SEIKAGAKU CORPORATION

CONDOLIASE (SI-6603)

FOR THE TREATMENT OF RADICULAR LEG PAIN ASSOCIATED WITH CONFIRMED NERVE ROOT IMPINGEMENT CAUSED BY LUMBAR DISC HERNIATION IN ADULTS

SPONSOR BRIEFING DOCUMENT

ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE

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Abbreviation:	Definition
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AGEP	acute generalized exanthematous pustulosis
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BLA	Biologics License Application
BMI	body mass index
CI	confidence interval
CSR	clinical study report
DHL	disc height loss
EQ-5D-5L	EuroQol Group 5-Dimension Quality of Life instrument, 5-level version
FDA	Food and Drug Administration
GAG	glycosaminoglycan
iPSP	initial pediatric study plan
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	intent to treat
LDH	lumbar disc herniation
LOCF	last observation carried forward
LS	least squares
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MNAR	missing not at random
MoA	mechanism of action
MRI	magnetic resonance imaging
NASS	North American Spine Society
NSAID	nonsteroidal anti-inflammatory drugs
ODI	Oswestry disability index
PD	pharmacodynamic
PGIC	patient global impression of change
PK	pharmacokinetic
PRO	patient-reported outcome
PT	preferred term
QoL	quality of life
RCT	randomized clinical trial
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation:	Definition
SCAR	severe cutaneous adverse reactions
SD	standard deviation
SE	standard error
SJS	Stevens-Johnson Syndrome
SLR	straight leg raise
SMQ	standardized MedDRA query
ULN	upper limit of normal
VAS	visual analog scale

1 EXECUTIVE SUMMARY

1.1 Introduction

Seikagaku Corporation (SKK) has submitted a Biologics License Application (BLA) seeking approval of condoliase (SI-6603) as a single-dose injection for the treatment of radicular leg pain associated with confirmed nerve root impingement caused by lumbar disc herniation (LDH) in adults.

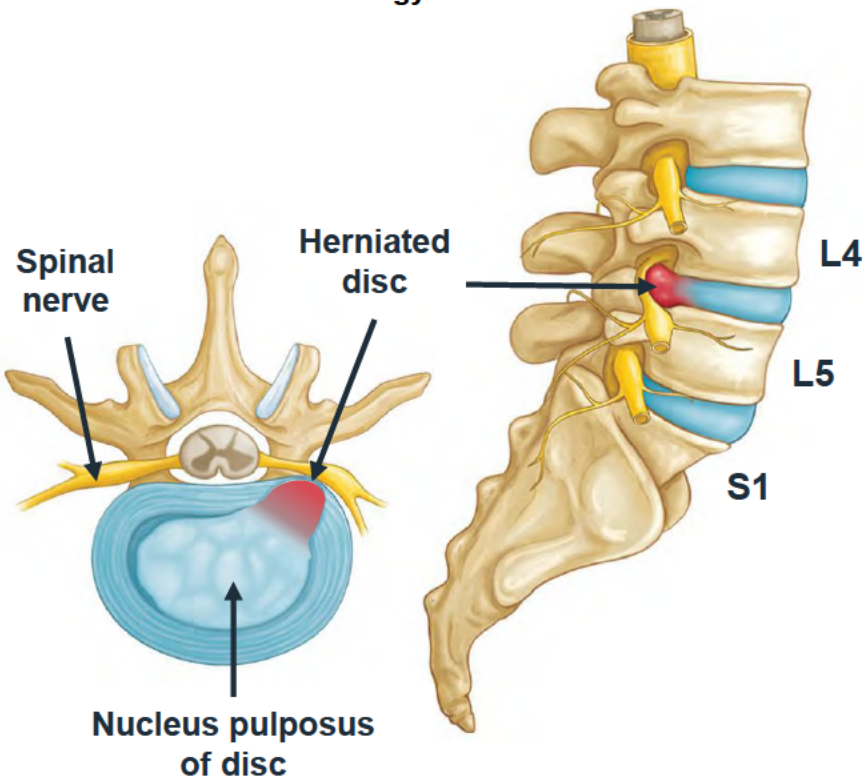
1.2 Background and Unmet Need on Lumbar Disc Herniation (LDH)

1.2.1 Pathophysiology and Symptoms

Lumbar disc herniation occurs as a result of the displacement of the nucleus pulposus of an intervertebral disc following disruption of the posterior or posterolateral aspect of the annulus fibrosus (Figure 1). As a result, the herniated disc compresses the spinal nerve root, causing symptoms such as leg pain, numbness, or low back pain (Kreiner et al, 2012; Haro et al, 2022). Approximately 95% of herniations are LDH, occurring in the L4-L5 or L5-S1 region of the spine.

Persistent unresolved leg pain that does not respond to conservative treatment often results in worsening health, long-term disability, increased caregiver burden, and lost days from work (Wong & Transfeldt, 2007; Haro et al, 2022).

Figure 1: Lumbar Disc Herniation Pathology



Source: Adapted from American Academy of Orthopaedic Surgeons.

1.2.2 Epidemiology

The prevalence of LDH in the US is an estimated 1% to 3% of the population (Haro et al, 2022; Shiga, 2022; Anderson et al, 2021; Lilly et al, 2021).

Disc herniation is most often the result of a gradual, aging-related wear and tear called disc degeneration. As people age, the discs become less flexible and more prone to tearing or rupturing (Mayo Clinic, 2023). Sometimes, using the back muscles instead of the leg and thigh muscles to lift heavy objects or twisting and turning while lifting can cause a herniated disc. In rare instances, a specific event such as a fall can be the cause. Several changes in the biology of the intervertebral disc are also thought to contribute to LDH, including water retention in the nucleus pulposus, increased type I collagen within the nucleus pulposus and inner annulus fibrosus, and degradation of collagen and extracellular matrix materials (Amin et al, 2017).

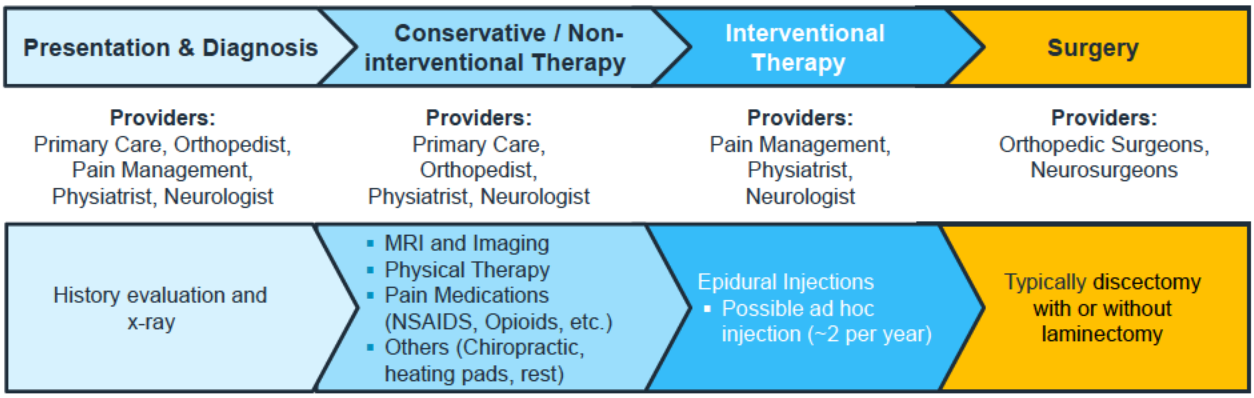
1.2.3 Standard of Care

1.2.3.1 Conservative Therapy

Non-operative management of symptomatic LDH via conservative therapy is the treatment of choice for most patients (Amin et al, 2017; Yaman et al, 2024) (Figure 2). Non-operative management consists of a multimodal approach, including anti-inflammatory medications, education, and physical therapy (Wong et al, 2017). Interventions can include bed rest, lumbar support, traction therapy, thermotherapy, spinal manipulation, exercise, oral steroids, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), epidural block, nerve-root block, epidural steroid injections (ESIs), traditional Chinese medicine, and alternative medicine (Haro et al, 2022; Lilly et al, 2021; Wang et al, 2020; Zou et al, 2023). Traditional western formal physical therapy focused on exercise, core strengthening, and joint mobility have also shown improvement in symptoms related to LDH (Jewell & Riddle, 2005). However, physical therapy procedures have not consistently demonstrated meaningful efficacy, and the therapeutic benefits appear to be limited (Haro et al, 2022; Yaman et al, 2024). The duration of conservative therapy should be individualized based on the patient's pain, lost functionality and/or diminished QoL (Costa et al, 2024).

If symptoms persist, transforaminal or interlaminar epidural steroid injections may be considered for pain relief in some patients with LDH and radiculopathy (Ackerman et al, 2007; Beall et al, 2024). ESIs seem to be effective in relieving symptoms in the short term and delaying surgery, while evidence of any long-terms benefits is still lacking (Carassiti et al, 2021; de Bruijn et al, 2021; Verheijen et al, 2021).

Figure 2: LDH Treatment Algorithm



LDH: lumber disc herniation; MRI: magnetic resonance imaging; NSAIDS: non-steroidal anti-inflammatory drugs.

1.2.3.2 Surgical Intervention

Surgery is the next option for the approximately 20% to 50% of patients who have persistent pain that impedes function and/or quality of life and do not respond to conservative treatment (Peul et al, 2007; Weinstein et al, 2006; Shiga, 2022). Surgical interventions can include sequestrectomy, discectomy, laminectomy, lumbar fusion, and implantation of a spinal cord stimulator (Kreiner et al, 2012). The surgical treatment of LDH has evolved over the past years, with the progressive availability of different minimally invasive techniques (including tubular microscopic, also known as microendoscopic discectomy, and percutaneous endoscopic discectomy) that have been introduced as alternatives to the standard open lumbar discectomy (Costa et al, 2024). (Section 2.2.1.3). While surgical intervention generally provides more relief than conservative care (Peul et al, 2007; Weinstein et al, 2006; Shiga, 2022), the benefits are often moderate and tend to decrease over time (Dydyk et al, 2023).

Additionally, surgery is associated with multiple risks, including infections, neurological complications, and complications related to anesthesia and the surgical procedure (Steadman et al, 2017) (Table 12). Surgical treatment of lumbar disc herniation generally has a favorable prognosis, but some patients may require reoperation. The most common reason for reoperation is recurrence of herniation, and the rate of reoperation for recurrent lumbar disc herniation increases as the follow-up duration becomes longer; the cumulative reoperation rate ranges from 1.5% to 8.5% at 5 years after surgery (Haro et al, 2022).

1.2.4 Patient Unmet Need

There are no approved pharmacological therapies for patients with leg pain due to impingement of the root nerve by the LDH that provide early and long-term reduction in leg pain resulting from nerve root impingement while improving functionality. Alternative treatment options are needed for patients with radicular leg pain who do not respond to conservative therapy and seek non-surgical solutions.

1.3 Product Description

1.3.1 Condoliase

Condoliase is a single-dose drug product that is injected directly into the intervertebral disc for the treatment of radicular leg pain associated with nerve root impingement caused by LDH in adults. The drug product is a lyophilized powder for reconstitution into an aqueous, injectable solution. It is a non-surgical treatment that does not require general anesthesia.

Condoliase injections must be administered with the use of C-arm fluoroscopy, which allows for real-time, continuous imaging. This real-time imaging capability enables the treating doctor to insert the needle precisely and safely into a patient's intervertebral disc. (Section 3.1)

1.3.2 Proposed Indication and Administration

The proposed indication of condoliase is for the treatment of radicular leg pain associated with confirmed nerve root impingement caused by lumbar disc herniation in adults.
Condoliase is administered as a single-dose injection into the nucleus pulposus of the herniated intervertebral disc for a nonsurgical treatment option. The proposed dose of 1.25 U of condoliase is consistent, regardless of patient demographics or medical characteristics. The 1.25 U dose corresponds with a protein concentration of approximately 3 µg/mL of solution.

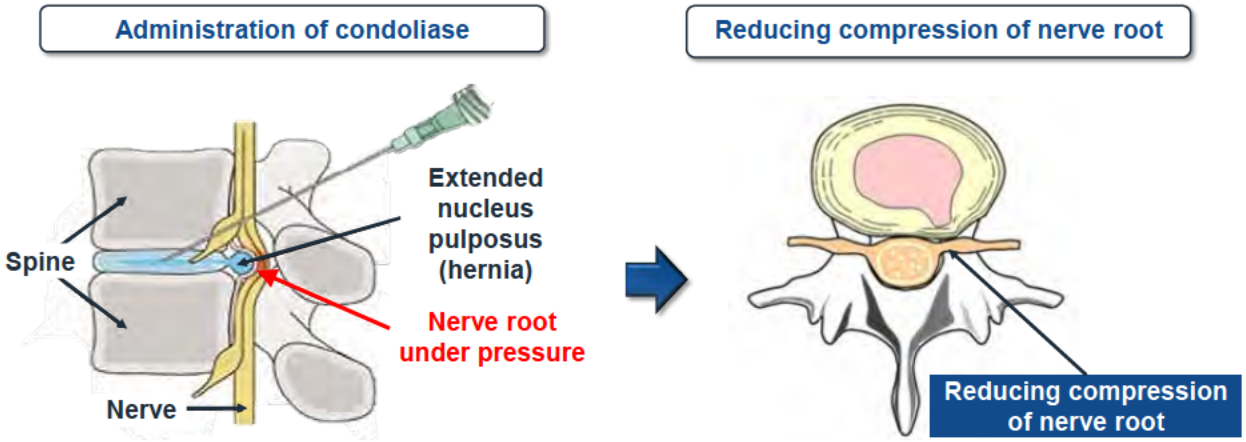
1.3.3 Mechanism of Action

Condoliase is a glycosaminoglycan (GAG)-degrading enzyme isolated and purified from a gram-negative rod (*Proteus vulgaris*) that specifically degrades chondroitin sulfate (Section 3.3). Importantly, condoliase does not degrade surrounding proteins, including collagen, which is an important component of intervertebral discs and the surrounding microenvironment. Therefore, condoliase degrades the offending herniated disc, without damaging surrounding tissues and proteins.

Condoliase injection is considered a chemonucleolysis treatment. When injected into the nucleus pulposus of the herniated intervertebral disc, condoliase specifically acts on and degrades chondroitin sulfate GAG chains of the proteoglycans, the water-retaining component of the vertebral disc. This GAG-specific degradation shrinks the herniated disc, as consistently demonstrated across nonclinical and clinical studies, thereby reducing nerve root compression and pressure on the impinged nerve, which in turn alleviates pain and other LDH-associated clinical symptoms (Figure 3).

Importantly, because condoliase is injected directly into the intervertebral disc, treatment does not require a general anesthetic and is less invasive than surgery.

Figure 3: Condoliase Mechanism of Action



GAG: glycosaminoglycan.
Note: Condoliase selectively degrades chondroitin sulfate GAG chains. Drug administration does not require anesthesia and is less invasive than surgical treatment.

1.4 Development Program

1.4.1 Approval in Japan

In March 2018, condoliase (HERNICORE®) 1.25 U was approved in Japan to treat LDH with no sufficient improvement after conservative therapy. Since approval in Japan, it is estimated that approximately 27,000 patients have received condoliase injections outside of the clinical development program as of the data cut-off date, March 11, 2024.

1.4.2 Nonclinical Program Summary

Nonclinical pharmacology studies consistently demonstrated the effects of condoliase in reducing nucleus pulposus swelling (rabbits) and intradiscal pressure and disc height (sheep). Symptom improvement was demonstrated in dogs with disc herniation syndrome. After intradiscal injection in dogs, condoliase remains in the intervertebral disc and the exposure in plasma was extremely low, indicating that condoliase slowly and minimally distributes to the whole body after injection into the intervertebral disc. In addition, condoliase showed a favorable safety profile after intradiscal administration, with no systemic toxicity, genotoxicity, or reproductive and developmental toxicity concerns raised in the nonclinical studies.

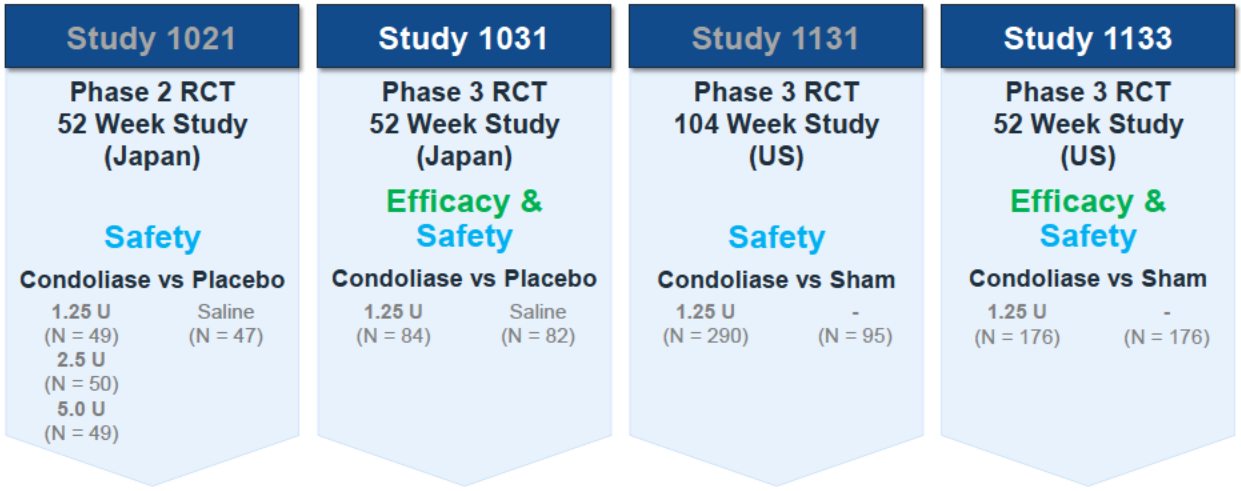
1.4.3 Clinical Program Summary

A comprehensive clinical development program has characterized efficacy and safety of condoliase to support the proposed dose of 1.25 U for the treatment of radicular leg pain associated with confirmed nerve root impingement caused by lumbar disc herniation in adults.

The data supporting a positive benefit-risk for condoliase in the proposed indication come from four Phase 2 and 3 randomized control trials (Figure 4).

Additional study details are provided in Section 4.2.2 for the pivotal Phase 3 studies and Section 4.2.3 for the studies contributing supportive safety data.

Figure 4: Overview of Clinical Development Program



RCT: randomized, controlled trial; U=units.
Note: Condoliase approved in Japan in 2018 with an estimated 27,000 patients treated in postmarketing setting.

1.5 Efficacy

Study 1031 (Section 7.3; Japan) and Study 1133 (Section 7.5; US) demonstrate substantial evidence of efficacy in patients with radicular leg pain caused by visible nerve root impingement due to LDH.

1.5.1 Pivotal Studies 1031 and 1133 Study Designs

1.5.1.1 Overview of Common Design Features

Common design elements of the pivotal Phase 3 studies are presented in Table 1.

Study 1031 and Study 1133 were both Phase 3, randomized, double-blind, multi-center studies of a single injection of condoliase 1.25 U compared to either placebo (Study 1031) or sham (Study 1133) (Figure 5). Both studies used common endpoints to assess the impact of LDH on worst leg pain (as assessed by 100 mm Visual Analog Scale [VAS], patient's function (Oswestry Disability Index [ODI]), and herniation volume. Both studies were assessed in the modified Intent to Treat Population (mITT; details in Section 1.5.1.4.)

