.4)			
Cardiac disorders				
Arrhythmia	1 (0.4)			
Vascular disorders				
Flushing	1 (0.4)			
Orthostatic hypotension	1 (0.4)			
Hypertension	1 (0.4)			
Respiratory, thoracic and mediastinal disorders				
Asthma	2 (0.7)			
Upper respiratory tract inflammation	1 (0.4)		1 (0.8)	
Pneumothorax spontaneous	1 (0.4)			
Hyperventilation			1 (0.8)	
Allergic cough			1 (0.8)	
Gastrointestinal disorders				
Diarrhoea	3 (1.1)		1 (0.8)	
Nausea	3 (1.1)		2 (1.6)	
Anal fissure	2 (0.7)			
Haemorrhoids	2 (0.7)			
Vomiting	1 (0.4)	1 (0.4)	2 (1.6)	1 (0.8)
Gastritis atrophic	1 (0.4)			
Gastritis erosive	1 (0.4)			
Dental caries	1 (0.4)		1 (0.8)	
Varices oesophageal	1 (0.4)			
Gastrooesophageal reflux disease	1 (0.4)		2 (1.6)	
Duodenal ulcer			1 (0.8)	
Abdominal discomfort			1 (0.8)	
Constipation			1 (0.8)	
Gastric polyps			1 (0.8)	
Gastric ulcer			1 (0.8)	
Gastritis			2 (1.6)	
Lower gastrointestinal haemorrhage			1 (0.8)	
Hepatobiliary disorders				
Hepatic function abnormal	2 (0.7)			
Alcoholic liver disease	1 (0.4)			
Hepatic steatosis	1 (0.4)			

Adverse event SOC/PT	SI-6603 Group (N=269)		Placebo Group (N=128)	
	AE Subjects (%)	Drug related AE Subjects (%)	AE Subjects (%)	Drug related AE Subjects (%)
Skin and subcutaneous tissue disorders				
Dermatitis contact	7 (2.6)		1 (0.8)	
Rash	6 (2.2)	4 (1.5)	1 (0.8)	
Pruritus	2 (0.7)	2 (0.7)		
Urticaria	2 (0.7)	2 (0.7)		
Toxic skin eruption	2 (0.7)	1 (0.4)		
Blister	1 (0.4)	1 (0.4)		
Drug eruption	1 (0.4)	1 (0.4)		
Skin warm	1 (0.4)	1 (0.4)		
Erythema	1 (0.4)			
Eczema	1 (0.4)		2 (1.6)	
Alopecia	1 (0.4)			
Musculoskeletal and connective tissue disorders				
Back pain	95 (35.3)	64 (23.8)	42 (32.8)	6 (4.7)
Pain in extremity	46 (17.1)	11 (4.1)	35 (27.3)	3 (2.3)
Myalgia	7 (2.6)			
Arthralgia	3 (1.1)			
Osteoarthritis	3 (1.1)			
Musculoskeletal pain	2 (0.7)	1 (0.4)	2 (1.6)	1 (0.8)
Intervertebral disc protrusion	2 (0.7)		8 (6.3)	
Periarthritis	1 (0.4)		1 (0.8)	
Arthritis	1 (0.4)			
Tendonitis	1 (0.4)			
Myofascial pain syndrome	1 (0.4)			
Muscular weakness	1 (0.4)		2 (1.6)	1 (0.8)
Neck pain	1 (0.4)	1 (0.4)	2 (1.6)	
Muscle fatigue	1 (0.4)	1 (0.4)		
Limb discomfort	1 (0.4)	1 (0.4)	1 (0.8)	
Muscle spasms			1 (0.8)	
Muscle tightness			1 (0.8)	
Renal and urinary disorders				
Haematuria			1 (0.8)	
Reproductive system and breast disorders				
Cervical polyp	1 (0.4)			
Prostatitis			1 (0.8)	
General disorders and administration site conditions				
Injection site pain	33 (12.3)		10 (7.8)	
Pyrexia	5 (1.9)	4 (1.5)	7 (5.5)	4 (3.1)
Chills	1 (0.4)			
Injection site discomfort	1 (0.4)			
Feeling hot	1 (0.4)			
Vessel puncture site pain			1 (0.8)	
Investigations				

Adverse event SOC/PT	SI-6603 Group (N=269)				Placebo Group (N=128)			
	AE Subjects (%)		Drug related AE Subjects (%)		AE Subjects (%)		Drug related AE Subjects (%)	
Nuclear magnetic resonance imaging abnormal	69	(25.7)	60	(22.3)	16	(12.5)	10	(7.8)
Spinal X-ray abnormal	52	(19.3)	38	(14.1)	10	(7.8)	3	(2.3)
Blood triglycerides increased	11	(4.1)	2	(0.7)	5	(3.9)		
Neutrophil count decreased	10	(3.7)	6	(2.2)	8	(6.3)	7	(5.5)
Gamma-glutamyltransferase increased	10	(3.7)			1	(0.8)		
C-reactive protein increased	9	(3.3)	3	(1.1)	2	(1.6)	1	(0.8)
Alanine aminotransferase increased	8	(3.0)	1	(0.4)				
White blood cell count decreased	5	(1.9)	2	(0.7)	3	(2.3)	3	(2.3)
Aspartate aminotransferase increased	4	(1.5)	1	(0.4)				
Blood uric acid increased	4	(1.5)			1	(0.8)		
Blood bilirubin increased	3	(1.1)	1	(0.4)	1	(0.8)	1	(0.8)
Protein total increased	2	(0.7)						
White blood cell count increased	2	(0.7)			1	(0.8)	1	(0.8)
Lasegue's test positive	2	(0.7)	1	(0.4)				
Blood glucose increased	1	(0.4)						
Eosinophil count increased	1	(0.4)	1	(0.4)	1	(0.8)	1	(0.8)
Body temperature increased	1	(0.4)						
Platelet count decreased	1	(0.4)	1	(0.4)				
Weight increased	1	(0.4)						
Band neutrophil count increased	1	(0.4)						
Blood pressure increased	1	(0.4)			1	(0.8)		
Blood pressure systolic increased	1	(0.4)						
Liver function test abnormal	1	(0.4)			1	(0.8)		
Lymphocyte count increased	1	(0.4)						
Blood creatinine increased					1	(0.8)	1	(0.8)
Blood pressure diastolic increased					1	(0.8)		
Glucose urine present					1	(0.8)		
Neutrophil count increased					1	(0.8)	1	(0.8)
Injury, poisoning and procedural complications								
Ligament sprain	2	(0.7)			1	(0.8)		
Foot fracture	1	(0.4)						
Contusion	1	(0.4)			1	(0.8)		
Bone contusion	1	(0.4)						
Muscle strain	1	(0.4)			1	(0.8)		
Animal bite					2	(1.6)		
Wound					1	(0.8)		
Arthropod sting					1	(0.8)		
Spinal compression fracture					1	(0.8)		

AE: Adverse event, SOC: System organ class, PT: Preferred term, N: number of patient

1.3.2 Possible Benefits

Non-clinical data suggests SI-6603 appears to decrease pressure in the intervertebral disc by reducing the high water-holding capacity of proteoglycan, thereby reducing excessive pressure on the nerve root due to lumbar disc herniation. Clinical data suggests single administration of 1.0 mL of the 1.25 U/mL, 2.5 U/mL, and 5.0 U/mL formulations injected into the intervertebral disc relieved leg pain; the major complaint of patients with lumbar disc herniation.

Data suggesting efficacy of 1.25 U/mL SI-6603 administration from the Japanese Phase II/III and Phase III studies is summarized below.

1.3.2.1 Improvement of Leg Pain

In the Japanese Phase III study, statistically significant differences were observed in the LSM change from baseline in worst leg pain at Week 13 in the 1.25 U dose group compared to the placebo group, at –34.3 mm in the placebo group and –49.5 mm in the 1.25 U dose group. This finding demonstrates superiority of SI-6603 over placebo. The mean worst leg pain at baseline was 74.6 mm in the placebo group and 72.4 mm in the 1.25 U dose group. At Week 13, the mean worst leg pain that is assessed during 7 days prior to Week 13 visit was 39.2 mm in the placebo group and 22.9 mm in the 1.25 U dose group. The decrease in mean worst leg pain in the treatment groups continued beyond Week 13, and 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.

In the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT recommendation), Dworkin et al. advocated that an improvement of ≥30% is “moderately important” while an improvement of ≥50% is “substantial improvement”.[16] The ratio of patients in the Japanese Phase III study in the 1.25 U dose group who exhibited a ≥50% improvement in worst leg pain was higher than placebo at all time points. At Week 13, the ratio was 50.6% in the placebo group and 72.8% in the 1.25 U dose group. At Week 52, it was 63.0% in the placebo group and 79.3% in the 1.25 U dose group.

A common surgical procedure for the treatment of lumbar disc herniation is a lumbar discectomy whereby the hernia is extracted after making an incision in the back either under direct vision or using a microscope or endoscope. Leg pain scores typically shift by an average of 20 mm following lumbar discectomy.[14] The ratio of patients in the Japanese Phase III study in the 1.25 U dose group whose worst leg pain improved to ≤20 mm was higher than placebo at all time points. At Week 13, the ratio was 40.7% in the placebo group and 67.1% in the 1.25 U dose group. At Week 52, it was 55.6% in the placebo group and 72.0% in the 1.25 U dose group.

These results in worst leg pain evaluation indicate that SI-6603 treatment has clinically significant effects to improve leg pain.

1.3.2.2 Improvement of Back Pain

In the Japanese Phase III study, the LSM change from baseline in worst back pain at Week 13 was –21.4 mm in the placebo group and –28.5 mm in the 1.25 U dose group. No statistically significant differences were observed in the 1.25 U dose group compared

to the placebo group. The mean worst back pain at baseline was 52.4 mm in the placebo group and 50.2 mm in the 1.25 U dose group. The mean worst back pain at Week 13 was 30.2 mm in the placebo group and 22.2 mm in the 1.25 U dose group. Statistically significant differences were observed in the LSM change from baseline in worst back pain at Week 52 in the 1.25 U dose group compared to the placebo group, at −24.5 mm in placebo group and −34.0 mm in the 1.25 U dose group.

A study by McGirt, et al. assessing the VAS scores of 108 lumbar discectomy patients showed that back pain improved from 4.6 cm before surgery to 2.1 cm at 6 weeks post surgery. The back pain continued to be the same up to 24 months post surgery.[14] In the Japanese Phase III study, mean worst back pain at baseline in the treatment groups was 52.4 mm in the placebo group and 50.2 mm in the 1.25 U dose group. At Week 13, it was 30.2 mm in the placebo group and 22.2 mm in the 1.25 U dose group. At Week 52, back pain had decreased to 26.9 mm in the placebo group and 16.8 mm in the 1.25 U dose group. These results indicate that improvement in back pain is considered to be clinically beneficial.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary study objective is to evaluate the safety of a single-dose intervertebral disc injection of SI-6603 at a dose of 1.25 U in patients with lumbar disc herniation, for a 26-week follow-up period.

2.2 Secondary Objective

The secondary study objective is to evaluate the efficacy of a single-dose intervertebral disc injection of SI-6603 at a dose of 1.25 U in patients with lumbar disc herniation, for a 26-week follow-up period.

3 OVERALL DESIGN AND PLAN OF THE STUDY

3.1 Overview

This is a multicenter, open-label study where a single intradiscal injection of SI-6603 1.25 U will be administered to all patients. The study will be conducted at approximately 60 sites in the USA and European Union (EU).

The study duration for each patient will be approximately 30 weeks: a 4-week Screening period, a 1-day Treatment Administration Day, and a 26-week follow-up period (see Figure 1).

The study population will consist of 1000 male and female patients, 30 to 70 years of age at the time of informed consent, with lumbar disc herniation between adjacent lumbar vertebra (L1–L2, L2–L3, L3–L4, L4–L5), or between the 5th lumbar vertebra and the 1st sacral vertebra (L5–S1) "protrusion type" or "extrusion type" in the posterior lateral or central location as assessed by MRI and clinical symptoms corresponding to the level of the impaired nerve root. Following the 4-week Screening period, on Day 0 all patients will receive a single intradiscal injection of SI-6603 1.25 U. The patients will then have a 26-week follow-up period for evaluation of safety and secondary efficacy endpoints (for schedule of assessments, see Table 3).

Safety will be assessed throughout the study. All AEs will be followed until they are resolved or stabilized; however, if AEs are ongoing at the time of the last study visit, only treatment-related AEs will be followed beyond 26 weeks after investigational drug administration.

The end of the study is last patient, last visit.

Screening	Treatment	Evaluation Period/Follow-up			
Eligible patients (n=1000) →	SI-6603 1.25 U intradiscal Appendix 11.1				
X	Before administration ↓ After administration	X	X	X	X
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Days –28 to –1	Day 0	Week 1 (±3 days)	Week 6 (±14 days)	Week 13 (±14 days)	Week 26 (±14 days)
Section 7.2.1	Section 7.2.2	Section 7.2.3	Section 7.2.4	Section 7.2.5	Section 7.2.6

Figure 1: Study Design

3.2 Criteria for Evaluation of the Study

3.2.1 Safety Endpoints

The following safety endpoints will be assessed:

- Occurrences of AEs
- Stability evaluation of vertebral bodies by X-ray at the times specified in the schedule of events
  - Translation of vertebral body
  - Vertebral body angle formed by flexion
- Changes from baseline in disc height (disc index) assessed by X-ray at the times specified in the schedule of events
- Changes of disc degeneration, vertebral body endplates, and adjacent bone marrow assessed by MRI at the times specified in the schedule of events
  - Modic classification
  - Pfirrmann classification
- Clinically significant change in vital signs at the times specified in the schedule of events
- Clinically significant change in clinical laboratory tests at the times specified in the schedule of events
- Serum anti-SI-6603 antibody at the times specified in the schedule of events
- Occurrence of post-treatment lumbar surgery other than surgery for lumbar disc herniation at the same level of the investigational drug administration

3.2.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be assessed at the times specified in the schedule of events and overall time-course, and changes from baseline will be analyzed:

- Worst leg pain during the past 24 hours assessed by VAS.
- Worst back pain during the past 24 hours assessed by VAS.
- Functional disability measured by the Oswestry Disability Index (ODI).
- Change of neurological status from baseline determined by neurological examinations:
  - Femoral Nerve Stretching (FNS) test for patients with lumbar disc herniation L1−L2, L2−L3, or L3−L4 or
  - Straight Leg Raising (SLR) test [for patients with lumbar disc herniation L4−L5 or L5−S1, and
  - Sensation, muscle strength, and deep tendon reflex.
- Occurrence of post-treatment surgery for lumbar disc herniation at the same level of administration of the investigational drug up to Week 26 including patients who discontinued from the study.

3.3 Justification of the Study Design

This study is planned to investigate the safety and efficacy of SI-6603 as a single intradiscal injection for the treatment of lumbar disc herniation.

An open-label single treatment group design has been chosen to assess the safety of the treatment in a large number of patients.

The patients in the current study are people who have lumbar disc herniation and who have seen no improvement from adequate conservative treatment prior to screening. There will be no limitations on concomitant medications used to treat lumbar disc herniation, in order to enable data collection from a population that more realistically represents the target population.

The study has been designed to ensure the safety of the patients. The dosing scheme has been chosen on the basis of data currently available. Efficacy will be assessed as secondary endpoints using validated tools (VAS, ODI) and neurological examinations.

A 26-week follow-up period is considered adequate to assess safety effects of a single-dose treatment.

4 STUDY POPULATION

The study population will consist of patients with lumbar disc herniation (L1–L2, L2–L3, L3–L4, L4–L5, or L5–S1) "protrusion type" or "extrusion type" in the posterior lateral or central location as assessed by MRI and clinical symptoms corresponding to the level of the impaired nerve root. Patients must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

The Investigator is responsible to ensure the patient fulfills all the inclusion criteria, does not meet the exclusion criteria, and provides written consent to participate in the study on a voluntary basis.

4.1 Inclusion Criteria

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

1. Patients who have given their written informed consent to participate in a clinical study based on voluntary agreement after a thorough explanation of the patient's participation is provided to them. Patients must have adequate reading and writing abilities such that they can comprehend and answer the questions on the patient-completed assessments and Informed Consent Form (ICF).
2. Patients with lumbar disc herniation (L1–L2, L2–L3, L3–L4, L4–L5, or L5–S1) "protrusion type*" or "extrusion type**" in the posterior lateral or central location as assessed by MRI and clinical symptoms corresponding to the level of the impaired nerve root; if the sixth lumbar vertebra (L6) is present, patients with impaired L5 or S1 nerve root and corresponding clinical symptoms

   * "Protrusion type" is herniation where the nucleus pulposus has disrupted the posterior lateral or central location of annulus fibrosus partially which leads to compression of the nerve root.

   **"Extrusion type" is herniation where the nucleus pulposus has disrupted the posterior lateral or central location of annulus fibrosus completely which leads to compression of the nerve root.
3. Patients with positive FNS ≤70° (L1–L2, L2–L3, or L3–L4) or SLR ≤70° (L4–L5 or L5–S1) on the symptomatic side
4. Patients with sciatica or anterior thigh pain/femoral neuropathy in either leg prior to the time of informed consent
5. Patients with no improvement from adequate conservative treatment* prior to the time of informed consent

   *Adequate conservative treatment includes pharmacotherapy (e.g., nonsteroidal anti-inflammatory drugs, opiate preparations, or nonopioid analgesics). Physical therapy and/or spinal injection, epidural injection, or nerve block may also be included.
6. Patients with the worst leg pain (by VAS ≥30 mm) during the past 24 hours at the time of informed consent.

7. Male or female patients 30 to 70 years of age at the time of informed consent
8. Female patients are not pregnant and do not plan to become pregnant during the study. Females of childbearing potential must provide a negative serum pregnancy test during the Screening period, must be using reliable contraception, and must continue to use reliable contraception until end of study (reliable methods of contraception are defined in exclusion criterion #6 below). Non-childbearing potential is defined as postmenopausal for at least 2 years or surgical sterilization or hysterectomy at least 3 months before study start.

4.2 Exclusion Criteria

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

1. Patients who have 2 or more symptomatic lumbar disc herniations as assessed by MRI

   Two or more level symptomatic lumbar disc herniations are defined as a patient having clinical symptoms and MRI findings consistent with radiculopathy in more than one nerve root distribution as assessed by the Investigator.
2. Patients with a contraindication to receiving an MRI
3. Patients in whom a rupture into the posterior longitudinal ligament as assessed by MRI shows sequestration (free fragment) type lumbar disc herniation. Transligamentous extrusion type of disc herniation is allowed.
4. Patients who previously received SI-6603 administration at any time
5. Patients who are pregnant, breast-feeding or women of childbearing potential with positive pregnancy tests. Female patients with posthysterectomy and/or bilateral tubal ligation or postmenopausal* do not need to take the pregnancy tests.

   * Postmenopausal is defined as either 12 months of spontaneous amenorrhea, or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml, or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.
6. Sexually active female patients of childbearing potential who are not willing to use adequate contraceptive measures to avoid pregnancy until end of the study. Sexually active male patients who are not willing to use adequate contraceptive measures until end of the study.

   Adequate methods of birth control include the following:

   - Hormonal contraception (female patients) or use of at least one acceptable double-barrier method

     Acceptable double-barrier methods include the following:
     - diaphragm plus a spermicidal agent
     - condoms (male or female) plus a spermicidal agent
   - Vasectomy, intrauterine device, and/or exclusive sexual partner for whom one of the above acceptable methods applies

7. Patients who have undergone lumbar operation, lumbar percutaneous nucleotomy or lumbar intradiscal therapies (e.g., chemonucleolysis or intradiscal electrothermal treatment) under any of the following conditions:
   - At the affected level of lumbar disc herniation
   - Within the last 2 years at any lumbar spine level other than affected level
   - With symptoms not completely improved by the above procedure at any lumbar spine level other than affected level
8. Patients with the following medical conditions or diseases:
   - Vertebral body angle formed by flexion ≥5°
   - Neurological disorders including cauda equina syndrome that is severe or that demonstrates rapid progression. Patient with clinically symptomatic neurological deficit (e.g., motor paresis, sphincter dysfunction), warranting an alternative option of care that would be more appropriate for their presentation, will be also excluded.
   - Spondylosis deformans, spondylolisthesis (translation of vertebral body ≥3 mm), spinal deformity, spinal canal stenosis (except for complication of lumbar disc herniation), spinal tumor, ankylosing spondylitis, diskitis, or clinically significant disorders of the lumbar spine other than disc herniation.
   - Osteophyte at lumbar spine (Nathan's classification ≥3rd degree)
   - Cancer: patients 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.
   - Human immunodeficiency virus (HIV) infection or a clinically significant infection
   - A clinically significant disorder such as cerebrovascular disease, pulmonary infarction, ischemic heart disease, cardiac dysrhythmia, myocardial infarction, or congestive heart failure
   - Chronic diseases such as osteoporosis, rheumatoid arthritis, uncontrolled diabetes mellitus, uncontrolled pulmonary disease (asthma), or uncontrolled hypertension
   - Patients who have evidence of major psychiatric disease, mental disorder, drug dependency, alcohol dependency, or substance use disorders.
   - Patients who have a tendency to bleed or with bleeding disorders such as (but not limited to) hemophilia, hypoplastic anemia, cirrhosis of the liver, leukemia and vitamin K deficiency. Patients using medication for purpose of anticoagulation, including heparin and warfarin which cannot be reversed preoperatively will also be excluded.
9. Patients with medical conditions and/or diseases that the Investigator believes could affect the study results or the safe conduct of the study.
10. Patients who meet any of the following criteria:

- Hepatic function: AST or ALT: ≥2.5 x upper limit of normal (ULN)
- Total-bilirubin: ≥1.5 x ULN
- Renal function: Serum creatinine: ≥1.5 x ULN

11. Patients who are receiving compensation according to the Workers' Compensation Act or are involved in personal injury litigation due to a lumbar-related injury.
12. Patients who participated in another clinical study within 4 months prior to the time of informed consent, or who are expected to participate in another study during the period of this study.