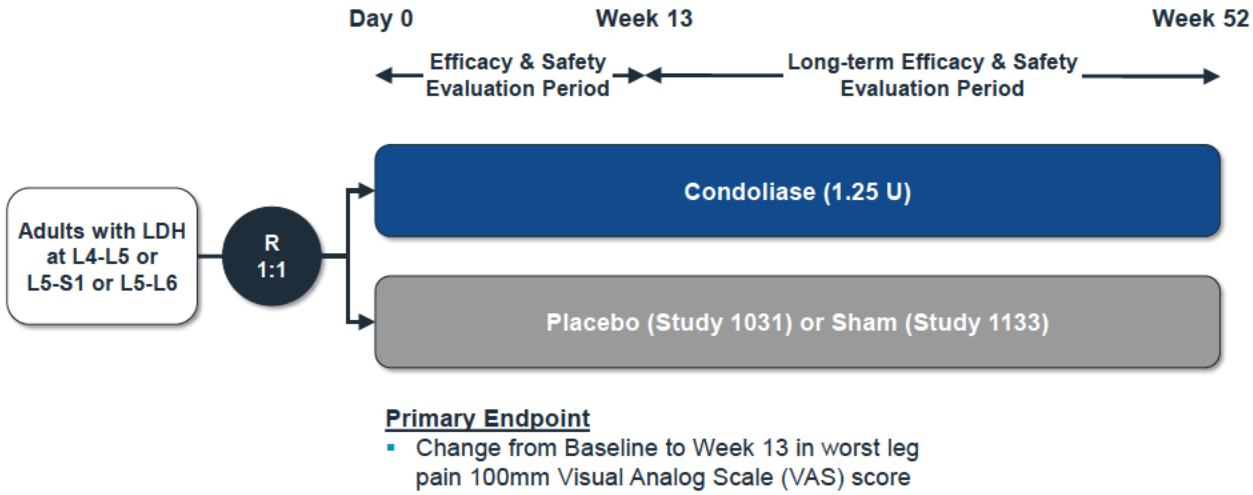
Table 1: Common Design Elements of Pivotal Phase 3 Studies — Study 1031 (Japan) and Study 1133 (US)

Design Parameter:	Study 1031 (Japan)	Study 1133 (US)
Diagnosis	Patients with lumbar disc herniation assessed by imaging (MRI), with clinical symptoms consistent with the location of the affected nerve root	
Primary endpoint	Change from baseline in average worst leg pain score at Week 13[1]	
Key secondary endpoints[2]	• Change from baseline in average worst led pain score ay Week 52[1] • Change from baseline in herniation volume at Week 13 • Change from baseline in Oswestry Disability Index (ODI) at Week 13	
Hernia type	Lumbar disc herniation without rupture of the posterior longitudinal ligament	

Design Parameter:	Study 1031 (Japan)	Study 1133 (US)
Hernia site	L4-L5 or L5-S1 (or L5-L6)	
Comparator	Placebo	Sham
Age	20-70 years	30-70 years
Region	Japan	US
Current episode	≥ 6 weeks	≥ 6 weeks and ≤ 1 year
Treatment history	Patients with inadequate improvement in pain caused by LDH, despite 6 weeks or more of conservative treatment	
Symptom	Worst leg pain (VAS mean score ≥ 50 mm, etc)	
BMI	< 35 kg/m^2	< 40 kg/m^2

BMI: body mass index; LDH: lower-disc herniation; MRI: magnetic resonance imaging; ODI: Oswestry Disability Index; VAS: visual analog scale.
1. Assessed by 100 mm VAS, with value over past 24 hours taken an average of 7 consecutive days prior to baseline and prespecified evaluation time points.
2. Prespecified as key secondary endpoints in Study 1133 and secondary endpoints in Study 1031.

Figure 5: Design Schematic of Pivotal Phase 3 Studies — Study 1031 (Japan) and 1133 (US)



LDH: lumbar disc herniation; R: randomized; VAS: Visual Analog Scale.

1.5.1.2 Patient Populations

The patient populations were similar for Study 1031 and Study 1133:

- LDH confirmation via magnetic resonance imaging (MRI) with symptoms representative of nerve root impingement of the appropriate nerve.
- Both studies intended to exclude patients with lower-back pain caused by disorders other than LDH to eliminate unrelated pain as a confounding factor.
- In Study 1133, the VAS score at baseline required a minimum of 5 days (out of the required 7 days) of reported scores between 50-90 mm. By comparison, Study 1031

required a minimum of 3 days (out of the required 7 days) of reported scores ≥ 50 mm on the VAS. Both stipulated the requirement that the variability in VAS be ≤ 25 mm.
- Both studies had specific exclusion criteria for drug and alcohol use, in addition to restrictions on the use of opioid and other analgesics, including cannabis in Study 1133. (Cannabis use is not permitted in Japan and therefore was not listed as an exclusion criterion in study 1031.)

1.5.1.3 Endpoint Definitions

Primary Endpoint: Mean change from baseline in average worst leg pain score at Week 13, as measured by the 100 mm VAS.

Secondary Endpoints:
The following were prespecified as key secondary endpoints in Study 1133 and secondary in Study 1031:

- Change from baseline in average worst leg pain score at Week 52[1] (measured by VAS)
- Change from baseline in herniation volume at Week 13
- Change from baseline in ODI score at Week 13

Patient-Reported Outcome (PRO) Endpoints:

Supportive quality of life analyses included the following PROs:

- Patient Global Impression of Change (PGIC) at Week 13
- EuroQol Group 5-Dimension Quality of Life instrument, 5-level version (EQ-5D-5L) at Week 13
- 36-Item Short Form Health Survey (SF-36) at Week 13

Other Endpoints:
The following additional endpoints were prespecified in Study 1133 or Study 1031:

- 50% responder analysis of worst leg pain at Week 13
- Negative Straight Leg Raise (SLR) test at Week 13

A summary of prespecified other supportive endpoints and results is presented in Table 41 (Appendix 13.2).

Worst Leg Pain: For the primary endpoint, the values of the worst leg pain over the past 24 hours were taken an average of seven consecutive days prior to the enrollment (baseline) for each patient and then again for seven consecutive days prior to observation at Week 13.

The 100 mm VAS assessment is a method in which patients indicate their pain intensity during the past 24 hours along a horizontal line which ranges in intensity from “no pain” to “pain as bad as you can imagine.” (See Section 7.1.1 for additional details on this assessment.)

Herniation Volume: Change from baseline to Week 13 in herniation volume was assessed by MRI through a central imaging facility after images were collected by the investigator or site staff. (See Section 7.1.2 for additional details on this assessment.)

[1] Assessed as post hoc analysis for Study 1031.

Oswestry Disability Index (ODI): Change from baseline to Week 13 in ODI as assessed by the patient.

The back pain-specific portion of the ODI (the Oswestry Low Back Pain Disability Questionnaire) is a questionnaire used to measure low-back pain and permanent functional disability. The test is considered the “gold standard” of low back functional outcome tools. A higher score on the ODI indicates more severe disability. (See Section 7.1.3 for additional details on this assessment.)

Patient-Reported Outcomes (PROs): The PROs used in these studies are widely used in clinical trials to measure patients’ perceptions about their own health and quality of life (QoL) over the course of a study. The PGIC was first administered 2 weeks after injection and then at each study visit thereafter through Week 52. The SF-36 was administered at baseline and then again at each visit starting 4 weeks after injection through Week 52. The EQ-5D-5L was administered at baseline, Week 13, and Week 52.

50% Responder Analysis of Worst Leg Pain: Patients whose weekly average worst leg pain improved ≥ 50% from baseline were considered responders for this analysis.

Negative Straight Leg Raise (SLR) test: Defined as the percentage of patients with negative SLR test at each time point. The SLR is a neurological exam for patients with low back pain administered to assess nerve root irritation when the leg is raised between 30° and 70°. To perform the SLR test, the patient lies on their back with one leg straight and the other leg raised by the examiner. The test is considered negative if the patient does not experience pain in the lower limb when the leg is raised to 70°.

Patient Global Impression of Change (PGIC): PGIC is a self-reported 7-point scale administered at each time point that reflects a patient's belief about the change from baseline in worst leg pain over time.

1.5.1.4 Statistical Analysis Plans

Endpoints were assessed in a hierarchical method (serial gatekeeping), in which the previous endpoint had to be met with statistical significance before significance could be claimed on a subsequent endpoint. Study 1031 was assessed only for the primary endpoint, while Study 1133 was assessed up to the key secondary endpoints using the hierarchical method.

Efficacy assessments were conducted using the following analyses:

- Prespecified primary analyses
  - **Study 1031**: analysis of covariance (ANCOVA) with last observation carried forward (LOCF)
  - **Study 1133**: mixed model for repeated measures (MMRM) assuming data missing at random (MAR)
- FDA-recommended primary analysis
  - **Studies 1031 and 1133**: multiple imputation (MI) assuming data missing not at random (MNAR)
  - Cross-study comparisons: MI (MNAR)

At the pre-BLA meeting (held prior to the Study 1133 database lock), FDA recommended changing the primary efficacy analysis to MI (MNAR) because pain-related assessments may have non-random missing data. However, based on previous agreement from FDA, Study 1133

was powered for MMRM (MAR) but not for MI (MNAR). Therefore, the statistical analysis plan (SAP) was finalized with MMRM (MAR) as the primary analysis. Sponsor understood that FDA would give greater weight to the MI approach in their review and MI (MNAR) was analyzed at the same time. Therefore, the results reported in this briefing document are presented as MI (MNAR), in alignment with FDA's recommendation. For completeness, the primary and key secondary endpoints are also presented with the MMRM (MAR) analysis.

1.5.2 Pivotal Studies 1031 and 1133 Results

Forest plots that summarize results from Studies 1031 and 1133 show statistically significant findings on several endpoints, including the primary endpoint of worst leg pain, secondary endpoints of ODI-assessed function and responder analyses, in addition to numerically favorable results on all assessments (Figure 16).

1.5.2.1 Patient Dispositions

Overall, the dispositions of patients were similar between Study 1031 and Study 1133, are presented in Section 7.3.2.1 and Section 7.5.2.1, respectively.

1.5.2.2 Demographics and Baseline Characteristics

Disease characteristics represented the general population of patients with leg pain due to LDH (Table 3). Despite being conducted in different regions, the demographics in these two pivotal studies were similar (Table 2). Differences in race, height, and weight can be explained by the fact that Study 1031 was conducted entirely in Japan, enrolling Japanese patients, while Study 1133 was enrolled entirely in the US. Study 1031 allowed enrollment from age 20 years, while Study 1133 allowed enrollment from age 30 years.

Table 2: Demographics in Pivotal Studies 1031 and 1133

	Study 1031 (Japan)		Study 1133 (US)	
Demographic, n (%):	**Condoliase (N=82)**	**Placebo (N=81)**	**Condoliase (N=169)**	**Sham (N=172)**
Age (years)				
Median	37.5	38.0	46.0	45.0
Age group, n (%)				
20 – 29 years	14 (17.1)	21 (25.9)	0	0
30 – 49 years	52 (63.4)	44 (54.3)	105 (62.1)	103 (59.9)
50 – 59 years	10 (12.2)	8 (9.9)	42 (24.9)	54 (31.4)
≥ 60 years	6 (7.3)	8 (9.9)	22 (13.0)	15 (8.7)
Sex, n (%)				
Male	51 (62.2)	48 (59.3)	95 (56.2)	89 (51.7)
Female	31 (37.8)	33 (40.7)	74 (43.8)	83 (48.3)

Demographic, n (%):	Study 1031 (Japan)		Study 1133 (US)	
	Condoliase (N=82)	Placebo (N=81)	Condoliase (N=169)	Sham (N=172)
Race				
American Indian or Alaska Native	0	0	1 (0.6)	0
Asian	82 (100)	81 (100)	6 (3.6)	9 (5.2)
Black or African American	0	0	18 (10.7)	14 (8.1)
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	0	0	137 (81.1)	142 (82.6)
Other	0	0	7 (4.1)	7 (4.1)
Ethnicity, n (%)				
Hispanic or Latino	NA	NA	47 (27.8)	43 (25.0)
Not Hispanic or Latino	NA	NA	122 (72.2)	129 (75.0)
Height, cm				
Median	168.5	168.0	172.7	172.1
Height group, n (%)				
< 170 cm	44 (53.7)	45 (55.6)	66 (39.1)	71 (41.3)
≥ 170 cm	38 (46.3)	36 (44.4)	103 (60.9)	101 (58.7)
Body weight (kg), median	65.0	64.9	84.8	84.1
BMI, kg/m^2				
Median	23.08	22.90	28.41	28.08
BMI group, n (%)				
< 18.5 kg/m^2	5 (6.1)	6 (7.4)	0	2 (1.2)
18.5 to < 25.0 kg/m^2	49 (59.8)	49 (60.5)	37 (21.9)	41 (23.8)
25.0 to < 35.0 kg/m^2	28 (34.1)	26 (32.1)	110 (65.1)	115 (66.9)
≥ 35.0 kg/m^2	0	0	22 (13.0)	14 (8.1)
Smoking history, n (%)				
Never smoked	39 (47.6)	35 (43.2)	106 (62.7)	103 (59.9)
Past smoker	26 (31.7)	16 (19.8)	34 (20.1)	36 (20.9)
Current smoker	17 (20.7)	30 (37.0)	29 (17.2)	33 (19.2)
Occupation, n (%)				
Light labor	32 (39.0)	28 (34.6)	130 (76.9)	123 (71.5)
Heavy labor	50 (61.0)	53 (65.4)	39 (23.1)	49 (28.5)

BMI: body mass index; US: United States.

Table 3: Baseline Disease Characteristics in Pivotal Studies 1031 and 1133

Baseline Characteristic:	Study 1031 (Japan)		Study 1133 (US)	
	Condoliase (N=82)	Placebo (N=81)	Condoliase (N=169)	Sham (N=172)
Herniation site, n (%)				
L4 – L5	45 (54.9)	37 (45.7)	70 (41.4)	71 (41.3)
L5 – S1	37 (45.1)	44 (54.3)	99 (58.6)	101 (58.7)
Days since onset of current radicular leg pain, median	142.0	127.0	139.0	153.5
VAS pain score for worst leg pain, median	73.29	74.57	73.14	71.93
VAS pain score for worst back pain, median	55.14	61.57	62.29	60.75
ODI score, median	37.0	40.0	48.0	49.0

ODI: Oswestry Disability Index; VAS: visual analog scale.

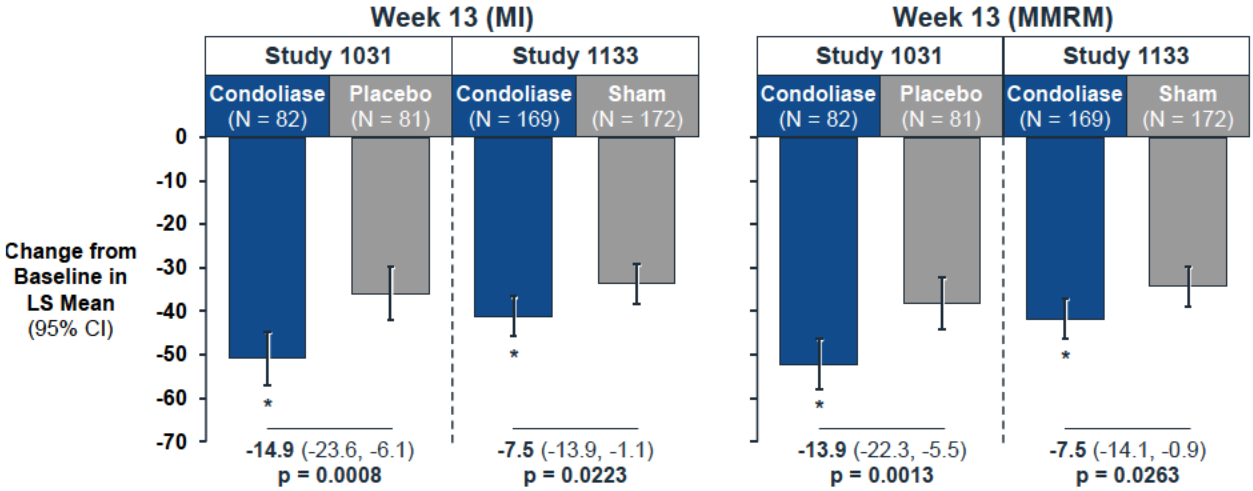
1.5.2.3 Primary Endpoint: Worst Leg Pain at 13 Weeks

Primary Analysis

Both pivotal Phase 3 Studies 1031 and 1133 met the primary efficacy endpoint of change from baseline to Week 13 in average worst leg pain score, as measured by the 100 mm VAS (Figure 6). Results were statistically significant when using either the FDA-recommended MI (MNAR) (Table 4) and the prespecified MMRM (MAR) analysis (Table 5).

An analysis of efficacy in subgroups is provided in Figure 20 (Section 7.3.3.1.2) for Study 1031 and Figure 25 (Section 7.5.3.1.2.1) for Study 1133.

Figure 6: Primary Results, Worst Leg Pain at Week 13 — Pivotal Phase 3 Studies



CI: confidence interval; LS: least squares; MI: multiple imputation; MMRM: mixed methods for repeat measures.
* p-value < 0.05

Table 4: Change from Baseline in Worst Leg Pain at Week 13 Using MI (MNAR) Analysis — Pivotal Phase 3 Studies (mITT)

	Study 1031 (Japan)		Study 1133 (US)	
Worst Leg Pain, VAS:	**Condoliase (N=82)**	**Placebo (N=81)**	**Condoliase (N=169)**	**Sham (N=172)**
Baseline, mean (SD)	72.4 (12.29)	74.6 (12.48)	72.0 (9.55)	71.8 (9.75)
Week 13, LS mean (SE)	22.7 (3.12)	37.6 (3.16)	30.7 (2.33)	38.2 (2.30)
Change from Baseline, LS mean (SE)	-50.8 (3.12)	-35.9 (3.16)	-41.2 (2.33)	-33.7 (2.30)
95% CI	(-56.9, -44.7)	(-42.1, -29.7)	(-45.8, -36.6)	(-38.2, -29.2)
Treatment difference for condoliase vs control				
Difference in LS means (SE)	-14.9 (4.44)		-7.5 (3.28)	
95% CI	(-23.6, -6.1)		(-13.9, -1.1)	
p-value	0.0008		0.0223	

CI: confidence interval; LS: least squares; MI: multiple imputation; mITT: modified intent to treat; MNAR: missing not at random; SD: standard deviation; SE: standard error; VAS: visual analog scale.