4.3 Patient Withdrawal and Replacement

Patients 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 patient 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 patient withdraws consent and still agrees to undergo a final examination, this will be documented in the eCRF.

A patient may also be withdrawn from study by the Investigator, Sponsor, Regulatory Authorities, or Institutional Review Boards (IRBs).

Patients will also be withdrawn if the entire study is terminated prematurely as described in Section 9.10.

Withdrawn patients will not be replaced.

4.3.1 Patient Withdrawal Criteria

The Investigator will withdraw a patient from the clinical study if any of the following situations occur:

1. When the patient withdraws his or her consent
2. When the occurrence of an AE, such as noted below, leads the Investigator to judge it necessary for the patient to have surgical intervention or to withdraw the patient from the clinical study:
   - Significant neurologic deficit, e.g., progressive weakness or sudden loss of muscle strength in L1–L2, L2–L3, L3–L4, L4–L5 or L5–S1 innervated muscles, bowel or bladder dysfunction, or other signs and symptoms of cauda equine/conus medullaris involvement, or
   - Abnormal X-ray or MRI findings coupled with correlating clinical symptoms posing safety concerns
3. When a poor response to the investigational drug leads the Investigator to judge it necessary to perform a surgical intervention for back pain/leg pain or to withdraw the patient from the clinical study

4. If the Investigator judges it inappropriate to include a patient in the efficacy/safety assessment
5. If a patient becomes pregnant
6. Others:
    - No investigational drug could be administered.
    - The continuation of the study makes the risk to a patient's health unacceptable.
    - The Sponsor prematurely terminates the study.
    - The Investigator judges it necessary to withdraw a patient from the study.

4.4 Planned Sample Size and Number of Study Centers

It is planned to recruit 1000 patients at approximately 80 sites in the USA and EU for this study. See Section 8.8 for a discussion of sample size.

4.5 Patient Identification and Randomization

4.5.1 Patient Identification

At the screening visit, a unique 6-digit patient number will be assigned consecutively for each patient after he or she signs the ICF. Unique patient numbers will begin with the clinical site number, e.g., 001 followed by a 3 digit number starting with 001. The unique patient numbers will be assigned sequentially. For example, for clinical site number 002, the unique patient numbers will be as follows: 002-001, 002-002, 002-003. The patient will keep this unique patient number for the duration of the study.

Patients who drop out of the study before randomization will retain their unique patient number (i.e., the patient number will not be reassigned). If a patient is rescreened after being designated as a screen failure, the patient will receive a new unique patient number upon rescreening.

4.5.2 Randomization Scheme

No randomization will be performed. All patients will be assigned into active treatment with SI-6603.

4.5.3 Allocation/Randomization of Patients to Treatment

Not applicable.

5 STUDY DRUG

For details and handling of the investigational drug (SI-6603), refer to the IB and Appendix 11.1, Injection Procedure, and Investigational Drug Management Procedure.

5.1 Identity

SI-6603 will be administered as a lyophilized injection which, when reconstituted with 1.2 mL of saline, provides 1.0 mL containing the ingredients given below.

Ingredient	
Active ingredient	Condoliase
Inactive ingredients	Monosodium phosphate dihydrate (United States Pharmacopoeia [USP]) Sodium dihydrogen phosphate dehydrate (European Pharmacopoeia[EP])
	Disodium hydrogen phosphate, dodecahydrate (USP) Disodium phosphate dodecahydrate (EP)
	Sucrose (National Formulary [NF], EP)
	Polyethylene glycol 3350 (NF) Macrogol 3350 (EP)

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

5.2 Administration

An SI-6603 for injection vial 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 administered into the intervertebral disc in a single-dose (see Appendix 11.1).

5.3 Packaging, Labeling and Storage

SI-6603 will be packaged by the vendor according to all local legal requirements. SI-6603 will be labeled in accordance with applicable regulatory requirements (see Appendix 11.2, Package Presentation and Labeling).

All SI-6603 supplies must be stored in the original boxes in accordance with the manufacturer's instructions (2 to 8°C and shielded from light). SI-6603 must be stored in a securely locked area, accessible to authorized personnel only.

5.4 Blinding and Breaking the Blind

The study is not blinded.

5.5 Drug Accountability

The Investigator is responsible for maintaining accurate SI-6603 accountability records throughout the study. Each dispensing of SI-6603 must be documented in the patient source record and eCRF. The Investigator is responsible for returning all unused or partially used SI-6603 to the Sponsor and must verify that no remaining supplies are in the Investigator's possession.

5.6 Compliance

Compliance with the injection procedure is to be monitored and recorded by site staff. Study treatment consists of the investigational drug administered on Day 0 (a single intradiscal injection of SI 6603).

5.7 Previous and Concomitant Medications

Any medication the patient takes other than the investigational drug, including herbal and other nontraditional remedies, is considered a concomitant medication. All concomitant medications must be recorded in the patient source record and eCRF for each concomitant medication as follows: generic name (for combination drug only, trade name must be recorded), route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the patient source record and eCRF.

Previous and concomitant medication data will be captured beginning at the time of informed consent. At screening, patients will be asked what medications they have taken during the last 6 weeks. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking or have taken since the last visit.

5.7.1 Permitted Concomitant Medication

Concomitant medications used in the treatment of lumbar disc herniation and complications associated with disc herniation are allowed. There is no restriction on concomitant medications used in treatment of diseases or disorders other than lumbar disc herniation.

5.7.2 Notes Concerning Concomitant Medication Before SI-6603 is Administered

SI-6603 is a foreign protein preparation of *Proteus vulgaris* and may have the potential to cause an allergic reaction. The concomitant use of drugs that are contraindicated during the use of epinephrine may interfere with the effect of the epinephrine, which is used for treatment in the early stage of anaphylactic reaction. Therefore, other alternatives should be considered for treatment of anaphylactic reaction for patients using the following classes of drugs:

- Contraindicated drug of epinephrine (e.g., antipsychotic drug or α-blocker)
- β-blocker

Intradiscal injection procedure itself has risk of bleeding and/or infection at the injection site. Patients continuously being treated with anticoagulants and/or immunosuppressants should be taken to in account for an extra caution before receiving intradiscal injection, according to following instructions:

- During the assessment of patient eligibility in screening visit and before performing the intradiscal injection, review patient medical records to assure there are no concomitant use of anticoagulants and/or immunosuppressants.
- If concomitant use of anticoagulants and/or immunosuppressants are recognized, investigators should assess whether such patients are eligible to go through intradiscal injection procedure.

5.8 Previous and Concomitant Therapies

Any therapy the patient uses in the treatment of lumbar disc herniation is considered a concomitant therapy. All concomitant therapies must be recorded in the patient source record and eCRF. The following information must be recorded in the patient source record and eCRF for each concomitant therapy: therapy name, frequency, start date, stop date. Any changes in the frequency and administration method of a concomitant medication must be recorded in the patient source record and eCRF.

Previous and concomitant therapy data will be captured beginning at the time of informed consent. At screening, patients will be asked what therapies they have used during the last 6 weeks. At each subsequent study visit, patients will be asked what concomitant therapies they are currently taking or have taken since the last visit.

5.8.1 Permitted Concomitant Therapies

The conservative therapies used in the treatment of lumbar disc herniation prior to the time of informed consent are allowed. There is no restriction on therapies used in treatment of diseases or disorders other than lumbar disc herniation.

5.8.2 Prohibited Concomitant Therapies

Lumbar operation, lumbar percutaneous nucleotomy, or lumbar intradiscal therapies (e.g., chemonucleolysis, intradiscal electrothermal treatment) for treatment of back pain and leg pain are prohibited from the time of informed consent up to the final observation (Week 26 after investigational drug administration). A patient who requires lumbar operation, lumbar percutaneous nucleotomy, or lumbar intradiscal therapies (e.g., chemonucleolysis or intradiscal electrothermal treatment) in the clinical study period must be discontinued from the clinical study.

In addition, discography for diagnostic purpose is also prohibited from the time of informed consent through Week 13 after investigational drug administration.

6 VARIABLES AND METHODS OF ASSESSMENT

6.1 Safety Variables

6.1.1 Adverse Events

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology (Section 9.4).

6.1.1.1 Collection of Adverse Events

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

6.1.1.2 Definitions

An AE is any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), 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
- Change in vertebral body endplates and adjacent bone marrow: Type 1, Type 2, or Type 3 change (Modic Classification)

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

All AEs, including intercurrent illnesses, occurring during the study will be documented in the eCRF. Concomitant illnesses, which existed before entry into the study, will not be considered AEs unless they worsen during the treatment period. All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, or reported by patient), must be documented.

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

A treatment-emergent adverse event will be defined as an AE that begins or that worsens in severity after the study drug has been administered.

6.1.1.3 Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the following categories.

6.1.1.3.1 Seriousness

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

- Results in death
- Is life-threatening
  This means that the patient 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
- Is a congenital anomaly or birth defect
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the patient 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.

6.1.1.3.2 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 patient's activities of daily living (ADL) or, despite slight interference, no particular intervention indicated; Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 (see Appendix 11.8)
- Moderate: Interference with the patient's ADL and minimal intervention indicated; CTCAE Grade 2
- Severe: Disabling and almost complete interference with the patient's ADL or systemic intervention indicated; CTCAE Grade 3/4

6.1.1.3.3 Causality

The Investigator will assess the causality / relationship between the study drug and the AE and record that assessment in the eCRF. Causality will be shown 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 on the eCRF with details of the concomitant disease or medication or other cause.

The causal relationship of the AE to the study drug will be described in terms of:

- Not related: There is no temporal correlation or attributability to the investigational medicinal product, but to any other factor, such as the underlying disease, a complication, a concomitant drug, a predisposition, or concomitant intervention, by which the AE can be explicitly explained.

- Related: There is a reasonable possibility that the relevant event can be judged to be at least due to the investigational drug or a causal relationship cannot be ruled out.

6.1.1.4 Recording Adverse Events

The AE recording into the eCRF will extend from the signing of the ICF until completion of final visit. All AEs will be followed until they are resolved or stabilized; however, if AEs are ongoing at the time of the last study visit, only treatment-related AEs will be followed beyond 26 weeks after investigational drug administration.

All AEs, regardless of the relationship to study drug, will be recorded in the eCRF system.

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

6.1.1.5 Reporting Serious Adverse Events

All SAEs that occur during the period of observation, and all SAEs occurring up to 26 weeks after receiving the dose of study drug, whether considered to be associated with the study drug or not, must be reported within 24 hours by fax, email or telephone to the PAREXEL Safety Contact using the numbers, and specific mailbox in the List of Study Personnel.

Any SAE occurring after the end of the study should be reported to the Sponsor/PAREXEL by the Investigator if the Investigator considers there is a causal relationship with the study drug.

The minimum information required for an initial report is:

- Name of person sending the report (i.e., name, address of Investigator)
- Patient identification (screening/randomization number, initials, NOT patient name)
- Protocol number
- Description of SAE
- Causality assessment, if possible.

However, as far as possible all points on the SAE form should be covered in the initial report, or the completed SAE form itself must be faxed to the PAREXEL Safety Contact. In addition, the event must be documented in the eCRF.

In case the PAREXEL Safety Contact cannot be contacted (e.g., out of normal working hours or at weekends), SAE reports will be received by PAREXEL. The required information should be faxed, emailed or a message should be left on the voicemail service (for phone/fax/email, see the contacts in the List of Study Personnel).

After receipt of the initial report, the safety center will review the information and, if necessary, contact the Investigator, to obtain further information for assessment of the event. PAREXEL will be responsible for all information processing and reporting according to local legal requirements. Where necessary, Investigators will inform Regulatory Authorities in their own countries.

PAREXEL International

SAE Fax (24-hour service):
USA and EU region (Billerica): +1 781 434 5957

Medical hotline:
USA and EU region (Billerica): +1 781 434 5010

Email:
USA and EU region: NorthAmerica_Medical@parexel.com

Medical Monitor:
USA region: [redacted]
EU region: [redacted]

Details for the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) can be found in Section 6.1.1.7.

6.1.1.6 Follow-up of Adverse Events

During the study, all AEs experienced by a patient, 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 patient is lost to follow-up, or until the patient has died. If the AEs are ongoing at the time of the last study visit, only treatment-related AEs will be followed beyond 26 weeks after investigational drug administration 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, or until there is a satisfactory explanation for the changes observed. Follow-up of the AEs beyond the entire study duration will be evaluated on case-by-case basis by the Medical Monitor and the Sponsor.

6.1.1.7 Suspected Unexpected Serious Adverse Reactions

Any AE that is serious, associated with the use of the study drug, and unexpected (SUSAR) has additional reporting requirements, will be reported to regulatory authorities and Independent Ethic Committees (IECs) according to the local requirements.

The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of patients. Follow-up information may be submitted if necessary.

The Sponsor will also provide annual safety updates to the Regulatory Authorities and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

6.1.1.8 Pregnancy

The Sponsor has a responsibility to monitor the outcome of pregnancies where there has been maternal exposure to the study drug.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug 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 (see below). Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

All pregnancies must be reported by the Investigator to PAREXEL on the initial pregnancy report form within 30 days after becoming aware of the pregnancy. The Investigator must follow up and document the course and the outcome of all pregnancies even if the patient was discontinued from the study or if the study has finished.

All outcomes of pregnancy must be reported by the Investigator to PAREXEL/Sponsor on the pregnancy outcome report form within 30 days after he or she has gained knowledge of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy (including SAEs occurring after last administration of study drug) must be recorded on the SAE report form (e.g., maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

If a female partner of a male study patient who has been exposed to the investigational drug becomes pregnant before the end of Week 26, the pregnancy and outcome of pregnancy should be reported.

6.1.2 Laboratory Variables

Laboratory assessments will be performed by a central laboratory, as identified in the List of Study Personnel. The Investigator or site staff will collect blood samples according to the "Investigator Laboratory Manual for SI-6603" separately specified.

The following laboratory variables will be determined in accordance with schedule of assessments Table 3.

Table 2: Laboratory Assessments

Hematology:	hemoglobin hematocrit platelets red blood cell count white blood cell count with differential		
Clinical chemistry:	creatinine C-reactive protein	Liver enzymes:	alkaline phosphatase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT)

	total protein direct bilirubin total bilirubin total cholesterol triglycerides urea nitrogen uric acid		lactic dehydrogenase γ-glutamyl transpeptidase albumin
Electrolytes:	calcium chloride magnesium potassium sodium	Serological marker:	Human immunodeficiency virus (HIV) test will be performed at Screening
Pregnancy test:	In women with childbearing potential a serum pregnancy test will be performed at Screening. A urine pregnancy test will be performed at Visit 1		

Approximately 15 to 20 mL (3 to 4 teaspoons) of blood will be collected each time at Screening, Evaluation period visits or upon discontinuation. In addition, before administration of the investigational drug, at Week 13, at Week 26, or upon discontinuation, approximately 3 mL (½ teaspoon) will be collected for the serum anti-SI-6603 antibody. All blood samples collected for the serum anti-SI-6603 antibody will be appropriately stored and will be destroyed upon completion of the measurements of serum anti-SI-6603 antibody. If necessary, the blood samples collected for the serum anti-SI-6603 antibody will be used for assay development and will be destroyed upon completion of the assay development. All other blood samples collected will be destroyed at the end of the study or completion of all laboratory assessments.

For serum anti-SI-6603 antibody, titer of SI-6603 specific antibody will be measured, and isotype of immunogloblin (IgG, IgM or IgE) will be identified on blood samples which contain SI-6603 specific antibody.

6.1.3 X-ray Imaging

Disc height, intervertebral posterior angle, and translation of vertebral body will be assessed by X-ray in accordance with the schedule of assessments Table 3.

The following will be reported as AEs:

- a decrease in disc height ≥30% compared to baseline
- vertebral body angle formed by flexion of ≥5°
- vertebral body translation of ≥3 mm

Events are limited to the targeted level of the investigational drug administration and the adjacent vertebral bodies (see Appendix 11.7).

Anteroposterior and lateral-intermediate, flexion, and extension spinal x-rays will be obtained according to the "*Procedure Manual for Radiographic Examinations of the Lumbar Spine*". The X-ray images obtained will be sent to the central imaging reader (BioClinica) for assessment.

6.1.3.1 Disc Height (Disc Index)

The central imaging reader will measure the disc index for the intervertebral disc treated with the investigational drug using

a) the posterior height of the superior vertebral body adjacent to the target segment,

b) the anterior disc space, and

c) the posterior disc space.

A decrease in disc height ≥30% compared to baseline value will be recorded as an AE (see Appendix 11.7 for additional details regarding imaging tests).

6.1.3.2 Intervertebral Posterior Angle

The central imaging reader will measure the intervertebral posterior angle of the intervertebral disc treated with the investigational drug. When the measured value is ≤-5°, the relevant result will be entered as "posterior intervertebral angulation" in the eCRF. A vertebral body angle formed by flexion of ≥5° will be recorded as an AE (see Appendix 11.7 for details regarding imaging tests).

6.1.3.3 Vertebral Body Translation

The central imaging reader will determine the difference in vertebral body translation at the extension and flexion positions of the intervertebral disc treated with the investigational drug. When the post-treatment vertebral body translation is ≥3 mm, the relevant result will be entered as "vertebral body translation" in the eCRF. A vertebral body translation of ≥3 mm will be recorded as an AE (see Appendix 11.7 for details regarding imaging tests).

6.1.4 Magnetic Resonance Imaging

Changes of disc degeneration, vertebral body endplates, and adjacent bone marrow will be assessed by MRI in accordance with the schedule of assessments Table 3.

The criteria are as follows: Modic Type 1, Type 2, or Type 3 change in vertebral body endplates and adjacent bone marrow (see Appendix 11.5) and Grade I (mild), Grade II (moderate), or Grade III (severe) in disc degeneration using Pfirrmann classification (see Appendix 11.6). When the post-treatment Modic Type 1, Type 2, or Type 3 change in vertebral body endplates and adjacent bone marrow occur, the relevant result will be entered as "Modic Type 1", "Modic Type 2" or "Modic Type 3" in the eCRF. Modic Type 1, Type 2, or Type 3 change in vertebral body endplates and adjacent bone marrow will be reported as an AE.

The MRI will be obtained according to the "*Procedure Manual for MRI Examination*". All MRIs obtained will be sent to the central imaging reader (BioClinica) for assessment.

6.1.5 Vital Signs

The following vital signs will be assessed in accordance the schedule of assessments Table 3:

- Blood pressure (systolic and diastolic; mmHg) after being supine for 5 minutes
- Heart rate (beats per minute)
- Body temperature (°F/C)

- Respiration rate (breaths per minute)

6.1.6 Physical Examinations

Physical examinations will be performed in accordance with the schedule of assessments Table 3. The physical examination should include evaluation of the skin, head, neck, throat, ears, eyes, nose, heart, lungs, abdomen, extremities, and musculoskeletal systems.

6.1.7 Neurological Examinations and Pain Assessments

Neurological examinations and pain assessments will be performed in accordance with the schedule of assessments Table 3.

Neurological testing will include an FNS or SLR test, sensation, muscle strength, and deep tendon reflex. Any neurological finding that worsens after the administration of the investigational drug and that is considered to be clinically significant in the Investigator's judgment meets AE reporting criteria.