Table 5: Change from Baseline in Worst Leg Pain at Week 13 Using MMRM (MAR) Analysis — Pivotal Phase 3 Studies (mITT)

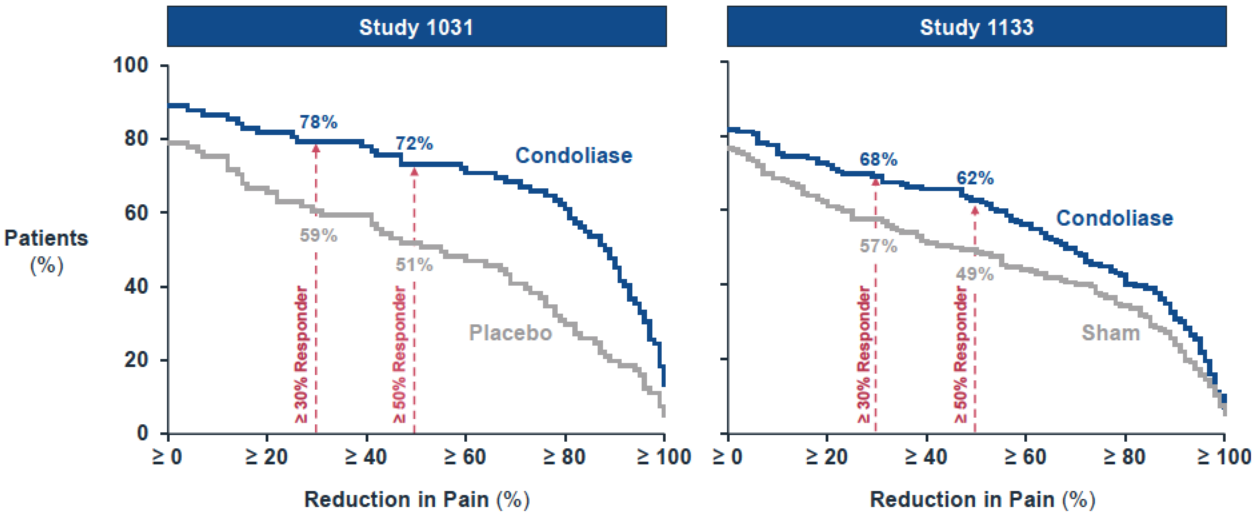
	Study 1031 (Japan)		Study 1133 (US)	
Worst Leg Pain, VAS:	**Condoliase (N=82)**	**Placebo (N=81)**	**Condoliase (N=169)**	**Sham (N=172)**
Baseline, mean (SD)	72.4 (12.29)	74.6 (12.48)	72.0 (9.55)	71.8 (9.75)
Week 13, LS mean (SE)	21.1 (2.97)	35.0 (3.05)	29.9 (2.38)	37.4 (2.36)
Change from Baseline, LS mean (SE)	-52.1 (2.97)	-38.2 (3.05)	-41.7 (2.38)	-34.2 (2.36)
95% CI	(-58.0, -46.3)	(-44.2, -32.2)	(-46.4, -37.0)	(-38.9, -29.6)
Treatment difference for condoliase vs control				
Difference in LS means (SE)	-13.9 (4.26)		-7.5 (3.35)	
95% CI	(-22.3, -5.5)		(-14.1, -0.9)	
p-value	0.0013		0.0263	

CI: confidence interval; LS: least squares; MAR: missing at random mITT: modified intent to treat; MMRM: mixed methods for repeated measures; SD: standard deviation; SE: standard error; VAS: visual analog scale.

Cumulative Distribution for Worst Leg Pain at 13 Weeks

Results from the cumulative distribution plot for leg pain scores at Week 13 for the mITT Population support the results of the primary efficacy analysis for both Study 1031 and Study 1133. Figure 7 displays the cumulative distribution plot for leg pain scores at Week 13 and showed clearly separated distribution lines. The condoliase group showed a consistently higher percentage of patients across all percentages of pain reduction compared to control.

Figure 7: Cumulative Distribution of Decreases from Baseline in Weekly Average Worst Leg Pain through 13 Weeks — Studies 1031 and 1133 (mITT)



mITT: Modified Intent to Treat.

1.5.2.4 Secondary Endpoints

All secondary and supporting endpoints were analyzed by MI (MNAR), as recommended by FDA and agreed by Sponsor as the appropriate method. For completeness, results of the MMRM (MAR) analyses are provided in Appendix 13.3.2 (Study 1031) and Appendix 13.5.2 (Study 1133).

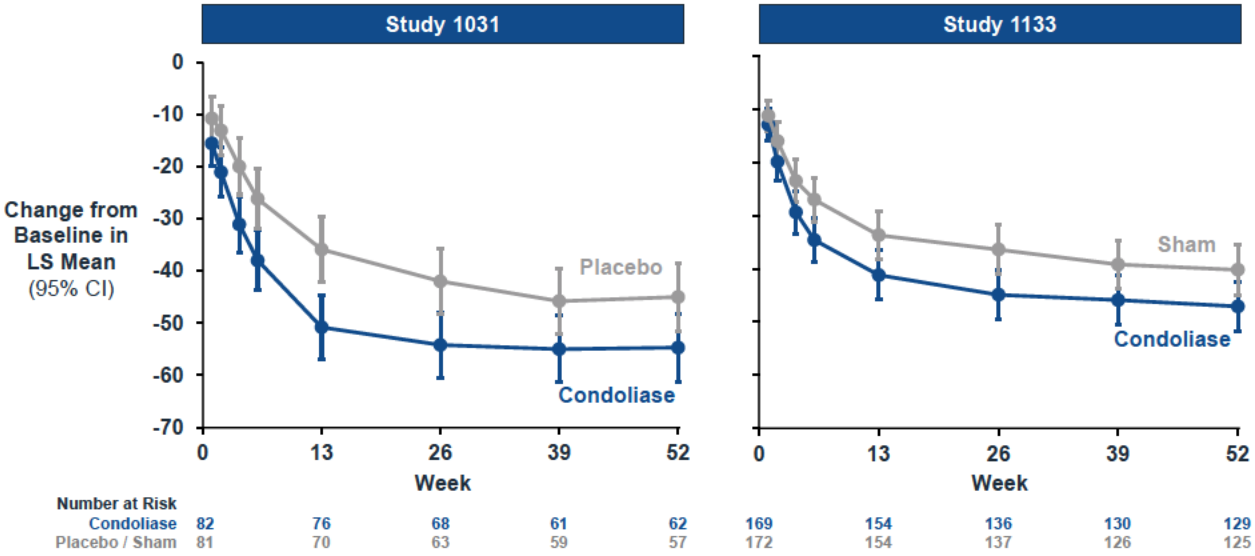
1.5.2.4.1 Worst Leg Pain over Time, through Week 52

Change from Baseline over Time

Figure 8 shows the change from baseline in weekly averages of worst leg pain in the mITT Populations of the pivotal Phase 3 studies. In both studies, condoliase showed a greater LS mean improvement from Baseline across all time points with effects that were sustained through Week 52.

Table 20 (Study 1031; Section 7.3.3.2.1) and Table 28 (Study 1133; Section 7.5.3.2.1) summarize the results of average worst leg pain score at each time point. Statistically significant treatment effects for condoliase vs control were reported as early as Week 2 in Study 1031 (p=0.0194) and Week 4 in Study 1133 (p=0.0420).

Figure 8: Change in Weekly Average Worst Leg Pain over Time, through Week 52 — Pivotal Phase 3 Studies (mITT)

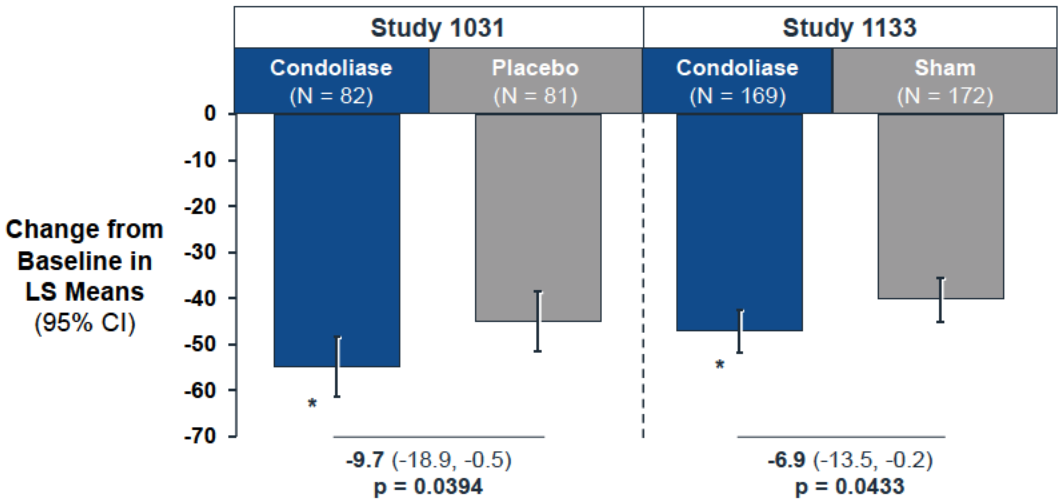


CI: confidence interval; LS: least squares; mITT: modified intent to treat.

Change from Baseline at Week 52

A year after treatment with condoliase, patients reported statistically significant reduction in worst leg pain compared to placebo/sham control in both pivotal Phase 3 studies (Figure 9).

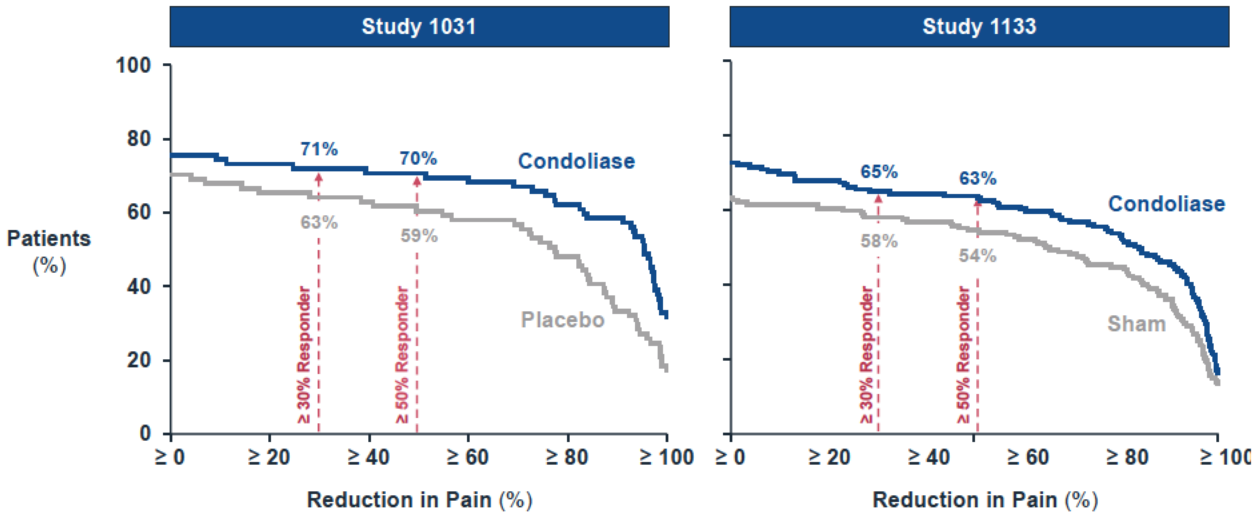
Figure 9: Worst Leg Pain at Week 52 — Pivotal Phase 3 Studies (mITT)



CI: confidence interval; LS: least-squares; mITT: modified intent to treat
* Nominal p < 0.05.

Figure 10 displays the cumulative distribution plot for leg pain scores at Week 52 for Studies 1031 and 1133. The condoliase group showed a consistently higher percentage of patients across all percentages of pain reduction compared to control. Detailed results are presented in Section 7.3.3.2.1. (Study 1031) and Section 7.5.3.2.1 (Study 1133).

Figure 10: Cumulative Distribution of Percent Improvement in Weekly Average Worst Leg Pain through Week 52 — Pivotal Phase 3 Studies (mITT)

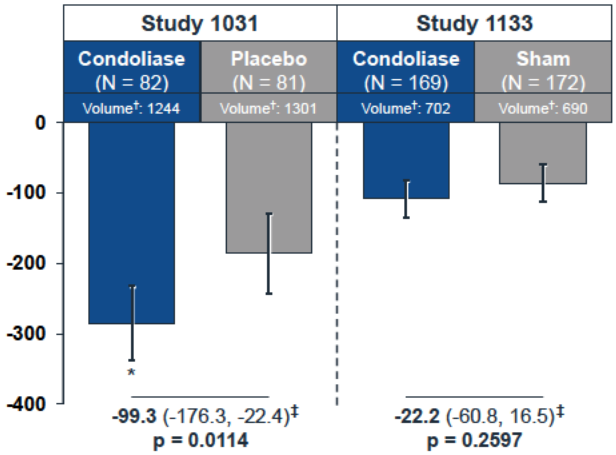


mITT: Modified Intent to Treat.

1.5.2.4.2 Herniation Volume at 13 Weeks

The results of the change from baseline in herniation volume at Week 13 following a single injection of condoliase for the mITT Population are presented in Figure 11. At Week 13 for Study 1031, the LS mean (95% CI) treatment group difference from placebo control was -99.3 (-176.3, -22.4; p=0.0114) mm^3; there was no statistically significant treatment group difference at Week 13 in Study 1133 (p=0.2597).

Figure 11: Change from Baseline in Herniation Volume at Week 13 — Pivotal Phase 3 Studies (mITT)



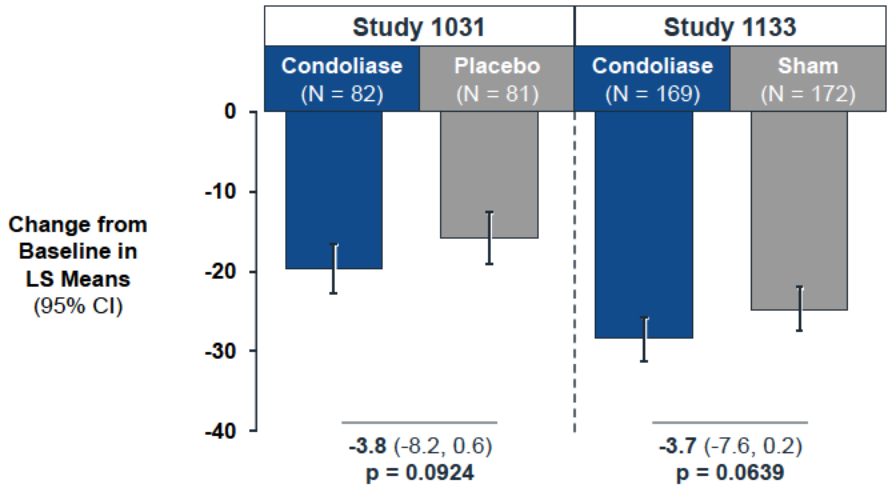
CI: confidence interval; LS: least-squares; mITT: modified intent-to-treat.
* Nominal p < 0.05. † Baseline herniation volume (mm^3). ‡ Studies 1031 and 1133 had difference in average baseline herniation volume.

1.5.2.4.3 Oswestry Disability Index

Oswestry Disability Index at 13 Weeks

At Week 13, patients who received condoliase showed a trend for improvement over controls in ODI scores at Week 13, but the treatment differences were not statistically significant (Figure 12).

Figure 12: Change in Oswestry Disability Index at Week 13 — Pivotal Phase 3 Studies (mITT)



CI: confidence interval; LS: least-squares; mITT: modified intent to treat.

Oswestry Disability Index Change Over Time

There were no statistically significant differences in ODI scores between condoliase vs controls the pivotal studies at Week 13, but ODI scores were improved compared to controls at all time points.

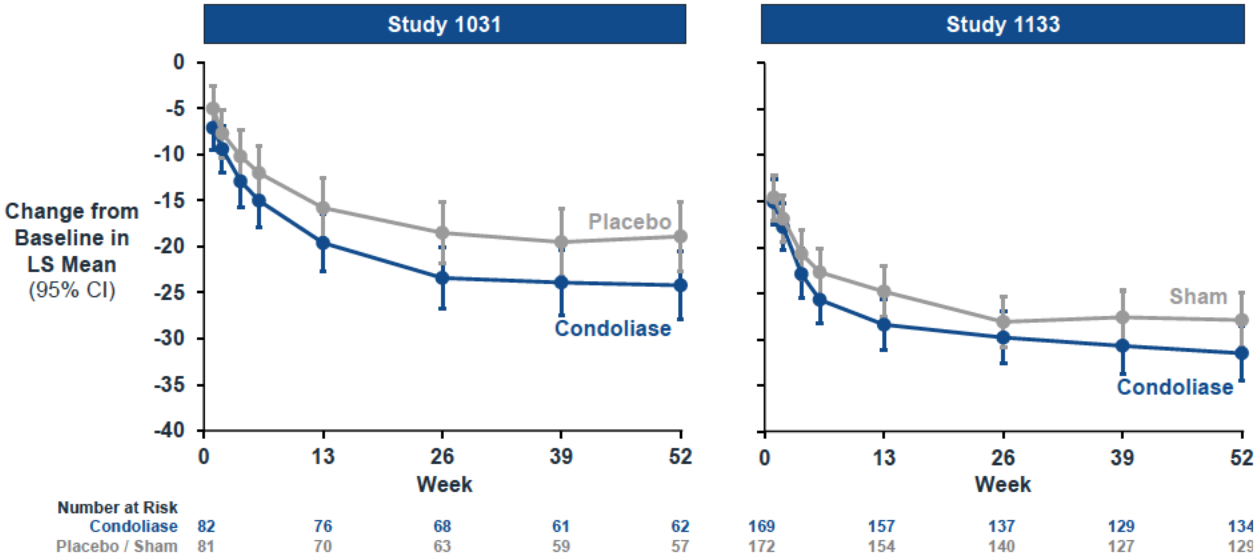
Patients who received condoliase in Study 1031 showed statistically significant ($p < 0.05$) improvement in ODI scores vs placebo at Weeks 26 and 52 (Figure 13). The treatment differences at those time points were:

- Study 1031 at Week 26: -4.9 (95% CI: -9.6, -0.2); p=0.0411
- Study 1031 at Week 52: -5.3 (95% CI: -10.5, -0.1); p=0.0474

At no time did patients in Study 1133 show statistically significant improvement in ODI scores as compared to sham.

Results at all time points in both studies numerically favored treatment with condoliase vs controls.

Figure 13: Change from Baseline in Oswestry Disability Index over Time, through Week 52 — Pivotal Phase 3 Studies (mITT)



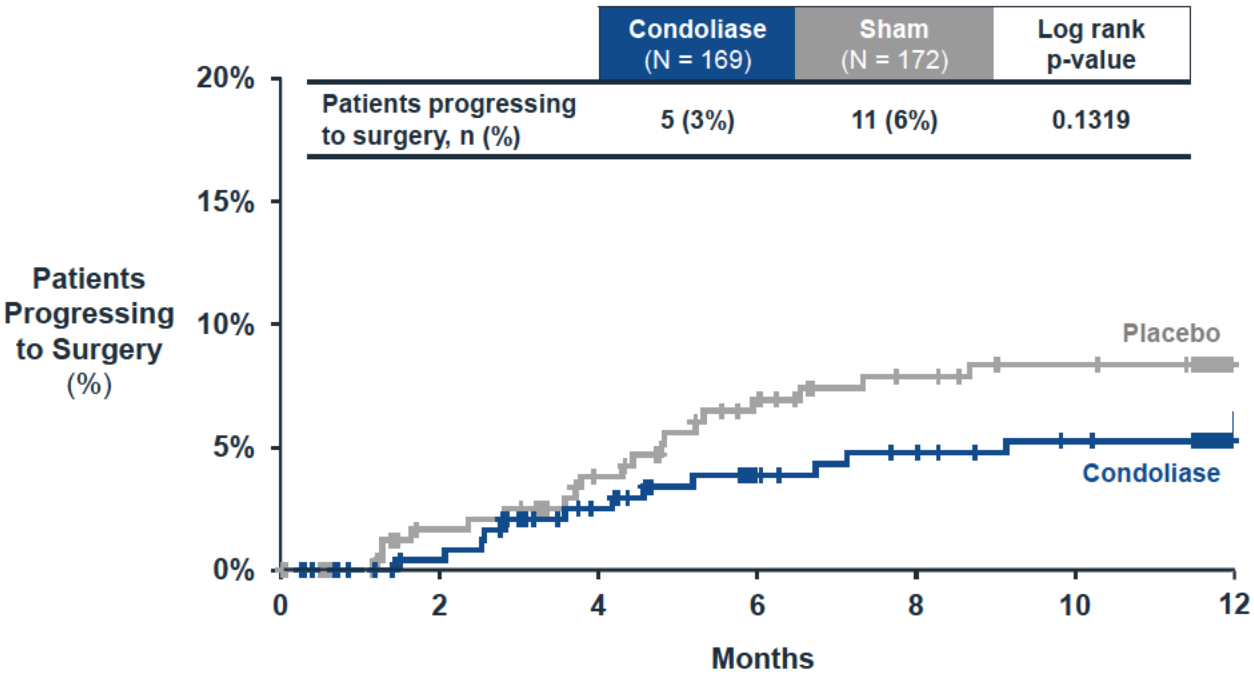
CI: confidence interval; LS: least square; mITT: modified intention to treat.