Cases where leg pain or back pain increase over the Screening period (baseline value) and, in the Investigator's judgment, is clinically aggravated, meet AE reporting criteria. Cases considered clinically exacerbated, in the Investigator's judgment, based on post treatment improvement followed by the reappearance of pain of equal severity than before improvement meet AE reporting criteria.

6.2 Efficacy Variables

The following efficacy variables will be used for assessment of the secondary endpoints in this study (for secondary efficacy endpoints, refer to Section 3.2.2, for times of assessment, refer to Table 3).

- VAS (see Appendix 11.3) for assessment of worst leg pain and worst back pain
- ODI (see Appendix 11.4) for assessment of functional disability
- FNS or SLR test, sensation, muscle strength, and deep tendon reflex for assessment of neurological status
- Record of occurrence of post-treatment surgery for lumbar disc herniation at the same level of administration of the investigational drug up to Week 26 including patients who discontinued from the study.

6.3 Demographics and Baseline Characteristics

6.3.1 Patient Demography

For patient demography the following will be documented:

- Year of birth
- Age
- Gender
- Race
- Smoking history
- Occupation (Heavy labor/Light labor)

6.3.2 Disease History

For disease history the following will be documented:

- Lumbar disc herniation (L1–L2, L2–L3, L3–L4, L4–L5, or L5–S1) "protrusion type" or "extrusion type" in the posterior lateral or central location as assessed by MRI
- A positive FNS ≤70° (L1–L2, L2–L3, or L3–L4) or SLR ≤70° (L4–L5 or L5–S1) on the symptomatic side
- No improvement from adequate conservative treatment prior to the time of informed consent
- Sciatica or anterior thigh pain/femoral neuropathy in either leg prior to the time of informed consent
- A worse leg pain by VAS ≥30 mm during the past 24 hours at the time of informed consent

6.3.3 Medical History

For documentation of the 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 documented.

The medical history will be obtained by interviewing the patient or by inspecting his/her medical records.

For coding of medical history, see Section 9.4.

6.3.4 Previous and Concomitant Medications/Therapies

Previous and concomitant medication/therapy will be documented as described in Section 5.7 and Section 5.8. For coding of previous and concomitant medications/therapies, see Section 9.4.

7 STUDY CONDUCT

7.1 Schedule of Procedures

Each patient will be asked to complete 6 study visits including a screening evaluation:

- Screening visit
- Treatment Day 0
- Evaluation period/Follow-up visits at Week 1, Week 6, Week 13, and Week 26
- Patients terminating the study early will be asked to complete a discontinuation visit.

Table 3: Schedule of Assessments and Procedures

Observation Period / Observation / Examination Items	Before 4 Weeks (Day −28 to Day 0)	Treatment Administration Day 0		Week 1	Week 6	Week 13	Week 26	Upon Discontinuation
	Outpatient[a]							
	Screening Period	Before Administration	After	Evaluation Period/ Follow-up				
	Visit 1	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6	
Permissible lag time for observation/examination				±3D	±14D	±14D	±14D	+14D
Verify conformance with entry criteria Obtain informed consent	X							
Patient characteristics	X							
Serum/urine pregnancy test[b]	X	X						
Patient enrollment		X						
Administration of the investigational drug		▼						
Pain assessment by patients (VAS)	X	X		X	X	X	X	X
ODI		X		X	X	X	X	X
Physical examination	X	X						
Neurological examination	X			X	X	X	X	X
Imaging (X-ray, MRI)[c]	X				X	X	X	X
Vital signs	X	X	X	X	X	X		X
Laboratory tests	X			X	X	X		X
Serum anti-SI-6603 antibody[d]		X				X	X	X
Concomitant drug/therapy	→	→	→	→	→	→	→	X
AE/SAE	→	→	→	→	→	→	→	X
Record occurrence of lumbar surgery[e]	→	→	→	→	→	→	→	X

▼=Administration of the investigational drug; D=day; X=Essential examination
AE=Adverse event; MRI=Magnetic Resonance Imaging; ODI=Oswestry Disability Index; SAE=Serious adverse event; VAS=Visual Analog Scale

7.2 Procedures by Visit

Visits should occur within the time indicated for each scheduled visit. All times should

[a] *Hospitalization on the day at administration is allowed if it is required by the site.*
[b] *Serum pregnancy test will be performed at Screening, and urine pregnancy test will be performed at Visit 2 before administration of the investigational drug.*
[c] *If repeat imaging is needed, the permissible lag time will be extended by a maximum of an additional 14 days.*
[d] *Examined when considered necessary in unscheduled visit*
[e] *Patients who discontinued the study will be followed until the Week 26 visit.*

be recorded using the 24-hour clock (e.g., 23:20, not 11:20 pm).

7.2.1 Screening (Visit 1)

- Obtain written informed consent
- Record demographic and medical history
- Record the use of concomitant drug/therapy
- Document occurrence of lumbar surgery
- Verify conformance with entry criteria
- Perform vital signs assessments (temperature, blood pressure, heart and respiration rate)
- Perform physical examination
- Perform neurological examination
- Complete pain assessment (VAS)
- Perform imaging tests (X-ray and MRI)
- Obtain study entry laboratory specimens (blood for HIV; pregnancy [for women of childbearing potential]; and hematology, hepatic, and chemistry panels)

7.2.2 Treatment Day 0 (Visit 2)

The following will be performed on the day of study drug administration (Day 0) before study drug administration:

- Enroll the patient if not done the day before
- Record concomitant drug and therapy information, including drugs or therapy used to treat an AE
- Record AEs and SAEs since previous visit
- Document occurrence of lumbar surgery
- Perform vital sign assessments (temperature, blood pressure, heart and respiration rate)
- Perform physical examination
- Complete pain assessment (VAS) and ODI
- Obtain blood specimen for serum anti-SI-6603 antibody
- Perform urine pregnancy test
- Administration of SI-6603

The following will be done after study drug administration:

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

- Record concomitant drug and therapy information, including drugs or therapy used to treat an AE
- Record AEs and SAEs

- Perform vital sign assessments (temperature, blood pressure, heart and respiration rate)

7.2.3 Evaluation Period, Week 1 (Visit 3)

- Complete pain assessment (VAS) and ODI
- Record concomitant drug and therapy information, including drugs or therapy used to treat an AE
- Record AEs and SAEs since previous visit
- Document occurrence of lumbar surgery
- Perform vital sign assessments (temperature, blood pressure, heart and respiration rate)
- Perform neurological examination
- Obtain laboratory specimens (blood for hematology, hepatic, and chemistry panels)

7.2.4 Evaluation Period, Week 6 (Visit 4)

- Complete pain assessment (VAS) and ODI
- Record concomitant drug and therapy information, including drugs or therapy used to treat an AE
- Record AEs and SAEs since previous visit
- Document occurrence of lumbar surgery
- Perform vital sign assessments (temperature, blood pressure, heart and respiration rate)
- Perform neurological examination
- Perform imaging tests (X-ray and MRI)
- Obtain laboratory specimens (blood for hematology, hepatic, and chemistry panels)

7.2.5 Evaluation Period, Week 13 (Visit 5)

- Complete pain assessment (VAS) and ODI
- Record concomitant drug and therapy information, including drugs or therapy used to treat an AE
- Record AEs and SAEs since previous visit
- Document occurrence of lumbar surgery
- Perform vital sign assessments (temperature, blood pressure, heart and respiration rate)
- Perform neurological examination
- Perform imaging tests (X-ray and MRI)
- Obtain laboratory specimens (blood for hematology, hepatic, and chemistry panels)

- Obtain blood specimen for serum anti-SI-6603 antibody

7.2.6 Evaluation Period, Week 26 (Visit 6)

- Complete pain assessment (VAS) and ODI
- Record concomitant drug and therapy information, including drugs or therapy used to treat an AE
- Record AEs and SAEs since previous visit
- Document occurrence of lumbar surgery
- Perform neurological examination
- Perform imaging tests (X-ray and MRI)
- Obtain blood specimen for serum anti-SI-6603 antibody

7.2.7 Discontinuation Visit

- Complete pain assessment (VAS) and ODI
- Record concomitant drug and therapy information, including drugs or therapy used to treat an AE
- Record AEs and SAEs since previous visit
- Document occurrence of lumbar surgery
- Perform vital sign assessments (temperature, blood pressure, heart and respiration rate)
- Perform neurological examination
- Perform imaging tests (X-ray and MRI)
- Obtain laboratory specimens (blood for hematology, hepatic, and chemistry panels)
- Obtain blood specimen for serum anti-SI-6603 antibody

Patients who discontinue early from the study should, if possible, have a Discontinuation Visit. This visit should take place as soon as possible after it was learned that the patient will not be able to complete the study (see also Section 4.3).

8 STATISTICAL METHODS

The statistical considerations summarized in this section outline the plan for data analysis of this study.

Before database lock, a Statistical Analysis Plan (SAP) will be finalized, providing detailed methods for the analyses outlined below. The analyses specified in the SAP will be performed and the Clinical Study Report (CSR) will be prepared upon database lock.

Any changes from the planned analyses will be described and justified in the final CSR.

8.1 Study Patients

8.1.1 Disposition of Patients

Patient disposition and reasons for discontinuation will be summarized for all enrolled patients.

8.1.2 Analysis Sets

The following populations will be assessed:

- Safety: All patients who were treated with an investigational drug.
- Intent-to-Treat (ITT): All patients who were treated with an investigational drug.

If considered necessary, further populations may be defined in the SAP.

8.2 General Considerations

Categorical variables will be summarized in a contingency table by the number and percentage of patients in each category. Continuous variables will be summarized by the number of observations, mean, standard deviation (SD), median, inter-quartile range, minimum, and maximum. Where data are collected over time, both the observed data and change from the Screening period (baseline) will be summarized at each time point. All eCRFs collected and derived data will be listed.

Methods for imputation of missing data and criteria for inclusion of patients in efficacy analyses will be specified.

All statistical tests will be performed 2-sided with a significance level of 5%, unless otherwise stated.

Analysis and Data Conventions:

Definition of baseline

For vital signs, laboratory tests, imaging procedures, neurological examinations, and ODI, the last valid assessment made before administration of investigational drug will be used as the baseline for all analyses of that parameter.

For the efficacy parameters of pain assessment measured by VAS, the baseline value of the worst leg pain and back pain over the past 24 hours (VAS) will be the VAS obtained on the day of enrollment (Day −1/Day 0).

Visit windows

All data collected during study 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

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 presented in the summary tables. If more than one laboratory value is available for a given visit, the last assessment will be used at the Screening visit, and the first valid observation will be used at all other post-baseline visits in summary tables and all observations will be presented in listings. It is noted that invalid laboratory data may not be used (from hemolyzed samples, mishandled samples, quantity not sufficient, or other conditions that would render values invalid).