1.5.3 Rates of LDH Surgery from 1133 and Survey of 1021 and 1031

In Study 1133, the incidence of post-treatment surgery for LDH at the same disc level of condoliase or sham group administration were recorded up to 52 weeks. Patients were less likely to undergo surgery for LDH a year after treatment with condoliase vs sham: 5/169 (3.0%) vs 11/172 (6.4%) patients progressed to surgery at any time during the year after condoliase vs sham, respectively (Kim et al, 2024) (Figure 14).

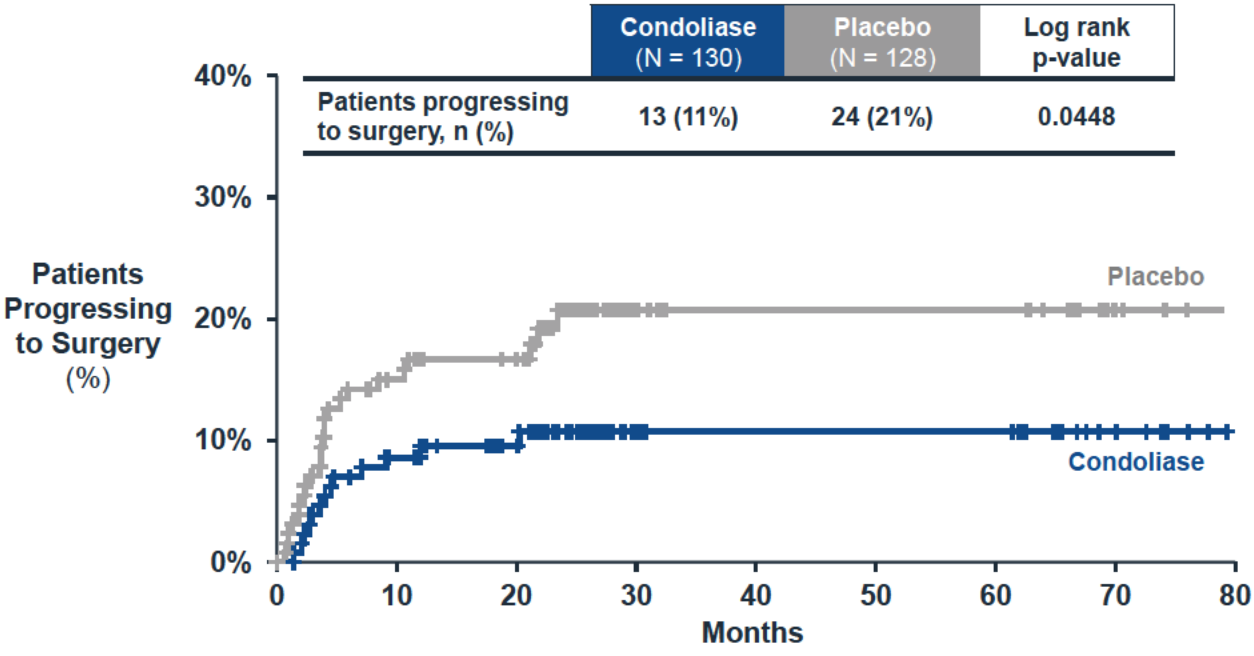
Additionally a long-term follow-up survey of patients from studies 1021 and 1031 recorded incidence of post-treatment surgery for LDH at the same disc level of condoliase or placebo group administration. This long-term comparison of surgical rates among patients who participated in clinical trials in Japan (Studies 1021 or 1031) showed condoliase reduced rate of surgery by approximately half. Among patients treated with the 1.25 U dose in Japan, 10.8% vs 20.7% of condoliase-treated patients vs placebo had surgery for LDH (p=0.0448), with a median follow-up duration of 2 years for Study 1031 patients and 5 years for Study 1021 patients (Figure 15) (Matsuyama et al, 2023).

Figure 14: Time to Surgery during First Year after Injection with Condoliase vs Sham — Study 1133 (mITT)



mITT: Modified Intent to Treat.
Source: Adapted from Kim et al (2024); Figure 6.

Figure 15: Time to Surgery up to 5 Years after Injection with Condoliase vs Placebo (Published Results of Follow-up Survey to Clinical Trials in Japan)



Source: Adapted from Matsuyama, Seo, & Chiba (2023); Supplemental Figure 2.

1.5.4 Similarities Between US and Japan in LDH Epidemiology and Treatment

The percentage of LDH at the L4-L5 vertebral level is 55.6% in Japan and 46.7% in the US, and the percentage of LDH at the L5-S1 vertebral level is 15.0% in Japan and 47.0% in the US (Table 6). The L4-L5 and L5-S1 vertebral levels are the most commonly affected in both Japan and the US. Surgical care practices are also similar between Japan and the US (Table 7).

Table 6: Similarity of Epidemiology in Japan and USA

Parameter:	Japan	United States
Estimated annual prevalence	Approximately 1% (based on global review of studies in patients who visited medical institutions or patients who underwent surgery, and summarized epidemiological characteristics)[1]	
Affected disc levels	The most commonly affected vertebral levels are L4/5 and L5/S1[1]	
	Comprise 90.2% of the total[4] • L4/5=55.6% • L5/S1=15.0% • Double L4/5, L5/S1=19.6%	Comprise 93.7% of the total[3] • L4/5=46.7% • L5/S1=47.0%
Demographics	Average age 41 (20 - 75) years[2] 82% of patients from 20's to 40's[4] More men than women; ratio of 3.3 to 1[4]	Average age: 42 (16 - 77) years[3] More men than women; ratio of 1.75 to 1[3]

1. Haro et al, 2022; 2. Komori et al, 1998; 3. Davis et al, 1994; 4. Kirita, 1975.

Table 7: Similarity of Surgical Care in Japan and USA

Japan[1]	United States[2]
Various surgical procedures are used for treatment of LDH, and good results have been obtained with all procedures in general. Surgical treatment is superior to conservative treatment in terms of pain alleviation and functional improvement evaluated between immediately and at least 6 months after surgery. • Discectomy • Herniotomy or Nucleotomy	Discectomy is suggested to provide more effective symptom relief than medical/interventional care for patients with LDH with radiculopathy whose symptoms warrant surgical intervention. • Discectomy • Nucleotomy

LDH: lumbar disc herniation.
1. Haro et al, 2022; 2. Kreiner et al, 2012.

1.5.5 Representativeness of Study 1031 and 1133 of US Patients with LDH

While there are clear demographic differences between patients living in Japan and the US, the results from both studies provide replication of condoliase benefit in patients who suffer from radicular leg pain caused by LDH. Whether in the US or Japan, the clinical diagnosis, treatment

options, standard of care and sequencing of interventions are interchangeable. Regardless of race, the hernia pathology that impinges on the nerve root and results in leg pain are the same.

As shown in side-by-side clinical characteristic comparisons (Table 3), these patients have similar baseline clinical characteristics and attain similar benefits from condoliase, as predicted by the mechanism of action (MoA).

The safety profile (summarized in Section 1.6 and presented in full in Section 9) is also similar across studies, regardless of country of origin. Thus, Study 1031 results are applicable to US patients.

1.5.6 Efficacy Conclusions

The condoliase clinical development program demonstrates evidence of efficacy from two randomized controlled clinical studies in patients with radicular leg pain associated with confirmed nerve root impingement caused by LDH conducted in Japan (1031) and the US (1133). Overall, the available clinical data show the following clinically significant therapeutic benefits of condoliase as a treatment option for radicular leg pain associated with confirmed nerve root impingement caused by LDH in adults:

- Reduces worst leg pain for at least 52 weeks
- Reduces herniation volume (as predicted by the MoA)
- Improves patient functionality

As predicted by a GAG-specific mechanism of action, clinical studies confirm that condoliase selectively shrinks the nucleus pulposus, condoliase met the primary endpoint in both pivotal studies, demonstrating improvement in worst leg pain compared with the control group (placebo or sham) at Week 13 when assessed using both the MI (MNAR) and MMRM (MAR) analyses. The robustness of the results from the primary efficacy endpoint was analyzed with sensitivity analyses, further suggesting treatment with condoliase significantly improved worst leg pain at Week 13 relative to placebo in Study 1031 (MI [MNAR]), p=0.0008; MMRM (MAR), p=0.0013) and relative to sham Study 1133 (MI [MNAR], p=0.0223). In both studies, treatment differences were observed as early as 2-to-4 weeks post-injection.

In both pivotal Phase 3 studies, treatment with condoliase led to statistically significant reduction in leg pain compared to control at least 52 weeks (one year) after injection. Patient functionality was measured by ODI, and numerical results favored condoliase compared to control at Week 13 in both Study 1133 and Study 1031.

In Study 1031, treatment with condoliase led to a statistically significant reduction in herniation volume as compared to placebo at Week 13. In Study 1133, trends favoring condoliase treatment in reduction of herniation volume were observed in favor of treatment with condoliase.

These results were consistently supported by other prespecified endpoints that measure response to treatment (50% responder, SLR, PGIC) or quality of life measures. These measures were either nominally statistically significant or favored condoliase therapy (Figure 16).

In line with the mechanism of action of condoliase, Studies 1031, 1131 and 1133 collectively demonstrated the importance of confirming that the LDH impinges on the nerve root associated with leg pain. Appendix 13.6 provides example LDH images showing LDH with (Figure 36) and without (Figure 37) nerve root impingement.

Overall, the well-controlled Studies 1031 and 1133 provide robust data that alleviation of radicular leg pain aligns with improved function in patients diagnosed with LDH.

1.6 Safety

1.6.1 Summary of Safety

1,679 patients have been treated with a single injection of condoliase in six completed clinical studies (1031, 1133, 1131, 1021, 1121, 1132). Condoliase is well-tolerated, with an acceptable safety profile, for the treatment of radicular leg pain associated with LDH.

The safety population representative of condoliase safety in the proposed indication comprises four randomized controlled studies: the Pooled Phase 2/3 RCTs Safety Set, which includes Studies 1021, 1031, 1131, and 1133. Patients included in the Pooled Phase 2/3 RCTs Safety Set are all randomized patients from the four studies who received either condoliase at the proposed dose of 1.25 U or matching control.

All four studies conducted full safety monitoring through the primary efficacy analysis at the Week 13 Visit (Table 8). Additionally, safety data were collected through 52 weeks according to the following schedule:

- **US Study 1133:** full safety monitoring through Week 52
- **US Study 1131:** full safety monitoring through Week 104[2]
- **Japan Studies 1021 and 1031:** Adverse events (AEs) related to the intervertebral disc and surrounding tissues, in addition to all serious AEs (SAEs), regardless of proximity to injection site, through Week 52

The safety profile observed in clinical trials is supported by postmarketing surveillance and clinical use of condoliase in approximately 27,000 patients. (See Section 1.6.3.)

Table 8: Safety Data Collection and Window, by Study (Pooled Phase 2/3 RCTs)

Study (Phase):	Weeks 0–13	Weeks 14–26	Weeks 27–52
US-based studies			
Study 1131 (Phase 3)	Full safety monitoring		
Study 1133 (Phase 3)	Full safety monitoring		
Japan-based studies			
Study 1021 (Phase 2/3)	Full safety monitoring	• AEs related to intervertebral disc and surrounding tissues • All SAEs, regardless of proximity to injection site	
Study 1031 (Phase 3)	Full safety monitoring	• AEs related to intervertebral disc and surrounding tissues • All SAEs, regardless of proximity to injection site	

AE: adverse event; RCT: randomized, controlled trial; SAE: serious adverse event.

[2] Included to fulfill regulatory exposure requirements through 2 years

An overview of the summary of pooled Phase 2/3 randomized, controlled trial safety is provided in Table 9.

Table 9: Summary of Adverse Events (Pooled Phase 2/3 RCTs)

	Day 0 to Week 13		> 13 to 26 Weeks		> 26 to 52 Weeks	
AE, n (%):	Condoliase (N=578)	Control (N=396)	Condoliase (N=421)	Control (N=252)	Condoliase (N=388)	Control (N=233)
Any AE	381 (65.9)	215 (54.3)	94 (22.3)	41 (16.3)	113 (29.1)	67 (28.8)
Related AE	149 (25.8)	52 (13.1)	6 (1.4)	2 (0.8)	11 (2.8)	3 (1.3)
Severe AE	33 (5.7)	19 (4.8)	9 (2.1)	7 (2.8)	8 (2.1)	4 (1.7)
Any SAE	15 (2.6)	13 (3.3)	9 (1.7)	6 (1.7)	14 (2.8)	6 (1.8)
Related SAE	1 (0.2)	0	0	0	0	0
Death	0	0	1 (0.2)	1 (0.4)	1 (0.3)	0

AE: adverse event; RCT: randomized, controlled trial; SAE: serious adverse event
Note: Phase 2/3 RCTs include Studies 1021, 1031, 1131, 1133. For 1021 and 1031, only SAEs and AEs related to IV disc were recorded after Week 13. Therefore, subjects at risk for SAEs (>13 to 26 weeks) were 538 for condoliase and 359 for control; subjects at risk for SAEs (>26 to 52 weeks) were 493 for condoliase and 333 for control. Control includes pooled results from placebo and sham injection.

In the time interval of Day 0 to Week 13, the most common (≥ 2% of patients and occurred in greater frequency than control) AEs observed in the condoliase group were back pain, MRI spinal abnormal, nasopharyngitis, spinal x-ray abnormal.

The most common AEs reported in the condoliase group after Week 13 were MRI spinal abnormal and spinal X-ray abnormal. Serious AEs occurred at similar rates across the treatment arms across all time intervals. There were 2 deaths (not related to study drug) in the condoliase group and 1 death in the control group.

1.6.2 Safety Topics of Interest

Prespecified safety topics of interest were events that warranted additional investigations due to identified or potential risk. Safety topics potentially related to the injection procedure were discitis, osteomyelitis, hematomas, and medication error. Safety topics potentially related primarily to the drug were hypersensitivity, anaphylaxis, spinal abnormalities, paresis, and paralysis. The searches for these topics were carried out by either standard MedDRA queries (SMQ) or customized queries and agreed to with the FDA. See Appendix 13.8.4 for details of customized queries. Most safety topics of interest occurred infrequently in the pooled Phase 2/3 RCTs. Safety topics of interest for hypersensitivity and spinal abnormalities with overall reporting of more than 5 patients are summarized below.

1.6.2.1 Hypersensitivity

Hypersensitivity was searched utilizing the hypersensitivity SMQ narrow. Overall, hypersensitivity AEs occurred in 3.8% vs 3.3% of patients in the condoliase group vs controls (Table 10). Rash was the most common event, none of which were serious. (Additional details provided in Section 9.8.3; a list of all hypersensitivity AEs with the SMQ narrow search is provided in Table 35.)

Table 10: Summary of Hypersensitivity Adverse Events in ≥ 2 Patients (Pooled Phase 2/3 RCTs)

Category (SMQ) Preferred Term, n (%):	Condoliase (N=578)	Control (N=396)
Hypersensitivity (SMQ)	22 (3.8)	13 (3.3)
Rash	11 (1.9)	3 (0.8)
Dermatitis contact	3 (0.5)	1 (0.3)
Urticaria	3 (0.5)	1 (0.3)
Toxic skin eruption	2 (0.3)	0
Eczema	0	2 (0.5)
Anaphylactic reaction (SMQ)	0	0

SMQ: standardized MedDRA query; RCT: randomized, controlled trial.
Note: Adverse events were defined as events that begin or that worsen in severity after the investigational drug has been administered. Control includes pooled results from placebo and sham injection. Results are reported from a narrow SMQ database search.

1.6.2.2 Spinal Abnormalitiy

Spinal abnormalities were searched with a prespecified list of AEs that were agreed with the FDA. An assessment of spinal abnormality AEs showed no evidence of increased risk, with 0.9% of patients taking condoliase having events, compared to 1.3% of control (Table 11).

Most events occurred more than 6 months after injection and predominantly in the control group. (Details provided in Section 9.8.2).

Table 11: Summary of Spinal Abnormality AEs: All Time Intervals (Pooled Phase 2/3 RCT Safety)

Category Preferred Term, n (%):	Condoliase (N=578)	Control (N=396)
Any spinal abnormality	5 (0.9)	5 (1.3)
Spinal osteoarthritis	3 (0.5)	1 (0.3)
Spinal retrolisthesis	1 (0.2)	1 (0.3)
Spondylolisthesis	1 (0.2)	0
Spinal compression fracture	0	2 (0.5)
Vertebral foraminal stenosis	0	1 (0.3)

AE: adverse event; RCT: randomized, controlled trial.
Note: AEs were defined as adverse events that begin or that worsen in severity after the investigational drug has been administered. In category and preferred term summarization, a patient was counted once if he/she reported one or more events. Adverse events were classified according to MedDRA version 24.0. Percentages based on all patients in the Safety Population. Control includes pooled results from placebo and sham injection.

1.6.3 Postmarketing Pharmacovigilance

Since approval in Japan (March 2018), approximately 27,000 patients are estimated to have received treatment with condoliase. Postmarketing safety data are generally consistent with the

safety profile observed in clinical trials, with most events related to pain or hypersensitivity (See Section 10, Table 55).

1.6.4 Safety Conclusions

Overall, condoliase treatment was well tolerated, with an acceptable safety profile in patients with radicular leg pain caused by nerve root impingement from LDH in adults. The most common preferred terms (PTs) of AEs in the condoliase group that had an incidence greater than the placebo/sham control group were back pain, MRI spinal abnormal, and spinal X-ray abnormal. The incidence of serious AEs reported for the condoliase group and placebo/sham control group was similar across all time intervals and safety topics of interest AEs occurred at low incidence (less than 2%).

It is known that protein-based drugs carry the risk for hypersensitivity and anaphylaxis. Therefore, the Sponsor has proposed that these risks will be included in the prescribing information.

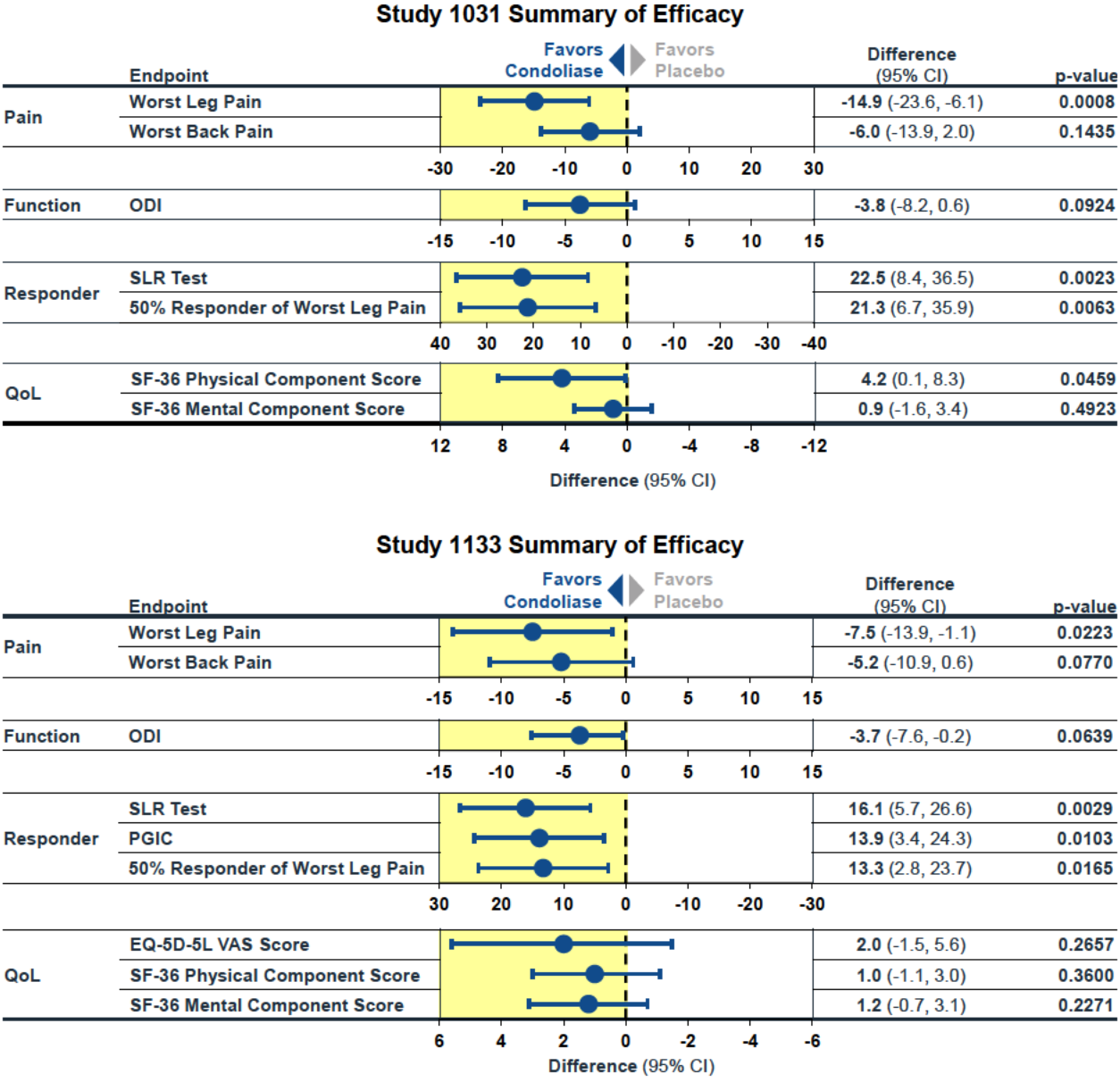
1.7 Benefit-Risk Summary

Condoliase has a favorable benefit-risk profile for patients with radicular leg pain corresponding with confirmed nerve root impingement by the herniation in adult patients diagnosed with LDH. (Figure 16 provides a summary of efficacy results across studies on the following page.)

As shown by example MRI images in Appendix 13.6, LDH impingement of the nerve root associated with leg pain is identifiable. Injection of condoliase into a LDH with confirmed impingement aligns with the established condoliase mechanism of action (Section 3.3, Figure 18; and Section 1.3.3, Figure 3), which causes shrinkage of the nucleus pulposus with the herniation to help alleviate the pressure on the nerve. Thus, it is important to confirm nerve root impingement by the herniation, such that shrinking the LDH with condoliase can help alleviate the leg pain.

Condoliase treatment in two pivotal Phase 3 studies resulted in consistent, beneficial effects across multiple clinically important endpoints. Condoliase reduced radicular leg pain early and with a durable effect up to 52 weeks. These changes were perceived as meaningful to patients based on measures of PGIC and QoL measures that consistently favored condoliase (Figure 16). The treatment benefit extended to improvements in functionality, as assessed by the ODI. Condoliase is also well tolerated, with an acceptable safety profile based on the clinical development program and postmarketing surveillance. With appropriate labeling and routine pharmacovigilance, the risks identified for clinical use of condoliase can be successfully managed.

Figure 16: Forest Plot of Efficacy Summary Results — Pivotal Phase 3 Studies (mITT)



CI: confidence interval; EQ-5D-5L: EuroQol Group 5-Dimension Quality of Life instrument, 5-level version; mITT: modified intent to treat; ODI: Oswestry Disability Index; PGIC: Patient Global Impression of Change; QoL: quality of life; SLR: straight leg raise; VAS: visual analog scale.

2 BACKGROUND ON LUMBAR DISC HERNIATION

Summary

- Persistent unresolved leg pain that does not respond to conservative treatment often results in worsening health, long-term disability, increased caregiver burden, and lost days from work.
- The principal treatment approach for LDH is conservative, resulting in a response in for most patients.
- Surgery is the next treatment option for patients seeking durable relief of leg pain who have not adequately responded to conservative treatment.
- Alternative non-surgical treatment options are needed for patients with radicular leg pain unresponsive to conservative therapy who do not consent to surgery or are ineligible for surgery.

2.1 Overview and Pathophysiology of Lumbar Disc Herniation

Lumbar disc herniation occurs as a result of the displacement of the nucleus pulposus of an intervertebral disc following disruption of the posterior or posterolateral aspect of the annulus fibrosus. As a result, the herniated disc compresses the spinal nerve root, causing symptoms such as leg pain, numbness, or low back pain (Wong & Transfeldt, 2007; Haro et al, 2022). Approximately 95% of herniations are LDH, occurring in the L4-L5 or L5-S1 region of the spine (Haro et al, 2022; Shiga, 2022).

2.1.1 Prognosis and Epidemiology

Persistent unresolved leg pain that does not respond to conservative treatment often results in worsening health, long-term disability, increased caregiver burden, and lost days from work (Wong & Transfeldt, 2007; Haro et al, 2022).

The overall prevalence of symptomatic LDH is approximately 1% to 3% of the United States (US) population (Haro et al, 2022; Shiga, 2022; Anderson et al, 2021; Lilly et al, 2021). Lumbar disc herniation most commonly affects levels L4-5 and L5-S1, the mean age of patients is 30 to 50 years (Dydyk et al, 2023), and the condition is rarely found among elderly (≥ 65 years) or young (< 20 years) individuals (Haro et al, 2022; Matsuyama et al, 2023).

2.1.2 Leg Pain Associated with LDH

Unlike mechanical back pain, herniated disc pain is often burning or stinging and may radiate into the lower extremity (Dydyk et al, 2023; Tang et al, 2019; Sopaj et al, 2022), resulting in lower back pain, neurological dysfunction, and buttock/leg pain (Zhang et al, 2023). Usually, leg pain is worse than back pain. Diagnostic imaging in patients with back pain and/or leg pain is often used to assess nerve root compression due to disc herniation or spinal stenosis (Lurie et al, 2016; de Schepper et al, 2016).

The duration of preoperative symptoms in lumbar disc herniation has been reported to be shorter than that in spinal canal stenosis. This is likely to reflect the fact that leg pain due to lumbar disc herniation develops suddenly and is often intense (Haro et al, 2022).

2.1.3 LDH Diagnosis

No single diagnostic technology or method has sensitivity and specificity sufficient for independent and direct diagnosis of lumbar disc herniation. Therefore, the integrated decision making based on relevant data/information, such as proper medical interviews, patient background, physical findings, and imaging findings in a comprehensive manner is important for diagnosis (Haro et al, 2022).

Pain history is the most important part of the clinical evaluation. It should include questions on intensity, onset, and localization of the pain. Pain caused by a herniated disc is radicular pain with specific dermatomal radiation in one or both legs. The pain should be assessed with visual or numerical analogue scale and the Oswestry disability index. Essential diagnostic tests for patients suspected of having a herniated disc include assessment of muscle strength, sensory impairment, and sphincter dysfunction, as well as the following studies: leg extension study in the supine position, Lasegue sign, and crossed Lasegue sign (Pojskic et al, 2024).

Lumbar disc herniation can be seen on imaging of asymptomatic individuals. Further evaluation and imaging are warranted if there is a clinical suspicion of severe underlying pathology or neurological compromise, if patients exhibit red flag symptoms, and if patients are unresponsive to conservative treatment after two to three months (Al Qaraghli & De Jesus, 2023).These evaluations and imaging studies include laboratory tests, X-rays, computed tomography (CT) scans, and MRI to ensure that patients considering alternatives to conservative treatment receive a thorough evaluation that confirms the diagnosis of disc herniation with nerve root impingement.

Laboratory tests are usually done to assess inflammatory markers if a chronic inflammatory condition or infection is suspected to be the cause. Lumbar X-ray films are the first-line imaging test performed in low back pain settings to evaluate the overall alignment of the spine, detecting fractures, as well as degenerative or spondylotic changes. If an acute fracture is detected, further investigation with CT scans or MRIs is required.

CT imaging is the most sensitive imaging modality for the spine as it allows for the evaluation of calcified herniated discs or any pathological process that may result in bone loss or destruction. However, it is deficient for the visualization of nerve roots, making it unsuitable in the diagnoses of radiculopathy. CT myelography is the imaging modality of choice to visualize herniated discs in patients with contraindications to MRI. However, due to its invasiveness, a trained radiologist is required. Myelography is associated with risks like post-spinal headache, meningeal infection, and radiation exposure. MRI is the gold standard study for confirming a suspected LDH. With a diagnostic accuracy of 97%, it is the most sensitive way to visualize a herniated disc due to its significant ability in soft tissue visualization. MRI also has higher inter-observer reliability than other imaging modalities. It suggests disc herniation when it shows an increased T2-weighted signal at the posterior 10% of the disc. When evaluating for postoperative lumbar radiculopathies, the recommendation is that the MRI is performed with contrast unless otherwise contraindicated (Al Qaraghli & De Jesus, 2023).

MRI is more effective than CT in distinguishing inflammatory, malignant, or inflammatory etiologies of LDH. It is indicated relatively early in the course of evaluation (<8 weeks) when the patient presents with indications like significant pain, neurological motor deficits, and cauda equina syndrome. Diffusion tensor imaging is a type of MRI sequence used for detecting microstructural changes in the nerve root. It may be beneficial in understanding the changes that occur after the herniated lumbar disc compresses a nerve root, and might help in differentiating the patients that need surgical intervention. In patients with a high suspicion of radiculopathy due to lumbar disc herniation, with MRI that is equivocal or negative, nerve conduction studies are indicated (Amin et al, 2017; Dydyk et al, 2023; De Cicco et. al, 2023; Dydyk et al, 2022).

2.2 Current Treatment Options — LDH Guidelines

Guidelines issued in 2012 by the North American Spine Society (NASS) state that “Most patients will improve independent of treatment. Disc herniation will often shrink/regress over time. Many, but not all, articles have demonstrated a clinical improvement with decreased size of disc herniations.” (Kreiner et al, 2012).

The principal treatment approach for LDH is conservative, resulting in a response in most patients (Dydyk et al, 2023; Lilly et al, 2021) within 12 weeks of symptom onset (Lilly et al, 2021; Amin et al, 2017; Shamim et al, 2010).

The World Federation of Neurosurgical Societies (WFNS) Spine Committee's evidence-based recommendations, based on literature from 2012 to 2022, state that conservative treatment should be the first line of treatment of LDH in the absence of cauda equina syndrome, motor, or other serious neurologic deficits. A combination of activity modification, pharmacotherapy, and physical therapy provides good treatment results in most LDH patients (Yaman et al, 2024).

2.2.1 Standard of Care

2.2.1.1 Conservative Therapy

Non-operative management of symptomatic LDH via conservative therapy is the treatment of choice for the majority of patients (Amin et al, 2017; Yaman et al, 2024). Non-operative management consists of a multimodal approach, including anti-inflammatory medications, education, and physical therapy (Wong et al, 2017). Interventions can include bed rest, lumbar support, traction therapy, thermotherapy, spinal manipulation, exercise, oral steroids, analgesics, NSAIDs, epidural block, nerve-root block, epidural steroid injections (ESIs), traditional Chinese medicine, and alternative medicine (Haro et al, 2022; Lilly et al, 2021; Wang et al, 2020; Zou et al, 2023). Traditional western formal physical therapy focused on exercise, core strengthening, and joint mobility have also shown improvement in symptoms related to LDH (Jewell & Riddle, 2005). However, physical therapy procedures have not consistently demonstrated meaningful efficacy, and the therapeutic benefits appear to be limited (Haro et al, 2022; Yaman et al, 2024). The duration of conservative therapy should be individualized based on the patient’s pain, lost functionality and/or diminished QoL (Costa et al, 2024).

ESIs are commonly used to treat lumbosacral radicular pain and to avoid surgery. Several studies have proved that ESIs are able to increase patients’ quality of life, relieve lumbosacral radicular pain and finally, reduce or delay more invasive interventions, such as spinal surgery. ESIs seem to be effective in relieving symptoms in the short term and delaying surgery, while

evidence of any long-terms benefits is still lacking (Carassiti et al, 2021; de Bruijn et al, 2021; Verheijen et al, 2021). The Spine Patient Outcomes Research Trial (SPORT), a prospective multi-center study of the operative versus non operative treatment of lumbar intervertebral disc herniation, found no improvement in short- or long-term outcomes in patients who received ESIs compared to patients who did not (Radcliff et al, 2012). Several other reports have investigated the therapeutic effect of ESIs on LDH and concluded that there is insufficient evidence to support a long-term benefit of ESIs, specifically (Carassiti et al, 2021; de Bruijn et al, 2021; Verheijen et al, 2021).

If symptoms persist, transforaminal or interlaminar epidural steroid injections may be considered for pain relief in some patients with LDH and radiculopathy (Ackerman et al, 2007; Beall et al, 2024).ESIs seem to be effective in relieving symptoms in the short term and delaying surgery, while evidence of any long-terms benefits is still lacking (Carassiti et al, 2021; de Bruijn et al, 2021; Verheijen et al, 2021).

2.2.1.2 Benefits and Risks of Conservative Therapy

Other forms of conservative therapy, such as the combination of herbal supplements, acupuncture, beevenom pharmacopuncture, and spinal manipulation have also been evaluated. However, although long-term (5-year) improvements were seen in VAS and ODI scores, nearly 53% had a relapse that required repeated therapy, injections, or surgery (Shin et al, 2016).

Data from US, Japan, and Europe demonstrate that 62%, 67%, and 57%-78% of patients from each respective region will experience spontaneous resorption of disc herniations with conservative therapy (Zou et al, 2023). Therefore, in the absence of cauda equina syndrome, motor, or other serious neurologic deficits, conservative treatment should be the first line of treatment for LDH (Yaman et al, 2024).

There is a risk of physiologic tolerance and addiction following long-term use of analgesics, as well as adverse events associated with NSAIDs, including ulcers, renal dysfunction, and hypertension (Alam et al, 2012). Moreover, a study conducted by Cummins et al found that patients with a herniated disc were significantly more likely to visit the emergency department, utilize opioids, muscle relaxants, or antidepressants than patients with any other lumbar spine disorder analyzed (Cummins et al, 2006).

2.2.1.3 Surgical Intervention

Surgical treatment is the next treatment option for the approximately 20% to 50% of patients who do not respond to conservative treatment (Peul et al, 2007; Weinstein et al, 2006; Shiga, 2022). Surgical interventions include sequestrectomy, discectomy, laminectomy, lumbar fusion, and implantation of spinal cord stimulation (Kreiner et al, 2012). The surgical treatment of LDH has evolved over the past years, with the progressive availability of different minimally invasive techniques (including tubular microscopic, also known as microendoscopic discectomy, and percutaneous endoscopic discectomy) that have been introduced as alternatives to the standard open lumbar discectomy (Costa et al, 2024). The procedures have varying levels of evidentiary support for both short- and long-term effectiveness, and the recommended option(s) depend on a variety of physiological and symptomatic parameters (Kreiner et al, 2012; Haro et al, 2022).

Guidelines issued by NASS in 2012 state that “surgical intervention prior to 6 months is suggested in patients with symptomatic LDH whose symptoms are severe enough to warrant

surgery." Earlier surgery (within 6 months to 1 year) is associated with faster recovery and improved long-term outcomes" (Kreiner et al, 2012). Gugliotta et al recently demonstrated equivalent medium- and long-term outcomes for conservative and surgical treatment of LDH (Amin et al, 2017; Gugliotta et al, 2016). Evidence from RCTs indicates that discectomy provides a greater reduction in leg pain than does nonsurgical treatment, but these benefits diminish over time (Liu et al, 2023). There has been no recent literature which clarifies the absolute non-operative versus operative criteria in LDH.

2.2.1.4 Benefits and Risks of Surgical Intervention

The benefits of surgical intervention are moderate and tend to decrease over time following surgery (Dydyk et al, 2023). Multiple risks associated with surgical interventions and postoperative complications have been reported (Table 12). Additionally, even as delivering anesthesia becomes safer due to improved medications, equipment, and monitoring, the continued study of perioperative morbidity and mortality discloses risk factors for poor outcomes (Steadman et al, 2017).

Table 12: Surgical Risks and Postoperative Complications

Infections	Anesthesia/Procedure	Neurological
• Discitis • Wound infection	• Dural sac injury • Dural tear • End-plate osteochondritis • Epidural hematoma • Facet injury • Nerve root injury	• Motor dysfunction • Neurologic deterioration • Paresthesia • Transient dysesthesia • Urinary retention

Source: Park et al, 2023; Shi et al, 2023; Song et al, 2021; Zeng et al, 2020; Jaiswal et al, 2019; Kong et al, 2019; Patil et al, 2018.

Surgical treatment of lumbar disc herniation generally has a favorable prognosis, but patients may require reoperation. The most common reason for reoperation is recurrence of herniation, and the rate of reoperation for recurrent lumbar disc herniation increases as the follow-up duration becomes longer; the cumulative reoperation rate ranges from 0.5 to 4.0% at 1 year after surgery, 1.6 to 9.6% at 2 years after surgery, and 1.5 to 8.5% at 5 years after surgery (Haro et al, 2022).

In a longitudinal observation study, data from herniated lumbar disc surgeries were retrieved from a large medical database using a combination of procedure and diagnosis codes from all public hospitals in Norway from 1999 to 2013 to determine the rates of surgical complications, reoperations, and readmissions following herniated lumbar disc surgery (Fjeld et al, 2019). Out of the 34,639 analyzed surgeries, 2.7% had a surgical complication, 2.1% had repeat surgery within 90 days, 2.4% had a non-surgical readmission within 90 days, and 6.7% experienced at least one of these unfavorable events.

2.3 Patient Unmet Medical Need for Non-Surgical Alternative

Alternative treatment options are needed for patients with radicular leg pain caused by nerve root impingement from the herniation who do not respond to conservative therapy and seek non-surgical solutions. Currently there are no approved therapies for patients with LDH that

deliver early and long-term reduction in leg pain that could improve functionality. A pharmacological treatment alternative would allow patients to avoid risks associated with long-term systemic analgesic and anesthetic use or invasive spinal surgery.