Missing data conventions

In general, data will not be imputed for safety analyses.

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

Demographic data and other baseline characteristics will be summarized by descriptive statistics with number of patients, mean, SD, median, inter-quartile range, minimum, and maximum. Categorical variables (e.g., sex and race) will be tabulated using frequency and percentage for each category of interest. Medical history and concomitant medication data will be provided in separate listings.

8.4 Treatment Compliance

Treatment compliance on administration volume (1.0 mL or any other amount) of investigational drug will be measured.

8.5 Efficacy Analyses

Efficacy analyses will be performed for the ITT population.

The following efficacy endpoints will be analyzed using the appropriate parametric or nonparametric statistical method:

- Worst leg pain during the past 24 hours assessed by VAS from baseline through Week 26
- Worst back pain during the past 24 hours assessed by VAS from baseline through Week 26
- Functional disability measured by the ODI from baseline through Week 26
- Change of neurological status from baseline determined by neurological examinations FNS or SLR test, sensation, muscle strength, and deep tendon reflex) from baseline through Week 26
- Occurrence of post-treatment surgery for lumbar disc herniation at the same level of administration of the investigational drug up to Week 26

The descriptive statistics of the worst leg pain, back pain, ODI, and their change from baseline will be calculated and presented for each time point. A longitudinal plot will be used to display the mean change from baseline and the associated 95% confidence intervals (CIs) at each time point.

For analysis of change of neurological status from baseline, the number (%) of patients with negative FNS or SLR test results, negative neurological tests for hypoesthesia, muscle weakness, or diminished deep tendon reflex results will be presented for each time point. Furthermore, the percentage of patients with a negative neurological test will be calculated and presented for each time point. The time-course changes will also be presented graphically with bar chart by time points.

In the analysis of occurrence of post-treatment surgery for lumber disc herniation at the same level of administered disc, the number (%) of patients having such surgery will be calculated and presented.

8.6 Safety Analyses

Evaluation of the safety of SI-6603 will be based on the occurrence of AEs, vital signs, laboratory, imaging, and other clinical assessments. The safety analyses will use the safety population.

8.6.1 Adverse Events and Treatment-Related Adverse Events

The incidence of AEs and associated 95% CIs will be determined and presented. A similar analysis will be conducted for each level of severity. After the terms of AEs observed are coded with corresponding MedDRA terms, data on the incidence of AEs will be compiled for each system organ class (SOC) or preferred term (PT). Furthermore, data on the incidence of AEs, as classified by SOC or PT, will be compiled for each level of severity. Of the AEs observed, those whose causal relationship to the investigational drug is classified as “related” will be defined as treatment-related AEs and evaluated in the same manner as AEs.

Concerning SAEs, their incidence and associated 95% CIs will be determined and presented. In addition, data on the incidence of SAEs, as classified by SOC or PT, will be compiled. The same analyses will be repeated for SAEs classified as “related”.

8.6.2 Vital Signs

For body temperature, blood pressure, heart rate and respiration rate, descriptive statistics will be calculated at each time point.

8.6.3 Laboratory Tests

For laboratory data, descriptive statistics will be calculated for each time point.

8.6.4 Serum Anti-SI-6603 Antibody

The proportion and 95% CI of patient with serum anti-SI-6603 antibody positive will be calculated for each group at each time point. Furthermore, the proportion of each isotype of immunoglobulin (IgG, IgM and IgE) will be calculated. The proportion and 95% CI of patient with immunogenicity status will be calculated for each group at each time point.

8.6.5 Disc Height (Disc Index)

For the change from baseline and percent change from baseline of intervertebral disc height, descriptive statistics will be calculated at each time point to make a time-course change plot. The percentage of the patients who showed an intervertebral disc height change of ≤30% and associated 95% CIs will be calculated and presented.

Association between decreased intervertebral disc height and leg pain (VAS) or back pain (VAS) will be assessed.

8.6.6 Intervertebral Posterior Angle

For the intervertebral posterior angle, descriptive statistics will be calculated for time point to draw a time-course change plot. The percentage of the patients who showed a posterior intervertebral angulation angle of ≥5° and associated 95% CIs will be calculated and presented.

Association between posterior intervertebral angulation and leg pain (VAS) or back pain (VAS) will be assessed.

8.6.7 Vertebral Body Translation

For the vertebral body translation, descriptive statistics will be calculated at each time point to make a time-course change plot. The percentage of the patients who showed a vertebral body translation of ≥3 mm and associated 95% CIs will be calculated and presented.

Association between vertebral body translation and leg pain (VAS) or back pain (VAS) will be assessed.

8.6.8 Change in Bone Marrow Adjacent to Vertebral Endplates (Modic Classification)

Modic classifications will be displayed in a tabular form using frequencies by observation day. Shift tables will also be constructed to display Modic classifications. These tables will illustrate the change in a patient's classification between baseline and follow up visits.

For Modic classifications, proportions of patients with Modic's Type 0, Type 1, Type 2, and Type 3 will be calculated. In addition, proportions of patients (for each of Type 1, Type 2, and Type 3) whose Modic's types changed from "No" to "Yes" and associated 95% CI will also be calculated and presented.

A cross-tabulation of patients with any Modic's types changing from "No" to "Yes" and patients with AEs associated with leg pain and back pain will be displayed. In addition, changes from baseline of leg pain (VAS) and back pain (VAS) across time will be displayed separately for those 2 different Modic groups.

8.6.9 Disc Degeneration (Pfirrmann Classification)

Pfirrmann classifications will be tabulated to display the proportion of patients per observation day. Shift tables will also be constructed to display Pfirrmann classifications. These tables will illustrate the change in a patient's classification between baseline and follow-up visits.

For Pfirrmann classifications, proportions of patients with Pfirrmann's Grade 0, Grade I, Grade II, and Grade III will be calculated.

The percentage of patients whose Pfirrmann's grade increased with respect to the grade at baseline and associated 95% CIs will be calculated, analyzed and presented.

A cross-tabulation of patients whose Pfirrmann's grade increased with respect to the grade at baseline and patients with AEs associated with leg pain and back pain will be displayed. In addition, changes from baseline of leg pain (VAS) and back pain (VAS) across time will be displayed separately for those 2 different Pfirrmann groups.

8.6.10 Occurrence of Post-Treatment Lumbar Surgery

As to occurrence of post-treatment lumbar surgery, the percentage of the patients having such surgery will be calculated and presented. In addition, the percentage of the patients with post-treatment lumbar surgery at the site of treatment injection and the percentage of the patients with post-treatment lumbar surgery at other sites will be calculated and reported.

8.7 Interim Analyses

No interim analysis is planned.

8.8 Determination of Sample Size

The total number of 1000 patients will be enrolled. In order to further characterize the frequency and outcome of the rather infrequent treatment-related AE, the current study will have approximately 1000 patients treated with SI-6603. This sample size will allow for estimating a cumulative incidence rate of 0.3% (n=3 patients with events) with a 95% CI of (0.06%, 0.87%), or an incidence rate of 1.5% (n=15 patients with events) with a 95% CI of (0.84%, 2.46%). This calculation assumes that distribution of treatment-related AE is binomially distributed. The 95% CI is calculated using the Clopper-Pearson method in SAS 9.2.

9 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1 Data Quality Assurance

The Sponsor (or Sponsor's designated agent) will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the 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 patients' source documentation (i.e., medical records).

9.1.1 Database Management and Quality Control

All data generated by the site personnel will be captured electronically at each study site using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the eCRF page. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp, will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training in the eCRF.

9.2 Case Report Forms and Source Documentation

All data obtained during this study should be entered in the eCRFs promptly. All source documents from which eCRF entries are derived should be placed in the patient's medical records. Measurements for which source documents are usually available include laboratory assessments, MRIs, and X rays.

The original eCRF entries for each patient may be checked against source documents at the study site by the PAREXEL site monitor.

After review by the site monitor, completed eCRF entries will be uploaded and forwarded to PAREXEL. Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

The specific procedures to be used for data entry and query resolution using the eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training in the eCRF.

9.2.1 Data collection

The Investigators (and appropriately authorized staff) will be given access to an eCRF system which is 21 CFR Part 11 compliant. This system is specifically designed for the collection of the clinical data in electronic format. Access and right to the eCRF system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the Investigator and authorized staff will be able to enter data and make corrections in the eCRFs.

The eCRF should be completed for each patient included in the study and should reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or immediately after the patient's visit or assessment. The Investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the eCRF.

Computerized data-check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved on-line. All discrepancies will be solved on-line directly by the Investigator or by authorized staff. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the Investigator will be required to electronically sign off the clinical data.

Data about all study drug dispensed to the patient and any dosage changes will be tracked on the eCRF.

9.3 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare eCRF entries and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the eCRF entries 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, IECs, and/or the Sponsor's Clinical Quality Assurance Group 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 PAREXEL and the Sponsor of the necessary support at all times.

9.4 Data Processing

All data will be entered by site personnel into eCRF as detailed in Section 9.2.1.

The data review and data handling document, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Query/correction sheets

for unresolved queries will be sent to the study monitors for resolution with the Investigator. The database will be updated on the basis of signed corrections.

Previous and concomitant medications will be coded using the World Health Organization (WHO) Drug Reference List (DRL), which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history, previous and concomitant diseases as well as AE will be coded using the MedDRA terminology.

The versions of the coding dictionaries will be provided in the CSR.

9.5 Archiving Study Records

According to International Conference on Harmonization (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.

9.6 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the Good Clinical Practice guidelines of the ICH, and of the Declaration of Helsinki (2013).[1] The study also will be carried out in keeping with local legal requirements.

9.7 Informed Consent

Before each patient is admitted to the study, informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. This consent form must be 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. The terms of the consent and when it was obtained must also be documented in the eCRF.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB, and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

9.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient 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/IEC/Competent Authority approval prior to implementation (if appropriate).

Following approval, the protocol amendment(s) will be submitted to the Investigational New Drug (IND) under which the study is being conducted.

Administrative changes (not affecting the patient 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.

9.9 Duration of the Study

For an individual patient, the maximum duration of the study will be up to 30 weeks (including up to 4 weeks for screening, 1 day treatment and up to 26 weeks follow-up).

The study will close when the last patient has completed the Visit Week 26 or the Discontinuation Visit.