3 PRODUCT DESCRIPTION

Summary

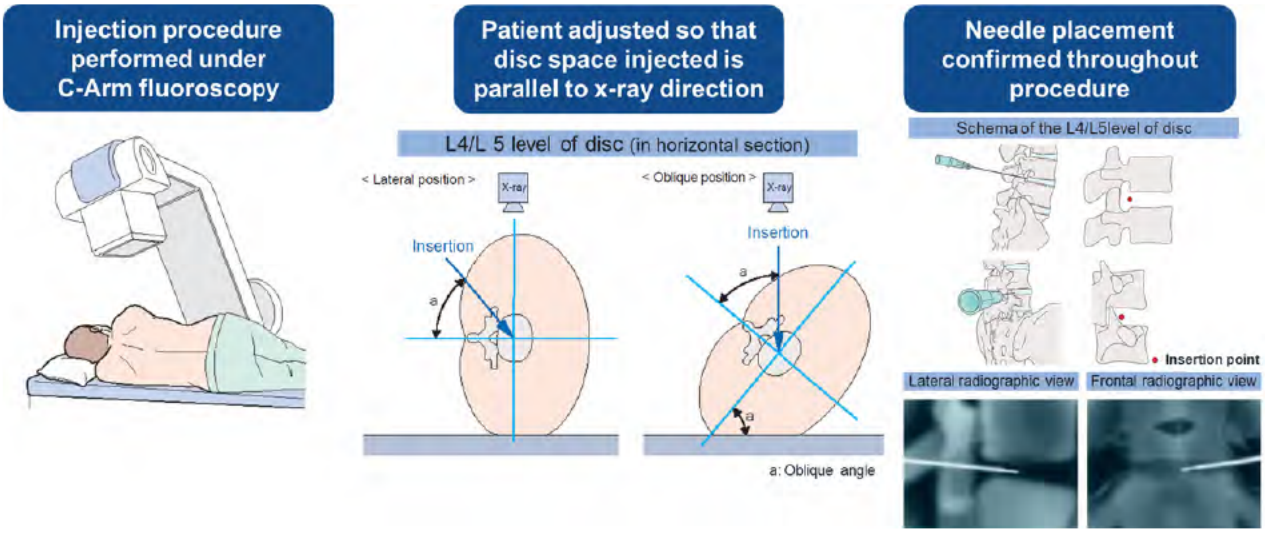
- Condoliase is a minimally invasive, localized intervention using an enzyme that reduces the water retention capacity of the nucleus pulposus and thereby decreases intradiscal pressure
- A single injection of condoliase is administered directly into the intervertebral disc for the treatment of radicular leg pain associated with LDH in adults
- Condoliase is a non-surgical treatment option for patients who are unresponsive to conservative therapy and choose to not undergo surgical treatment.

3.1 Product Overview

Condoliase is a single-dose drug product that is injected directly into the intervertebral disc for the treatment of radicular leg pain associated with confirmed nerve root impingement caused by lumbar disc herniation in adults. It is a non-surgical treatment option for patients who are unresponsive to conservative therapy and seek non-surgical solutions.

Condoliase as a non-surgical treatment does not require general anesthesia. Administration into the intervertebral disc uses C-arm fluoroscopy, which allows for real-time, continuous imaging that enables the treating doctor to insert needle precisely and safely into the center of a patient's intervertebral disc (Figure 17).

Figure 17: Overview of Fluoroscopic Guidance and Injection Procedure



Source: Image on file.

The drug product is a lyophilized powder for reconstitution into an aqueous, injectable solution. Condoliase is administered as a single-dose injection of 1 mL of 1.25 U/mL into the nucleus pulposus of the herniated intervertebral disc for a non-surgical treatment option. The proposed 1.25 U/mL dose corresponds with a protein content of approximately 3 µg/mL of solution.

3.2 Proposed Indication

The proposed indication of condoliase is for the treatment of radicular leg pain associated with confirmed nerve root impingement caused by lumbar disc herniation in adults.

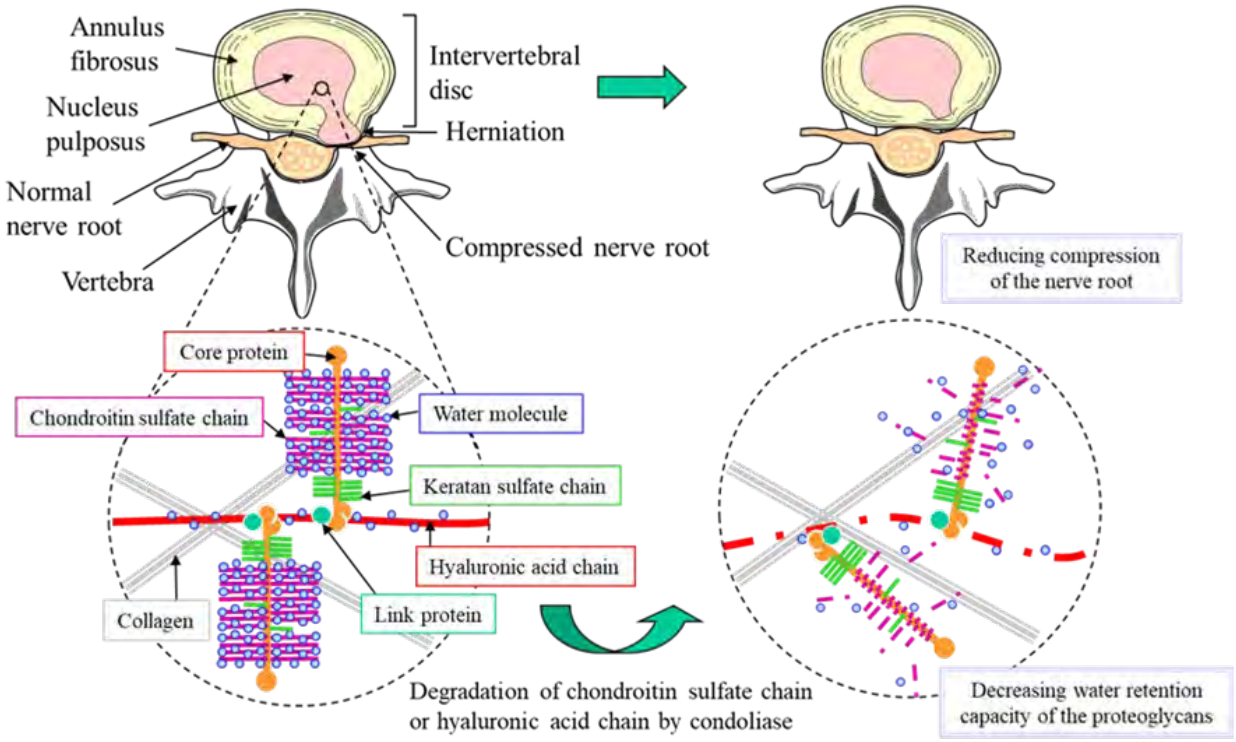
3.3 Mechanism of Action

Condoliase is a localized, single dose, chemonucleolysis injection that is an enzyme-isolated and purified from a gram-negative rod (*Proteus vulgaris*) (Yamagata et al, 1968).

Chemonucleolysis is a minimally invasive treatment using an enzyme injected into the intervertebral disc to reduce nerve root compression through lysis of the nucleus pulposus. Condoliase is a glycosaminoglycan (GAG)-degrading enzyme that specifically degrades chondroitin sulfate. It has little degradation activity against hyaluronic acid, and no degradation activity against keratan sulfate.

Nonclinical and clinical studies demonstrate that condoliase degrades the chondroitin sulfate GAG chains of proteoglycans in the nucleus pulposus, which reduces the disc's water-retention capacity, thereby resulting in a decrease in intradiscal pressure. This GAG-degradation results in shrinkage of the nucleus pulposus of the injected disc, thereby reducing the nerve root compression and the pressure on the impinged nerve, which in turn alleviates pain and other LDH-associated clinical symptoms. Furthermore, condoliase has the potential advantage of minimizing AEs, such as nerve tissue injuries in the area surrounding intervertebral discs, since condoliase does not degrade proteins like collagens that form the principal skeleton of the extracellular matrix of the intervertebral disc. Figure 18 provides an overview of the predicted effects of condoliase on proteoglycans.

Figure 18: Predicted Effects on Proteoglycan by Condoliase



Left Side: Model of proteoglycan in nucleus pulposus. Proteoglycan is rich in chondroitin sulfate, a component of glycosaminoglycan, which holds a large number of water molecules. From this, nucleus pulposus functions as a shock absorber that absorbs a physical load on the vertebral body.
Right Side: Model of proteoglycan in nucleus pulposus after administration of condoliase. After administration of condoliase, chondroitin sulfate chain and hyaluronic acid chain in proteoglycan of nucleus pulposus are degraded. This degradation reduces high water retention in proteoglycan, suppressing disc pressure and leading to pressure reduction of nerve root in lumbar disc herniation.

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- Approximately 27,000 patients are estimated to have been treated with condoliase since approval in Japan in March 2018 to treat LDH with no sufficient improvement after conservative therapy
- Throughout the development program, the Sponsor has obtained important advice from the FDA.

4.1 Regulatory Milestones

4.1.1 Approval in Japan

In March 2018, condoliase (HERNICORE®) 1.25 U was approved in Japan to treat LDH with no sufficient improvement after conservative therapy. Since approval in Japan, it is estimated that approximately 27,000 patients have received condoliase injections outside of the clinical development program as of the data cut-off date, March 11, 2024. Post-approval monitoring aligns with clinical results obtained from the randomized, controlled registration study (Study 1031), with most events related to pain or hypersensitivity.

4.1.2 FDA Regulatory History and Key Interactions

A comprehensive clinical development program has been conducted to support the BLA submission of a product dose of 1.25 U for indication in adults with LDH. Throughout the development program, Sponsor has obtained important advice from the FDA. The key regulatory interactions on safety information with FDA are summarized in Table 13.

Table 13: Regulatory Recommendations During Development of Condoliase

Date Range:	Regulatory Milestone	Key Outcomes
Pre-BLA Submission Interactions (March 2007 to March 2024)		
March 2007 to November 2007	Initiation and resolution of Full Clinical Hold due to safety concern of degenerative changes of the intervertebral discs	• Protocol revised; changes include: ○ Patients age < 30 years excluded from study ○ Maximum study drug dose < 2.5 U condoliase
August 2012 to July 2013	Special protocol assessment (SPA) request and FDA advice for Study 1131	• Key protocol parameters — eg, treatment population, imaging evaluation protocol, SAP — (3 rounds of comments)

Date Range:	Regulatory Milestone	Key Outcomes
August 2015	FDA Advice/Information Request Letter	• 1,000 patients followed for 6 months added to original safety database requirement of 1,500 patients exposed, 300 patients followed for 1 year, and 150 patients followed for 2 years
December 2016 to January 2017	Initial Pediatric Study Plan (iPSP)	• iPSP with request for full waiver pediatric (<18 years) studies based on low prevalence of lumbar disc herniation in the pediatric population was accepted.
July 2017 to August 2018	Type C Meeting and Follow-Up for Study 1133	In light of study 1131 not meeting primary endpoint, new Phase 3 study design (Study 1133) reviewed and agreed to (2 rounds of comments)
February 2023	Pre-BLA Type B Meeting	• Contents of BLA agreed to, including SAPs for ISE and ISS analyses • Change in 1133 primary analysis from MMRM to MI not agreed to. Sponsor acknowledged that choice of primary analysis would be a review issue.
September 2023	Type C Meeting	• Content and format of postmarketing data (condoliase approved in Japan 2018) proposal appeared acceptable
Post-BLA Submission Interactions (March 2024 to Present)		
March 2024	BLA submitted to FDA	• BLA accepted and filed by FDA in May 2024
May 2024	Filing communication from FDA	• Study 1031 completed in Japan. FDA will review pertinence of 1031 to US patients • Studies 1131 and 1133 are adequate, well-controlled trials conducted in the US; reasons that Study 1131 missed primary endpoint will be reviewed • Risk management, including hypersensitivity and spinal abnormalities, will be investigated
August 2024	Mid-cycle Communication Meeting	• Studies 1031, 1131, and 1133 show modest reduction in leg pain in patients with nerve root impingement confirmed by imaging • Randomized, controlled studies show no clear imbalances in AESIs; however, postmarketing data contain several cases of consequence • If approved, Sponsor is encouraged to develop a plan to ensure treatment with condoliase is limited to patients where the benefits outweigh the risks

AESI: adverse event of special interest; BLA: biologics license application; FDA: Food and Drug Administration; iPSP: Initial Pediatric Study Plan; ISE: integrated summary of efficacy; ISS: integrated summary of safety; MI: multiple imputation; MMRM: mixed methods for repeated measures; SAP: statistical analysis plan; SPA: special protocol assessment; US: United States.

4.2 Clinical Development Program

4.2.1 Overview of Clinical Program

The primary data set that supports a positive benefit-risk for condoliase consists of four Phase 2 and 3 randomized, controlled trials (Figure 4).

Studies 1021 and 1031 were conducted exclusively in Japan and resulted in the approval of condoliase in 2018 for the treatment of LDH with no sufficient improvement after conservative therapy. Since that time, an estimated 27,000 patients have been treated in the post-marketing setting in Japan.

Studies 1131 and 1133 were conducted exclusively in the US.

4.2.2 Pivotal Phase 3 Studies 1031 (Japan) and 1133 (US)

Efficacy and safety of condoliase are demonstrated by two pivotal, controlled Phase 3 Studies: Study 1031 (Section 7.3; Japan) and Study 1133 (Section 7.5; US), both of which evaluated the effectiveness of condoliase vs control (placebo in Study 1031 in Japan and sham in Study 1133 in the US) for treatment of radicular pain associated with LDH. These studies had the same overall design (Section 1.5.1). Both were multicenter, randomized, double-blind, controlled studies in adults with LDH, who were randomized 1:1 to receive either active treatment of single-dose condoliase or control (either placebo or sham), and were followed for 52 weeks.

Patients with contained posterolateral LDH at either intervertebral disc between the fourth and fifth lumbar vertebrae (L4-L5, the notation of other lumbar intervertebral discs is also similar) or L5-S1 (or L5-L6, if present) with nerve root impingement who met all other screening criteria were eligible to participate.

4.2.3 Studies Contributing Supportive Safety Data: Studies 1021 (Japan), 1131 (US), and 1132 (US and Europe)

Study 1021 was a multicenter, randomized, placebo-controlled, double-blind, dose-finding Phase 2/3 study assessing the efficacy, safety, and pharmacokinetics (PK) of single-dose condoliase at 1.25, 2.5, and 5 U/mL vs placebo for up to 52 weeks in Japan. Study 1021 utilized the same primary endpoint and primary analysis as Study 1031. Results are included in the Dose Justification Section (Section 6.2).

Study 1131 was a multicenter, randomized, double-blind, controlled (sham injection) study that investigated the injection of single-dose condoliase vs control for patients with LDH in the US. Results were analyzed at 13 weeks and then periodically for up to 52 Weeks. Study 1131 did not meet its primary endpoint; however, its safety data contributed to condoliase's clinical safety database. This study was the sole source of patients to meet the FDA safety requirement of 150 patients followed for a duration of 104 weeks or more. The results also highlighted the value of confirming nerve root impingement and guided adaptation of the inclusion/exclusion criteria used in Study 1133. (See Section 7.4.3.2 for Study 1131 learnings implemented in Study 1133.)

Study 1132 was a Phase 3 multicenter, open-label study to investigate the safety of a single dose of condoliase at 1.25 U in subjects with LDH for a 26-week follow-up period. The primary study objective was to evaluate safety. This study was conducted to help meet the FDA safety requirement of 1,000 patients followed for a duration of 26 weeks or more.

5 SUMMARY OF NONCLINICAL PROGRAM

Summary

- Nonclinical pharmacology studies in rabbits and sheep have demonstrated that a single injection of condoliase resulted in decreased nucleus pulposus swelling, intradiscal pressure and disc height. Furthermore, improvement of symptoms was demonstrated in dogs with herniated disc syndrome.
- In toxicity studies in cynomolgus monkeys, histological changes in the non-target sites (cartilaginous endplate, epiphyseal growth plate, and vertebral body) were observed, but the findings had stabilized by 26 weeks after condoliase injection.
- Nonclinical studies demonstrate no systemic toxicity by intradiscal administration, together with no genotoxicity, or reproductive and developmental toxicity.

Nonclinical pharmacology studies of condoliase focused on its impact on intervertebral discs and demonstrated the inhibitory effect of condoliase on nucleus pulposus swelling, a decrease in intradiscal pressure and disc height following condoliase injection, and improvement of symptoms in animals with disc herniation syndrome. In a pharmacology study in domestic dogs with herniated disc syndrome, intradiscal injection of condoliase (9.7 ± 6.8 U/disc) showed complete resolution of symptoms in 50% and 75% of animals by 7 days and 59 days, respectively, after injection. Safety pharmacology studies indicated no adverse effects on the central nervous and respiratory systems of rats or the cardiovascular system of dogs after a single subcutaneous administration of condoliase at dose levels up to 20 U/kg. Pharmacokinetic studies in beagle dogs using 2 U/disc condoliase or 50 U/disc radiolabeled condoliase (^{125}I-condoliase) demonstrated measurable enzyme activity of condoliase in the injected intervertebral disc for up to 14 days.

In toxicology studies, no condoliase-related changes were observed in any systemic organs and tissues after a single intradiscal administration of condoliase at doses up to 10 U/disc, 100 U/disc, and 50 U/disc in cynomolgus monkeys, rabbits, and dogs, respectively, indicating low risk for systemic toxicity of condoliase when used clinically as intended. No genotoxic potential was observed in genetic toxicity studies (bacterial reverse mutation assay, a chromosomal aberration assay with mammalian cultured cells, and an in vivo mouse micronucleus assay), and no effects on reproductive function of parental animals or on embryos, fetuses, or offspring were observed in reproductive and developmental evaluations in rabbit and rat studies. In local tolerance studies, irritation was observed in the nucleus pulposus after intradiscal administration, which is reflective of the expected pharmacological changes induced by condoliase. No irritation was noted after subarachnoidal or spinal nerve root administration, and slight irritation was seen following intramuscular administration that trended towards recovery after 7 days.

In toxicity studies in cynomolgus monkeys, which have an intervertebral disc structure similar to that of humans, microscopic evaluations showed that a single intradiscal administration of condoliase caused the expected pharmacological effects at the target sites (the nucleus pulposus and annulus fibrosus) due to chemonucleolysis, but also could cause tissue injury and reparative changes in tissues adjacent to the target sites (the cartilaginous endplate, epiphyseal

growth plate, and vertebral body). Although the histological changes in the adjacent tissue sites were observed at 0.25 U/disc (the lowest dose), 12× the proposed clinical dose when adjusted based on volume of the nucleus pulposus, the findings stabilized by 26 weeks after condoliase injection. In addition, histologic findings at non-target sites that persisted at 26 weeks in monkeys reflected findings reported in humans as spontaneous age-related changes (Bernick & Cailliet, 1982; Grignon et al, 2000; Muramatsu et al, 2020) and were therefore considered to be within physiological range.

Overall, the nonclinical evaluations support the pharmacological effect and safety of condoliase in the intended clinical use.

6 CLINICAL PHARMACOLOGY

Summary

- Plasma condoliase concentrations were below the limit of quantification (<100 µU/mL [0.27 ng/mL]) in all patients administered condoliase at doses of 0.5 to 10 U.
- The recommended dose of condoliase was determined to be 1.25 U based on its efficacy and safety.
- There was no consistent pattern observed with increase of anti-drug antibodies against condoliase and treatment-emergent adverse events.

Clinical pharmacology following a single injection of condoliase has been evaluated in a total of 3 studies (SKK6603J01, 1021, and 1121), all conducted in patients with LDH. Two of these studies were conducted in Japan and 1 study was conducted in the US.

As expected from a locally injected GAG-degrading enzyme product, the pharmacodynamic effect of condoliase will be almost exclusively localized to the treated disc, with nominal systemic plasma concentrations.

6.1 Pharmacokinetics

Plasma condoliase concentrations were below the limit of quantification (< 100 µU/mL [0.27 ng/mL]) in all patients in all studies in which PK was assessed. No assessments were made on the relationship between PK and safety. Patients were administered condoliase at doses of 0.5 to 10 U in these studies.

The results were reasonable considering the nonclinical data, in which the plasma condoliase concentrations were below the limit of quantification (ELISA [enzyme-linked immunosorbent assay]: < 360 µU/mL; radiometric enzyme activity assay: < 20,000 µU/mL) after single intradiscal administration of ^{125}I-condoliase to beagle dogs at a dose of 50 U/disc (equivalent to approximately 2800 times the clinical dose).

6.2 Dose Justification for 1.25 U/mL

Study SKK6603J01 was a Phase 1/2 open label dose finding study that assessed safety and tolerability of a single intradiscal injection of condoliase in patients with LDH. This study showed increased efficacy for a 2.5 U dose over a 0.5 U dose.

Study 1021 was a randomized, controlled study that evaluated single injections of condoliase at doses of 1.25 U, 2.5 U, or 5.0 U compared to placebo in patients with LDH who had no improvement after ≥ 6 weeks of conservative therapy. There were no major differences in efficacy or AEs between the 3 doses. Therefore, 1.25 U was selected because it was the lowest efficacious dose.

6.3 Special Studies (Immunogenicity)

As a foreign protein administered to humans, condoliase has the potential to induce an immune response.

Anti-drug antibodies (ADAs) generated against condoliase were measured in Studies SKK6603J01, 1021, 1031, 1121, 1131, and 1132. In each of the studies, ADA response dynamics and impact of ADA on PK, pharmacodynamic (PD), and safety were assessed, if applicable. Impact of ADA on efficacy was not assessed because condoliase is injected directly into the herniated disc as single dose treatment, and, therefore, the potential of correlation between ADA and efficacy is minimal.

The primary assessment of the impact of ADA on condoliase was an evaluation of the relationship between ADA and the incidence of hypersensitivity and anaphylaxis adverse events. There was no consistent pattern observed with ADA increase and treatment-emergent adverse events across studies. Overall, the immunogenicity risk for condoliase is low based on the comprehensive immunogenicity risk assessment and immunogenicity data generated in the clinical development program.

The relationship between condoliase exposure in plasma and ADA results were not investigated because plasma concentrations of condoliase were below the limit of quantification in all studies. The relationship of ADA to a potential PD marker, keratan sulfate, was evaluated in Studies 1021 and 1121. There was no clear relationship between change from baseline in serum keratan sulfate and elevated anti-condoliase IgG titers.

No neutralizing antibody assay was performed during the clinical development program. Condoliase is a foreign protein; therefore, a BLAST (basic local alignment search tool) search was performed to determine whether there were any conserved regions between condoliase and human proteins. No 100% identical peptide fragments with 13 amino acids or longer were found between condoliase peptide fragments and the human protein database. In addition, condoliase is structurally dissimilar with human hyaluronidase, human enzymes that degrade chondroitin sulfate, suggesting a different evolutionary process between the bacterial and human genes and that structural and amino acid sequence similarities of the catalytic domains between the enzymes are quite low. Therefore, the possibility of development of neutralizing antibodies to endogenous human proteins is considered low.

7 CLINICAL EFFICACY

Summary

- Condoliase met the primary endpoint in the two pivotal studies (1031 and 1133), showing significant improvement in both early and durable relief of worst leg pain after injection compared with the control group.
  - In Study 1133, statistically significant results favoring condoliase over sham were observed, where the LS mean treatment group difference in change from baseline of worst leg pain at Week 13 was -7.5 (95% CI: -14.1, -0.9; p=0.0263).
  - In Study 1031, statistically significant results favoring condoliase over placebo were observed, where the LS mean treatment group difference in change from baseline of worst leg pain at Week 13 was -13.9 (95% CI: -22.3, -5.5; p=0.0013).
  - In both Pivotal studies, condoliase showed statistically significant reduction in worst leg pain a full year (52 weeks) after treatment, compared to control.
- Condoliase also demonstrated a reduction in herniation volume and improvement in function at Week 13 that persisted over time.

Two pivotal Phase 3 randomized controlled studies support condoliase efficacy for the treatment of radicular pain associated with LDH: Study 1031 (conducted entirely in Japan) and Study 1133 (conducted entirely in the US).

7.1 Efficacy Endpoints

All Phase 3 studies used three common key endpoints to evaluate efficacy: worst leg pain, herniation volume, and ODI.

Based on the mechanism of action and localized pharmacodynamic effect following a single 1.25 U injection, key endpoints were evaluated at 13 weeks.

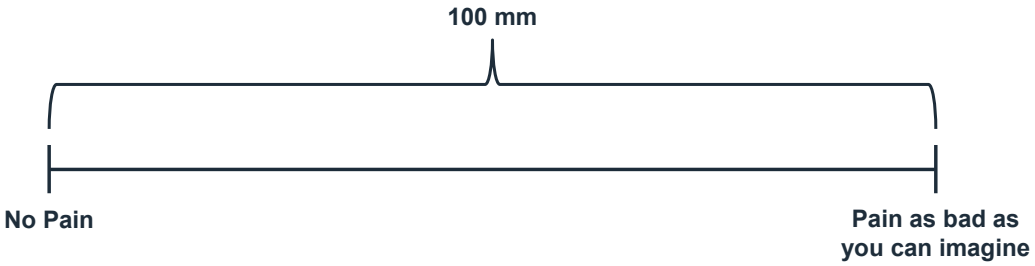
7.1.1 Worst Leg Pain

The primary endpoint used to evaluate efficacy was mean change from baseline in average worst leg pain score at Week 13.

The 100 mm VAS pain assessment tool was used to measure pain intensity daily, from screening until Week 52 (Figure 19). At the screening visit, the investigator provided a daily diary and instructed patients to record daily the pain intensity from LDH over the last 24 hours before going to bed. A patient's VAS recording was the distance in mm from 0 (no pain) to the pain intensity they indicated.

Change from baseline in average worst leg pain score was also collected at Week 52 in order to assess response durability.

Figure 19: 100-mm Visual Analog Scale



7.1.2 Herniation Volume

Change from baseline in herniation volume at Week 13 was a key efficacy measure used to evaluate the local effect on LDH.

Herniation volumes were assessed with MRI by a central imaging facility at screening and at prespecified timepoints throughout the studies. The investigator or site staff collected the images and transmitted them to the central imaging facility. Herniation volume was calculated as the cross-sectional area measured in each slice times multiplied by the slice separation. Total herniation volume was therefore equal to the sum of volume measurements from each slice.

7.1.3 Oswestry Disability Index (ODI)

The ODI, also known as the Oswestry Low Back Pain Disability Questionnaire, is a validated instrument to assess functional disability and is considered an important tool for clinical trials (Fairbank, 2000; Sheahan, 2015). Change from baseline in ODI score was measured at Week 13.

The questionnaire contains 10 sections of daily living, with statements to assess a patient's disability in each section. Scores from 0 (least disability) to 5 (greatest disability) are given for each statement, which are totaled to calculate the final ODI score. A higher score on the ODI indicates a more severe disability. The final index score is calculated as a percentage, with 0% indicating no disability and 100% indicating highest disability (Table 14).

Patients were instructed to complete the ODI questionnaire at each visit. An example of the 2-page ODI questionnaire is provided in Appendix 13.7.

Table 14: Scoring and Interpretation of the Oswestry Disability Index

Index Range / Disability	Interpretation
0% to 20% No disability	Most daily activities are manageable for the patient. Aside from guidance on lifting, sitting, and exercising, no therapy is usually necessary.
21% to 40% Mild disability	Sitting, lifting, and standing cause the patient extra discomfort and trouble. Travel and social activities are more difficult for them, and they may be unable to work. Personal hygiene, sexual activity, and sleeping are unaffected, and the patient can usually be handled conservatively.
41% to 60% Moderate disability	The primary issue in this group is pain, although daily activities are also impacted. These patients necessitate a thorough examination.
61% to 80% Severe disability	Back pain affects every part of the patient's life. Positive action is essential.
81% to 100% Complete disability	These patients are either confined to their beds or exaggerating their symptoms.

Sources: Fairbank, 2000 and Sheahan, 2015.

7.2 Statistical Analysis

7.2.1 Rationale for MI Approach

While the SAP with MMRM (MAR) as the primary analysis for Study 1133 was deemed acceptable by FDA in written response dated November 7, 2017, the FDA updated its advice at the time of the Pre-BLA. The agency stated concerns with the proposed primary endpoint analyses by MMRM (MAR) in Study 1133 because assuming the data MAR may not be reasonable for some study discontinuations such as discontinuation due to lack of efficacy, the need for concomitant therapies of lumbar surgery, or lumbar intradiscal therapies that may indicate the treatment does not work. Based on the Agency's pre-BLA feedback, the Sponsor decided to retain MMRM (MAR) as the primary analysis since the study was originally designed and powered under this assumption. In response to the Agency's position as MI (MNAR) being their preferred analysis, Study 1133 clinical study report (CSR) SAP included MI (MNAR) as a sensitivity analysis. The ISE SAP also included MI (MNAR) analyses for Study 1031.

7.2.2 Missing Data

For the efficacy analysis based on repeated-measures models of continuous endpoints, missing data was implicitly handled via a mixed-effect model, without explicit imputation. Inferences based on this approach are unbiased under the assumption of missing at random (MAR), which is a weaker and more generally true assumption than missing completely at random (MCAR) but may not be reasonable for some study discontinuations.

Primary efficacy and key secondary efficacy analyses, sensitivity analyses were performed based on MI (MNAR) methods that changed imputation methods by missing patterns, such as discontinuations due to AEs, lack of efficacy, and other reasons for both Study 1133 and Study 1031. Using MI (MNAR) methods ensured study discontinuations suggestive of poor treatment outcomes did not contribute any treatment benefit in the primary analysis. MI (MNAR) methods used imputed data for discontinuations assuming worsening outcomes using a scheme based on returning to baseline values.

Table 15 shows the different imputation strategies used in the 2 pivotal efficacy studies.

Table 15: Imputation Strategies of Study 1031 and Study 1133

Imputation Method:	Study 1031	Study 1133
Pre-specified CSR SAP	ANCOVA with LOCF	MMRM (MAR) without explicit imputation
Sensitivity analysis in CSR SAP	ANCOVA by observed case (without imputation)	MI (MNAR)
ISE SAP (post-hoc for Study 1031)	MMRM (MAR) without explicit imputation	Same as CSR SAP
Sensitivity analysis in ISE SAP	MI (MNAR)	Same as CSR SAP

ANCOVA: analysis of covariance; CSR: clinical study report; ISE: Integrated Summary of Efficacy; LOCF: last observation carried forward; MAR: missing at random; MI: multiple imputation; MMRM: mixed model for repeated measures; MNAR: missing not at random; SAP: statistical analysis plan.

When determining the mean worst leg pain score for analysis, data from the 7 consecutive days prior to each visit (the day of the visit was not included) were used as the worst leg pain score for each time point, after excluding the worst leg pain score on any of the following days:

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

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

For Study 1031 at Weeks 26 through 52, the worst leg pain score was collected only for the day before the visit, and therefore, the analysis value was based on a single assessment for these visits.

For the responder analysis, such as the cumulative distribution plot of the percentage improvement and 50% responder analysis, patients with missing values were considered non-responders/not having improvement.

7.3 Study 1031

7.3.1 Study 1031 Design

7.3.1.1 Study 1031 Clinical Design

Study 1031 was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study that investigated worst leg pain at 13 weeks after single-dose of 1.25 U of condoliase or placebo and was conducted at 35 sites in Japan. All eligible patients were randomized 1:1 to either condoliase or placebo (Figure 5). Patients were followed for up to 52 weeks to monitor the stability of the intervertebral disc and surrounding tissue. Study data were unblinded after all

patients completed the Week 13 visit for primary efficacy for the NDA submission in Japan. Patients and investigators remained blinded to study treatment throughout the 52-week study.

7.3.1.2 Study 1031 Enrollment Criteria

Eligible patients were males and females 20 to 70 years of age with confirmed LDH at L4-L5 or L5-S1 and radicular nerve leg pain corresponding to nerve root impingement who had shown no improvement after ≥ 6 weeks of appropriate conservative treatment at the time of informed consent.

Enrolled patients reported at bedtime their worst leg pain over the past 24 hours, corresponding to mean VAS scores ≥ 50 mm measured over 7 consecutive days along with no change in dosage of current concomitant medication being used for pain relief.

Please see Appendix 13.2 for the full list of inclusion and exclusion criteria in Study 1031.

7.3.1.3 Study 1031 Endpoint Selection

Primary Endpoint: Mean change from baseline in average worst leg pain score at Week 13

Secondary Endpoints

- Change from baseline in worst leg pain score at Week 52
- Change from baseline in herniation volume at Week 13
- Change from baseline in ODI score at Week 13

Other prespecified endpoints

- Worst back pain over the past 24 hours (VAS)
- 36-item Short Form Health Survey (SF-36) scores
- Negative SLR test (yes/no)
- Incidence of posttreatment surgery for LDH at the same level of condoliase injection

7.3.1.4 Study 1031 Statistical Analysis Plan

Sponsor performed the primary efficacy analysis using both the MI (MNAR) and MMRM (MAR) to ensure interpretability of study results. All secondary and supportive analyses are presented using the FDA-recommended MI (MNAR) analysis. For completeness, MMRM (MAR) results are provided in Appendix 13.3.2 (Study 1031) and Appendix 13.5.2 (Study 1133). MI (MNAR) can be problematic with small sample size. Therefore, subgroup analyses are consistently presented using the MMRM (MAR) approach.

(Additional details provided in Section 1.5.1.4.)

7.3.2 Study 1031 Patient Disposition, Demographics, and Baseline Disease Characteristics

7.3.2.1 Study 1031 Disposition

Study 1031 enrolled 166 patients; of these patients, 163 patients received 1 dose of the investigational drug (81 in the placebo group and 82 patients in the condoliase 1.25 U group; Table 16). Of these, 146 patients completed Week 13 (condoliase 76, placebo 70 patients).

Table 16: Patient Disposition — Study 1031 (All Randomized Patients)

Disposition, n (%):	Condoliase (N=84)	Placebo (N=82)
Modified ITT Population	82 (97.6)	81 (98.8)
Completed Week 13 Visit	76 (90.5)	70 (85.4)
Completed Study	62 (73.8)	57 (69.5)
Discontinued from the Study	22 (26.2)	25 (30.5)
Adverse Event	0	5 (6.1)
Pregnancy	1 (1.2)	0
Lack of efficacy	11 (13.1)	11 (13.4)
Withdrawal of subject consent	2 (2.4)	5 (6.1)
Other	8 (9.5)	4 (4.9)

ITT: intent-to-treat; U: unit
Note: Percentages were based on the number of patients randomized.

7.3.2.2 Study 1031 Demographics

Study 1031 population demographics are presented in Table 17 and are representative of the overall population in Japan for the proposed indication.

Table 17: Baseline Demographics — Study 1031 (mITT)

Demographic, Statistic:	Condoliase (N=82)	Placebo (N=81)
Age (years), median	37.5	38.0
Age group, n (%)		
20 – 29 years	14 (17.1)	21 (25.9)
30 – 49 years	52 (63.4)	44 (54.3)
50 – 59 years	10 (12.2)	8 (9.9)
≥ 60 years	6 (7.3)	8 (9.9)
Sex, n (%)		
Male	51 (62.2)	48 (59.3)
Female	31 (37.8)	33 (40.7)
Race, n (%)		
Asian	82 (100)	81 (100)
Ethnicity, n (%)		
Hispanic or Latino	NA	NA
Not Hispanic or Latino	NA	NA
Height, (cm) median	168.5	168.0
< 170 cm	44 (53.7)	45 (55.6)
≥ 170 cm	38 (46.3)	36 (44.4)

Demographic, Statistic:	Condoliase (N=82)	Placebo (N=81)
Baseline weight (kg), median	65.0	64.9
BMI (kg/m^2), median	23.08	22.90
< 18.5 kg/m^2	5 (6.1)	6 (7.4)
18.5 - < 25.0 kg/m^2	49 (59.8)	49 (60.5)
25.0 - < 35.0 kg/m^2	28 (34.1)	26 (32.1)
≥ 35.0 kg/m^2	0	0
Smoking history, n (%)		
Never smoked	39 (47.6)	35 (43.2)
Past smoker	26 (31.7)	16 (19.8)
Current smoker	17 (20.7)	30 (37.0)
Occupation, n (%)		
Light labor	32 (39.0)	28 (34.6)
Heavy labor	50 (61.0)	53 (65.4)

BMI: body mass index; mITT: modified intent to treat.

7.3.2.3 Study 1031 Disease Characteristics

Baseline disease characteristics of the patient population in Study 1031 are presented in Table 18.

Table 18: Baseline Disease Characteristics — Study 1031 (mITT)

Disease Characteristic, Statistic:	Condoliase (N=82)	Placebo (N=81)
Herniation site, n (%)		
L4 – L5	45 (54.9)	37 (45.7)
L5 – S1	37 (45.1)	44 (54.3)
Days since onset of current radicular leg pain, median	142.0	127.0
VAS pain score for worst leg pain, median	73.29	74.57
VAS pain score for worst back pain, median	55.14	61.57
ODI score, median	37.0	40.0

mITT: modified intent to treat; ODI: Oswestry Disability Index; VAS: visual analog scale.

7.3.3 Study 1031 Efficacy Results

7.3.3.1 Study 1031 Primary Efficacy Results

7.3.3.1.1 Primary Efficacy Analysis — Worst Leg Pain over Past 24 Hours at Week 13

Study 1031 met its primary endpoint with statistically significant and clinically meaningful reductions in leg pain by Week 13 (Table 19). Results were comparable and statistically significant using both the MI and MMRM analyses.

Table 19: Primary Efficacy Analysis: Change from Baseline to Week 13 in Worst Leg Pain — Study 1031 (mITT)

	MI (MNAR)		MMRM (MAR)	
Worst Leg Pain, VAS:	**Condoliase (N=82)**	**Placebo (N=81)**	**Condoliase (N=82)**	**Placebo (N=81)**
Baseline, mean (SD)	72.4 (12.29)	74.6 (12.48)	72.4 (12.29)	74.6 (12.48)
Week 13, LS mean (SE)	22.7 (3.12)	37.6 (3.16)	21.1 (2.97)	35.0 (3.05)
Change in LS means (SE)	-50.8 (3.12)	-35.9 (3.16)	-52.1 (2.97)	-38.2 (3.05)
Treatment difference for condoliase vs placebo				
Difference in LS means (SE)	-14.9 (4.44)		-13.9 (4.26)	
p-value	0.0008		0.0013	

LS: least squares; MAR: missing at random; MI: multiple imputation; mITT: modified intent to treat; MMRM: mixed model repeated measures; MNAR: missing not at random; SD: standard deviation; SE: standard error; VAS: Visual Analog Scale.