9.10 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 patients 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 of the study include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study (e.g., AE other than those listed in Table 1)
- The occurrence of an AE, 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, or
  b. Abnormal X-ray findings of instability, defined as vertebral body angle formed by flexion of ≥5° or vertebral body translation of ≥3 mm
  c. Abnormal X-ray or MRI findings which patients exhibit correlating clinical symptoms posing safety concerns, leading the Investigator to judge it necessary for the patient to have surgical intervention

  At time of occurrence of these treatment-related AEs, the Sponsor will notify the DSMB and provide the necessary information. DSMB chairperson will determine to make one of two decisions - (1) Continue the study as planned or (2) Request an ad hoc meeting. The Sponsor will judge discontinuation of the study based on the recommendation of the DSMB. The details of the DSMB procedure will be provided in the DSMB charter.
- Failure to enroll patients at an acceptable rate
- A decision on the part of the Sponsor to suspend or discontinue development of the drug

9.11 Confidentiality

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 patients must be maintained. Patients will be identified on the eCRF and other documents submitted to PAREXEL by their patient number, initials and/or birth date, not by name. Documents not to be submitted to PAREXEL that identify the patient (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

9.12 Other Ethical and Regulatory Issues

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 – Regulatory Authorities, Investigators, and IRB/IECs.

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 immediate update of informed consent.

9.13 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 patients 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.

9.14 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 (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance.

10 REFERENCE LIST

1 World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, the 35th WMA General Assembly, Venice, Italy, October 1983, the 41st WMA General Assembly, Hong Kong, September 1989, the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, the Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002, the Note of Clarification on Paragraph 30 added by the 55th WMA General Assembly, Tokyo 2004, the 59th WMA General Assembly, Seoul, South Korea, October 2008, and the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. *JAMA* 2013;310(20):2191-2194.

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10 Yamagishi M, Nemoto O, Shimmai M. Experimental and clinical medicine of chemonucleolysis. *Orthopedic Surgery* 1991;42(7):1117-1123.

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15 Ohtori S, Yamashita M, Yamauchi K, et al. Low back pain after lumbar discectomy in patients showing endplate modic type 1 change. *Spine* 2010;35(13):E596-600.

16 Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain.* 2008;9(2):105-121.

11 APPENDICES

11.1 Injection Procedure and Investigational Drug Management

11.1.1 Preparation Method for SI-6603

The SI-6603 will be prepared in an aseptic manner according to the following procedure:

1. Take one box of SI-6603 and saline out of the secure, temperature-controlled storage and allow it to stand at room temperature for about 20 minutes. The drugs must be kept in their original boxes during this time.
2. Using a disposable injection syringe, accurately aspirate 1.2 mL of saline from the saline vial in Step 1. Do not use glass syringes.
3. Slowly inject the 1.2 mL of saline aspirated in Step 2, into the SI-6603 vial from Step 1. If the SI-6603 vial does not have negative pressure, the vial should not be used.
4. Slowly reconstitute the SI-6603 in Step 3, avoiding bubbling and vigorous shaking.
5. After reconstitution, check the vial to ensure that the solution is a colorless, clear liquid free from suspended or other foreign materials. If turbidity or foreign materials are observed, the solution will not be used.
6. Record the drug preparation time in the medical records.
7. No other ingredient/substance should be added to the reconstituted SI-6603 from Step 5.
8. Following reconstitution, the SI-6603 will be kept at room temperature and must be administered within 2 hours.
9. Attach a needle to a syringe and aspirate 1.1 mL from the vial containing reconstituted SI-6603. Do not use glass syringes.
10. Any residual SI-6603 will not be used in any other patient.

11.1.2 Precautions in Administering Investigational Drug

1. The investigational drug must be administered in a study site location that has appropriate fluoroscopic equipment and must be administered within 2 hours of reconstitution.
2. Full/general anesthesia is prohibited during investigational drug administration.
3. Circulatory status should be closely monitored during investigational drug administration.
4. Preparations should be in place to provide appropriate emergency care to the patient. Preparations for the possible occurrence of an allergic reaction or anaphylaxis should include:
    - Establishing a peripheral intravenous line.

- Having medications for treatment of anaphylaxis (e.g., epinephrine, dopamine, antihistamine, adrenal cortex hormone) and intubation equipment (e.g., endotracheal tubes, handheld resuscitator), readily available in the case of signs and symptoms of anaphylaxis or any other cardio-respiratory emergency. For cautions on medications before investigational drug administration, please also see Section 5.7.2 *"Notes Concerning Concomitant Medication Before SI-6603 is Administered"*.

5. Giving close attention to the patient's general physical condition (e.g., respiratory status or any patient complaint) during and following investigational drug administration.
6. If anaphylaxis symptoms (e.g., breathing difficulties, hives, angioedema, or itching) appear during investigational drug administration, administration of the investigational drug must be discontinued immediately.

11.1.3 Intradiscal Administration Procedure for SI-6603

The intradiscal administration procedure for SI-6603 will be performed as follows:

1. Have the patient lie down on a fluoroscopy bench in lateral or prone position.
2. Under fluoroscopic guidance, position the patient so the intervertebral disc space is parallel to the X-ray.
3. Under fluoroscopic guidance, locate the insertion point while observing the target area.
4. Widely sterilize the operative field centering on the entry point and extending to the lateral region.
5. Insert the spinal needle in the median plane of the patient, carefully advancing the needle into the dorsal transverse temporal fibrous ring of the intervertebral disc. Do not make any median transdural punctures.
6. Under fluoroscopic guidance, insert the spinal needle tip into the center of the intervertebral disc, feeling the spinal needle as it penetrates into the nucleus pulposus through the annulus fibrosus.
7. After the puncture of the intervertebral disc, take a lateral X-ray image of the involved disc, then move the C-arm of the X-ray machine to accurately take a frontal view of the involved disc checking to ensure the needle tip is correctly positioned in the center of the intervertebral disc. The images will confirm correct needle placement and will be kept in the medical record. Send the copy of the images to BioClinica for confirmation of injection level.
8. Attach the syringe containing the previously drawn amount (1.1 mL) of reconstituted drug as outlined in Section 11.1.1.
9. Remove the inner needle and administer whole amount (1.1 mL) of the freshly reconstituted SI-6603 solution to deliver 1.0 mL to intervertebral disc. Inject the solution slowly and stop immediately if any resistance is felt.

10. Record the date, hour, and amount of SI-6603 administered in the eCRF. Any volume other than 1 mL will be recorded in the eCRF.
11. After the administration of SI-6603, antibiotics may be used for the prevention of infection at the site of injection.

11.2 Package Presentation and Labeling

This information will be provided later by the vendor.

11.3 Visual Analog Scale

VAS Measurement Method

The instructions for visual analog scale (VAS) measurements that will be recorded in the electronic case report form (eCRF) are explained in this manual. The purpose of this manual is to minimize the variation of the VAS values among measurers.

The patients will evaluate their pain by themselves on VAS Scale Form at each scheduled visit at the site.

Tools for measurement: Metallic straight measure is provided by Sponsor.

Method of VAS measurement:

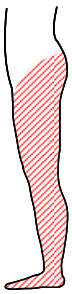
1. Principal Investigators, sub Investigators or study coordinator set the 0 mm point at the left edge of the left portion of the horizontal line on the VAS as the origination and measure the VAS from this point to the right.
2. Measure the distance from the point of origination at 0 mm to the point at the intersection of the written vertical VAS line by use of the specified mm scale on the horizontal line.
3. Set the VAS measurement value from 0 mm at the origination to 100 mm at the termination, read in 1 mm increments, and round off a VAS measurement value of less than 1 mm. If the VAS measurement value is under 0 mm, record 0 mm. If the VAS measurement value is over 100 mm, record 100 mm.
4. Record the VAS measurement value in the patient diary and the eCRF.

Notes at the time of pain evaluation:

1. Definition of leg pain and back pain

   Leg pain: Pain of the leg and the buttocks (belt)

   Back pain: Pain near the waist

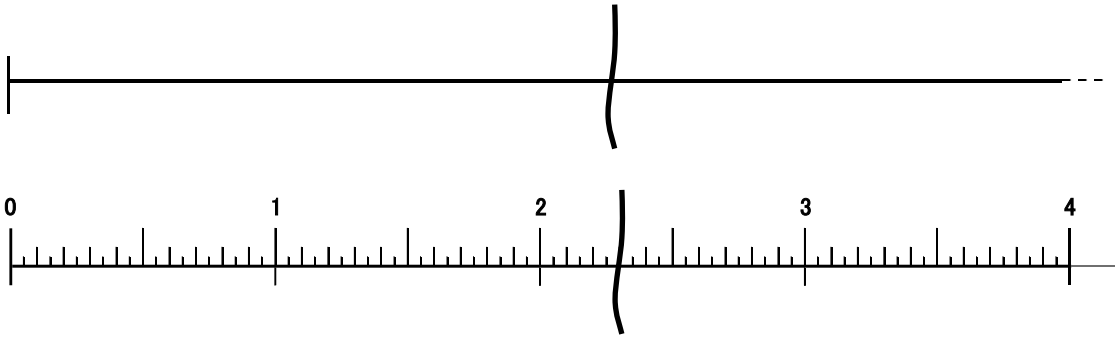


Investigator confirms patient's site of pain at the time of screening, and instructs a patient to evaluate the pain as leg pain and/or back pain. In addition, Investigator instructs a patient to evaluate pain only and not include numbness.

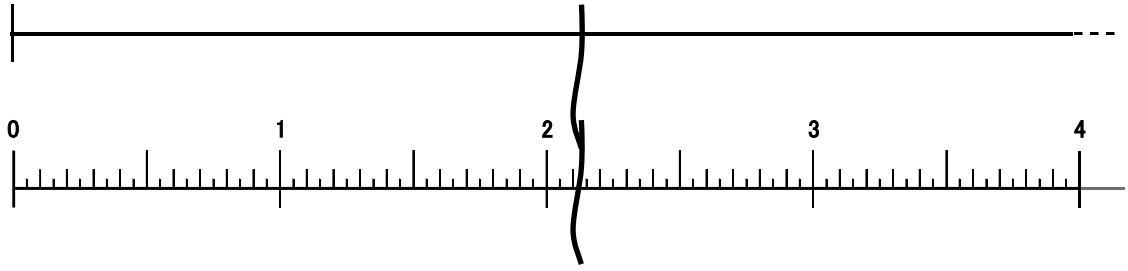
2. Definition of "the worst pain experienced in the past"

   The worst pain experienced by the lumbar disc herniation is considered as "the worst pain experienced in the past (100 mm)" and VAS of leg pain and back pain should be evaluated based on it.

Example 1: The VAS measurement value in this example below is 22 mm because the left edge point of intersection of the vertical written line lies to the left of the point of 23 mm.

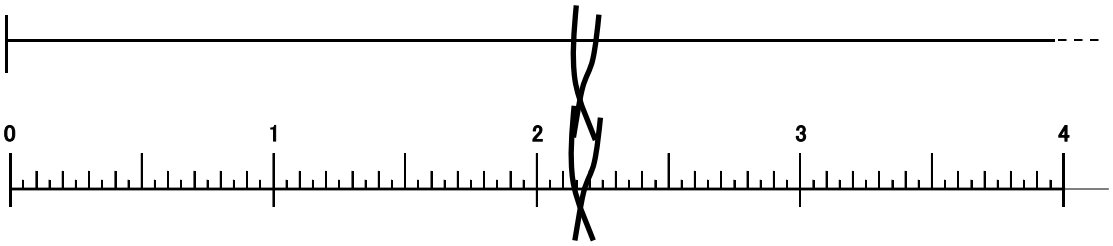


Example 2: The measurement value in this example below is 21 mm because the left edge point of the intersection of the vertical written line lies to the right of the point of 21 mm.



Measure the distance in mm from the origination at 0 mm to the point of the intersection of the vertical written line with the left edge point of written lines, if “X” is written in VAS.

Example 3: The measurement value in this example below is 21 mm because the left edge point of the intersection of the vertical written lines lies to the left of the point of 22 mm.



If ○ or ● is used to mark or indicate the VAS measurement on the horizontal, measure the distance from the origination at 0 mm to marks in the same way as measuring the vertical VAS written line.

11.4 Oswestry Disability Index, version 2.1a

This questionnaire is designed to give us information as to how your back (or leg) trouble affects your ability to manage in everyday life.

Please answer **every section**. Mark **one box only** in each section that most closely describes you **today**.

Section 1—Pain intensity

(0) I have no pain at the moment.

(1) The pain is very mild at the moment.

(2) The pain is moderate at the moment.

(3) The pain is fairly severe at the moment.

(4) The pain is very severe at the moment.

(5) The pain is the worst imaginable at the moment.

Section 2—Personal care (washing, dressing, etc.)

(0) I can look after myself normally without causing extra pain.

(1) I can look after myself normally but it is very painful.

(2) It is painful to look after myself and I am slow and careful.

(3) I need some help but manage most of my personal care.

(4) I need help every day in most aspects of self care.

(5) I do not get dressed, wash with difficulty and stay in bed.

Section 3—Lifting

(0) I can lift heavy weights without extra pain.

(1) I can lift heavy weights but it gives extra pain.

(2) Pain prevents me from lifting heavy weights off the floor but I can manage if they are conveniently positioned, e.g. on a table.

(3) Pain prevents me from lifting heavy weights but I can manage light to medium weights if they are conveniently positioned.

(4) I can lift only very light weights.

(5) I cannot lift or carry anything at all.

Section 4—Walking

(0) Pain does not prevent me walking any distance.

(1) Pain prevents me walking more than one mile.

(2) Pain prevents me walking more than a quarter of a mile.

(3) Pain prevents me walking more than 100 yards.

(4) I can only walk using a stick or crutches.

(5) I am in bed most of the time and have to crawl to the toilet.

Section 5—Sitting

(0) I can sit in any chair as long as I like.

(1) I can sit in my favorite chair as long as I like.

(2) Pain prevents me from sitting for more than 1 hour.

(3) Pain prevents me from sitting for more than half an hour.

(4) Pain prevents me from sitting for more than 10 minutes.

(5) Pain prevents me from sitting at all.

Section 6—Standing

(0) I can stand as long as I want without extra pain.

(1) I can stand as long as I want but it gives me extra pain.

(2) Pain prevents me from standing for more than 1 hour.

(3) Pain prevents me from standing for more than half an hour.

(4) Pain prevents me from standing for more than 10 minutes.

(5) Pain prevents me from standing at all.

Section 7—Sleeping

(0) My sleep is never disturbed by pain.

(1) My sleep is occasionally disturbed by pain.

(2) Because of pain I have less than 6 hours sleep.

(3) Because of pain I have less than 4 hours sleep.

(4) Because of pain I have less than 2 hours sleep.

(5) Pain prevents me from sleeping at all.

Section 8—Sex life (if applicable)

(0) My sex life is normal and causes no extra pain.

(1) My sex life is normal but causes some extra pain.

(2) My sex life is nearly normal but is very painful.

(3) My sex life is severely restricted by pain.

(4) My sex life is nearly absent because of pain.

(5) Pain prevents any sex life at all.

Section 9—Social life

(0) My social life is normal and causes me no extra pain.

(1) My social life is normal but increases the degree of pain.

(2) Pain has no significant effect on my social life apart from limiting my more energetic interests, e.g. sport, etc.

(3) Pain has restricted my social life and I do not go out as often.

(4) Pain has restricted social life to my home.

(5) I have no social life because of pain.

Section 10—Travelling

(0) I can travel anywhere without pain.

(1) I can travel anywhere but it gives extra pain.

(2) Pain is bad but I manage journeys over two hours.

(3) Pain restricts me to journeys of less than one hour.

(4) Pain restricts me to short necessary journeys under 30 minutes.

(5) Pain prevents me from travelling except to receive treatment.

Reference: Fairbank JCT, Couper J, Davies JB, O'Brien JP. The Oswestry Low Back Pain Disability Questionnaire. *Physiotherapy*. 1980;66:271-273

11.5 Modic Classification

Modic Classification of Abnormalities in Bone Marrow Adjacent to Vertebral Endplates (Sagittal MRI)

Modic Change	MRI Signal Intensity
0	Normal signal
Type 1	Decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images (inflammatory phase)
Type 2	Increased signal intensity on T1-weighted images and isointense or slightly increased signal intensity on T2-weighted images (fatty phase)
Type 3	Hypointense signal on T1- and T2-weighted images with marked sclerosis adjacent to the endplates

11.6 Pfirrmann Classification

Pfirrmann's Classification of Disc Degeneration
(T2-weighted sagittal MRI)

Pfirrmann Grade	Nucleus Pulposus and Fibrous Ring Differentiation	Signal Intensity (T2-weighted image) of Nucleus Pulposus
Grade 0 (normal)	Present	Hyperintense with horizontal dark bands
Grade I (mild)	Blurred	Slightly decreased with minor irregularities
Grade II (moderate)	Absent	Moderately decreased with hypointense zones
Grade III (severe)	Absent	Hypointense with or without horizontal hyperintense band (black disc)

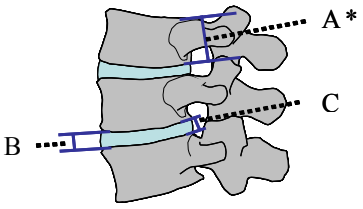
11.7 Imaging Tests (X-ray and Magnetic Resonance Imaging)

11.7.1 X-ray Imaging

In X-ray imaging, an anteroposterior and lateral-intermediate, flexion, and extension spinal will be obtained according to the "*Procedure Manual for Radiographic Examinations of the Lumbar Spine*".

11.7.2 Disc Height (disc index)

The central reader will measure the disc index for the intervertebral disc treated with the investigational drug using (A) the posterior height of the superior vertebral body adjacent to the target segment, (B) the anterior disc space and (C) the posterior disc space.



Neutral

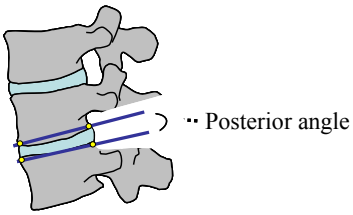
$$\text{Disc Index} = \frac{B + C}{2A}$$

*) The anatomical index (A) may be observed at another site according to the condition of the vertebral body. However, the index will be obtained at the same site (anterior or posterior) of the same vertebral body throughout this study.

Calculation of the disc height

11.7.3 Intervertebral Posterior Angle

The central reader will measure the intervertebral posterior angle of the intervertebral disc treated with the investigational drug.

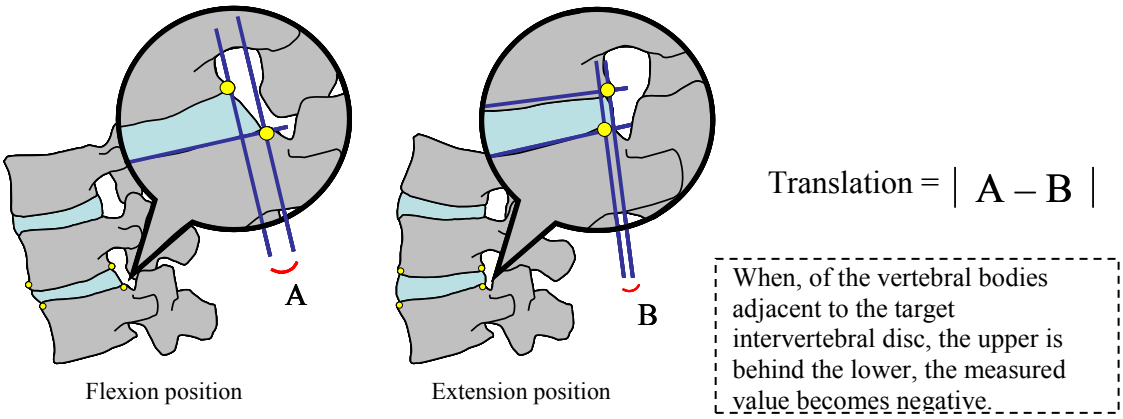


Flexion

Method of measuring the intervertebral posterior angle

11.7.4 Vertebral Body Translation

The central reader will determine the difference in vertebral body translation at the extension and flexion positions of the intervertebral disc treated with the investigational drug.



Flexion position

Extension position

Method of measuring vertebral body translation as an adverse event

11.7.5 Magnetic Resonance Imaging

An MRI image will be created by the T1-weighted fast spin echo technique, T2-weighted fast spin echo technique, and T2-weighted fast spin echo technique with fat suppression in the sagittal plane, and by the T1-weighted fast spin echo technique and T2-weighted fast spin echo technique in the axial plane according to the "*Procedure Manual for MRI Examination*".

11.8 Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.
*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.	
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.	
A semi-colon indicates ‘or’ within the description of the grade.	
A single dash (-) indicates a grade is not available.	

Publish Date: May 28, 2009