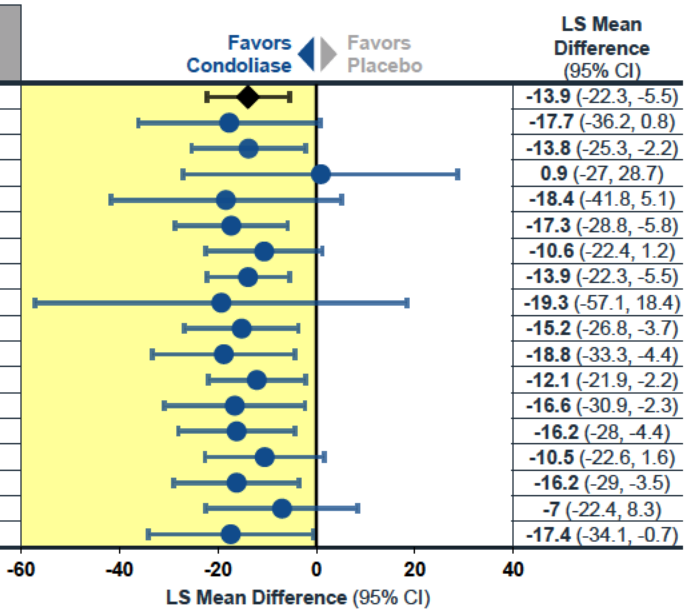
7.3.3.1.2 Additional Analysis of Primary Efficacy — Worst Leg Pain at Week 13 in Subgroups

Subgroup analyses show that single-dose condoliase provides meaningful reductions in leg pain, regardless of the patient's age, sex, BMI, height, disc level, or smoking history.

Patients who received condoliase showed improvements in worst leg pain at Week 13 compared to placebo (the primary endpoint), regardless of subgroup (Figure 20).

Figure 20: Forest Plot of Primary Efficacy in Subgroups — Study 1031 (mITT)

Subgroup		Condoliase N	Placebo N	LS Mean Difference (95% CI)
Overall		76	70	**-13.9** (-22.3, -5.5)
Age	20 – 29 years	12	19	**-17.7** (-36.2, 0.8)
	30 – 49 years	48	37	**-13.8** (-25.3, -2.2)
	50 – 59 years	10	7	**0.9** (-27, 28.7)
	≥ 60 years	6	7	**-18.4** (-41.8, 5.1)
Sex	Male	46	40	**-17.3** (-28.8, -5.8)
	Female	30	30	**-10.6** (-22.4, 1.2)
Race	Asian	76	70	**-13.9** (-22.3, -5.5)
BMI category	< 18.5 kg/m²	4	5	**-19.3** (-57.1, 18.4)
	18.5 to < 25.0 kg/m²	46	40	**-15.2** (-26.8, -3.7)
	25.0 to < 35.0 kg/m²	26	25	**-18.8** (-33.3, -4.4)
Height	< 170 cm	43	39	**-12.1** (-21.9, -2.2)
	≥ 170 cm	33	31	**-16.6** (-30.9, -2.3)
Disc level	L4 – L5	42	32	**-16.2** (-28, -4.4)
	L5 – S1/L6	34	38	**-10.5** (-22.6, 1.6)
Smoking history	Never smoked	36	31	**-16.2** (-29, -3.5)
	Past smoker	24	14	**-7** (-22.4, 8.3)
	Current smoker	16	25	**-17.4** (-34.1, -0.7)



BMI: body mass index; CI: confidence interval; LS: least squares; mITT: Modified Intent to Treat.

7.3.3.2 *Study 1031 — Secondary Efficacy Results*

All secondary and supporting endpoints were analyzed by MI (MNAR), as recommended by FDA and agreed by Sponsor as the appropriate method. For completeness, results of the MMRM (MAR) analyses are provided in Appendix 13.3.2. Additional discussion of analysis methods is presented in Section 1.5.1.4.

7.3.3.2.1 Change in Worst Leg Pain through Week 52

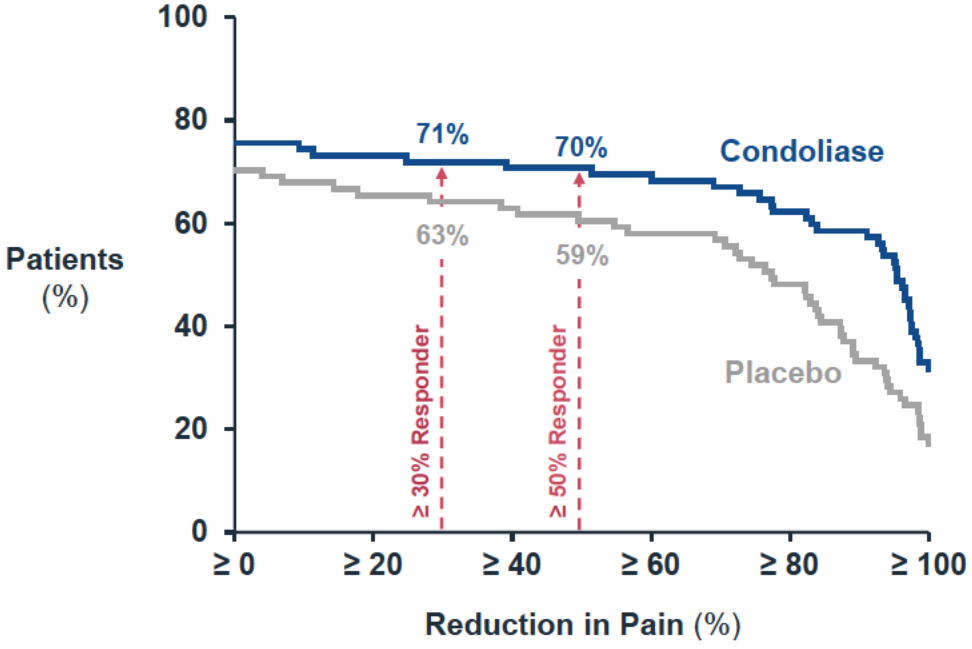
Starting two weeks after treatment, condoliase led to statistically significant reductions in worst leg pain that were reported at each subsequent timepoint and sustained for at least a year (Table 20; Figure 21). (Worst leg pain at Week 52 was a prespecified key secondary endpoint for Study 1133 and was not prespecified as a key secondary endpoint for Study 1031.)

Table 20: Change from Baseline in Weekly Average Worst Leg Pain at Each Time Point through 52 Weeks — Study 1031 (mITT)

Visit:	Difference in LS Means (95% CI)	p-value (Nominal)
Week 1	-4.9 (-10.8, 1.0)	0.1050
Week 2	-7.9 (-14.6, -1.3)	0.0194
Week 4	-11.1 (-18.7, -3.5)	0.0043
Week 6	-11.8 (-19.9, -3.6)	0.0046
Week 13	-14.9 (-23.6, -6.1)	0.0008
Week 26	-12.2 (-21.1, -3.3)	0.0075
Week 39	-9.2 (-18.1, -0.2)	0.0446
Week 52	-9.7 (-18.9, -0.5)	0.0394

CI: confidence interval; LS: least squares; mITT: Modified Intent to Treat.

Figure 21: Cumulative Distribution of Percent Reductions in Weekly Averages of Worst Leg Pain from Baseline to Week 52 — Study 1031 (mITT)

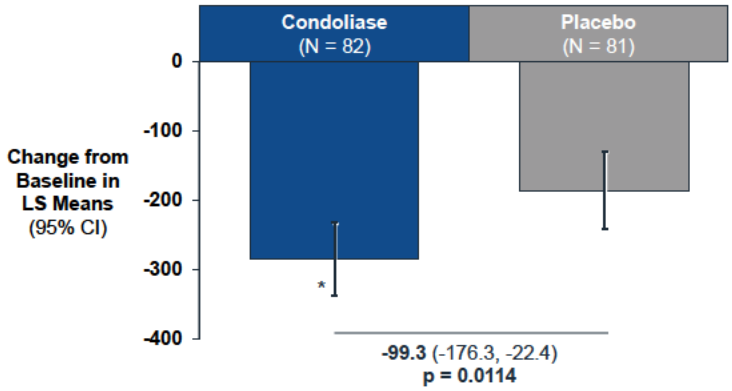


mITT: modified intent to treat.

7.3.3.2.2 Change in Herniated Disc Volume at Week 13

As expected with the reductions in worst leg pain at Week 13 (primary endpoint; Section 7.3.3.1.1) and condoliase's mechanism of action (Section 3.3), treatment with condoliase led to statistically significant reductions from baseline in disc herniation volume compared to placebo (Figure 22).

Figure 22: Change from Baseline in Disc Herniation Volume at Week 13 — Study 1031 (mITT)



CI: confidence interval; LS: least squares; mITT: modified intent to treat.
* nominal p-value < 0.05.

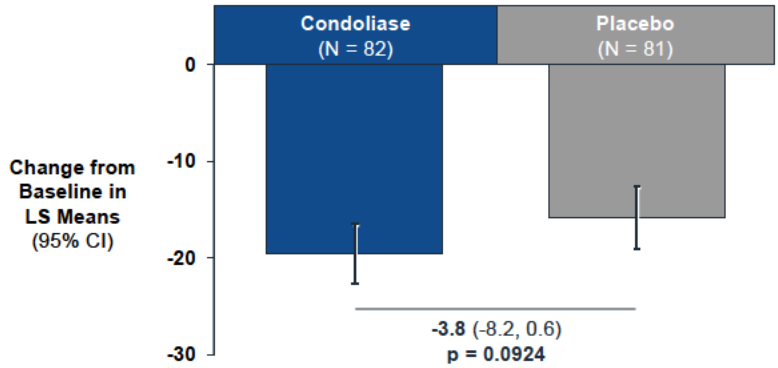
7.3.3.2.3 Change in Oswestry Disability Index (ODI)

Change in ODI at Week 13

Although patients who received condoliase showed a trend for improvement in ODI scores vs placebo, results were not statistically significant: -3.8 (95% CI: -8.2, 0.6); p=0.0924 (Figure 23).

Although patients did not report a statistically significant reduction in disability at Week 13, treatment with condoliase led to statistically significantly reduced ODI scores at Week 52 with condoliase showing increasing improvement vs placebo over time (Figure 24).Higher numbers reflect greater disability, and the maximum score is 50 points, with responses ranging from 0-to-5 points on each of 10 questions. (Additional details on the ODI are provided in Section 7.1.3; an example ODI questionnaire is provided in Appendix 13.5.2.)

Figure 23: Change from Baseline in ODI Score at Week 13 — Study 1031 (mITT)

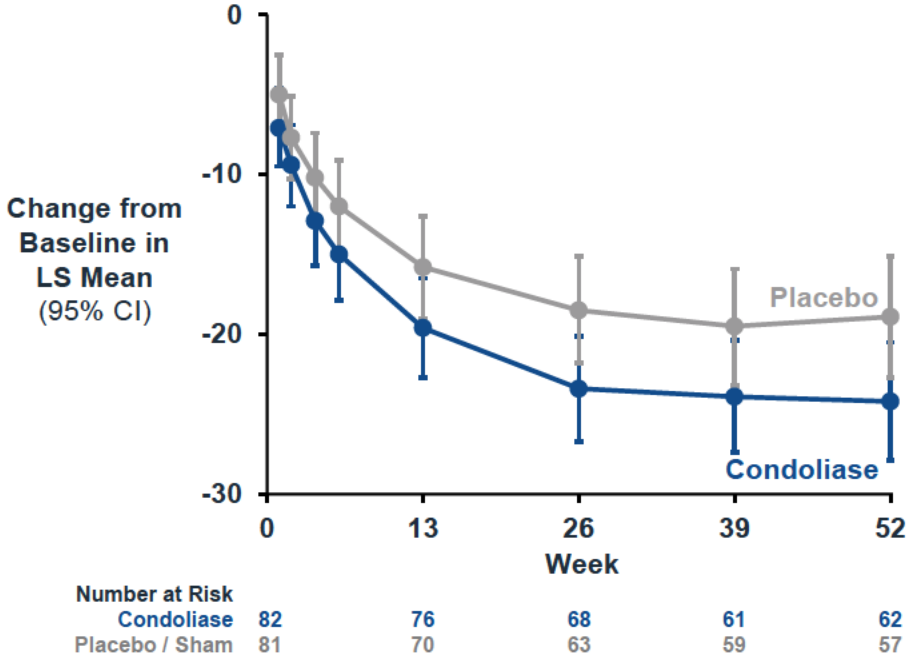


CI: confidence interval; LS: least-squares; mITT: modified intent to treat; ODI: Oswestry Disability Index.

Change in ODI over Time, through Week 52

The LS means change from Baseline in ODI scores at Week 52 was statistically significant for condoliase vs placebo: mean (95% CI) change from baseline was -24.2 (-27.9, -20.5) vs -18.9 (-22.7, -15.1); treatment difference=-5.3 (-10.5, -0.1); p=0.0474.

Figure 24: Change from Baseline in ODI over Time through Week 52 — Study 1031 (mITT)



CI: confidence interval; LS: least-squares; mITT: modified intent to treat; ODI: Oswestry Disability Index.

7.4 Study 1131

7.4.1 Study 1131 Design

7.4.1.1 Study 1131 Clinical Design

Study 1131 was a multicenter, randomized, double-blind, sham-controlled, comparative, Phase 3 study that investigated worst leg pain at 13 weeks after single-dose of condoliase or sham injection and was conducted at 37 sites in the US with a duration of 104 weeks (2 years).

Patients were randomized 3:1 to condoliase or sham injection. Patients were stratified by baseline disease and medical characteristics to ensure balance between treatment groups.

Study 1131 was intended to serve as 1 of the 2 pivotal studies (the other being Study 1031) for the US marketing application submission; however, Study 1131 did not meet statistical significance with its primary endpoint.

7.4.1.2 Study 1131 Enrollment Criteria

Patients eligible to be enrolled in the study were adults aged 30-70 years with LDH (L4-L5 or L5S1[L6]).

Complete inclusion and exclusion criteria implemented in Study 1131 is provided in Appendix 13.4.1.

7.4.2 Study 1131 Patient Disposition, Demographics, and Baseline Disease Characteristics

Patients in Study 1131 were generally representative of the overall US population of patients in the proposed indication for treatment with condoliase and were well balanced between treatment groups (condoliase vs sham injection).

The median (min, max) leg pain was 74.5 (17, 100) vs 77.0 (52, 100) points on the 100 mm VAS for condoliase vs sham, respectively. Patients in both treatment groups had moderate baseline disability, as assessed by self-reporting on the ODI: median (range) 46.0 (8, 100) vs 48.0 (24, 94) for condoliase vs sham, respectively. (Additional information on the ODI is provided in Section 7.1.3; interpretation of scores is presented in Table 14.)

Detailed patient information for Study 1131 is provided in Appendix 13.4.2, including participant disposition (Table 44), patient demographics (Table 45), and patient baseline disease characteristics (Table 46).

7.4.3 Study 1131 Efficacy Results

7.4.3.1 Study 1131 Primary Efficacy Results

The LS mean (95% CI) of change in worst leg pain at Week 13 was -37.7 (-41.8, -33.6) vs -39.6 (-46.2, -33.0) for condoliase vs sham injection, respectively (Table 21). The treatment difference (95% CI) between condoliase and sham did not achieve statistical significance: 1.9 (-5.6, 9.4); p=0.6212.

Table 21: Primary Efficacy Analysis: Change from Baseline to Week 13 in Worst Leg Pain — Study 1131 (mITT)

Worst Leg Pain, VAS:	Condoliase (N=280)	Sham (N=94)
Baseline, n	279	93
Mean (SD)	74.4 (14.03)	76.7 (12.82)
Week 13, n	255	88
Change from Baseline		
LS mean (SE) change from Baseline	-37.7 (2.11)	-39.6 (3.36)
(95% CI)	(-41.8, -33.6)	(-46.2, -33.0)
Treatment difference for condoliase vs placebo		
LS mean (SE) treatment difference	1.9 (3.82)	
(95% CI)	(-5.6, 9.4)	
p-value	0.6212	

CI: confidence interval; ITT: intent to treat; LS: least square; SD: standard deviation; SE: standard error; VAS: visual analog scale
1. Mixed model: Change from baseline=baseline score, duration of leg pain (< 90 days vs ≥ 90 days), treatment, week, week*treatment. Unstructured covariance matrix for the correlation of the repeated measures within patient.

7.4.3.2 Study 1131 Learnings

Because results diverged substantially from pivotal Study 1031 and previous clinical studies, the Sponsor conducted additional analyses of Study 1131 parameters and participants to identify causes that may have led to the discrepancies.

Key findings of the analysis included the following:

- The majority of patients in Study 1131 lacked definitive radiological evidence of visible impingement of the nerve root by disc herniation. Importantly, condoliase's mechanism of action (Section 3.3; Figure 18) would be expected to produce meaningful pain relief only in patients whose leg pain is caused by nerve root impingement. Leg pain with etiology other than nerve root compression would not be expected to respond to treatment with condoliase.
- Other confounders:
  - Study 1131 enrolled patients with substantially higher long-term back pain, as compared to Study 1031: VAS (SD)=74.8 (18.8) vs 51.3 (28.8) for Study 1131 vs Study 1031, respectively. This wide discrepancy may have masked changes in worst leg pain.
  - Study 1131's protocol allowed opioid, cannabis, and other prescription analgesics — both before and during the study — which may have confounded results.

Based on the learning from Study 1131, the protocol for Study 1133 was developed with the following refinements to inclusion/exclusion criteria:

- **Included patients with** demonstrable nerve root impingement by definitive appearance of herniation on MRI, as assessed by both the study investigator and an independent third-party central reader
- **Excluded patients with**:
  - Low-back pain caused by disorders other than LDH
  - Baseline back pain that exceeded the severity of leg pain
  - Received opioids or cannabis by any route of administration, or local anesthesia to the back, buttock, or posterior/lateral aspects of the affected leg within 7 days before randomization

A summary of inclusion/exclusion criteria, including demographics and baseline disease characteristics, for Studies 1031, 1131, and 1133 is provided in Table 22.

Table 22: Comparison of Demographics and Disease Characteristics across Clinical Studies

Characteristic:	Study 1031	Study 1131	Study 1133
Characteristics differing across studies			
Age	20 – 70 years	30 – 70 years	30 – 70 years
Current episode	≥ 6 weeks	≥ 6 weeks and ≤ 1 year	≥ 6 weeks and ≤ 1 year
BMI	< 35 kg/m^2	< 35 kg/m^2	< 40 kg/m^2

Characteristic:	Study 1031	Study 1131	Study 1133
Characteristics consistent across studies			
Diagnosis	Patients with lumbar disc herniation assessed by imaging (MRI) with clinical symptoms consistent with the location of the affected nerve root		
Hernia type	Lumbar disc herniation without rupture of the posterior longitudinal ligament		
Hernia site	L4-L5 or L5-S1 (or L5-L6)		
Treatment history	Patients with inadequate improvement in pain caused by LDH despite 6 weeks or more of conservative treatment		
Symptom	Patients with symptoms above criteria of VAS/ODI (Worst leg pain VAS mean score ≥ 50 mm etc)		
Baseline leg pain criteria			
Worst leg pain (VAS)	• Mean score ≥ 50 mm • At least 3 days of scores must be recorded in the 7 days before randomization • Range of fluctuation ≤ 25 mm	• Score ≥ 50 mm at both informed consent and enrollment	• Mean score 50–90 mm • At least 5 days of scores must be recorded in the 7 days before randomization • Range of fluctuation ≤ 25 mm
Worst back pain (VAS)	No limitation	No limitation	Exclusions: • Low back pain caused by disorders other than LDH • Mean score > 90 mm • Mean of worst back pain > 10 mm higher than mean of worst leg pain
ODI	No limitation	≥ 30	≥ 30

BMI: body mass index; LDH: lumbar disc herniation; MRI: magnetic resonance imaging; ODI: Oswestry Disability Index; RCT: randomized, controlled trial; VAS: visual analog scale.

7.5 Study 1133

7.5.1 Study 1133 Design

7.5.1.1 Study 1133 Clinical Design

Study 1133 was a multicenter, randomized, double-blind, sham-controlled, Phase 3 comparative study that investigated the efficacy and safety of condoliase vs sham injection for the treatment of radicular leg pain associated with lumbar disc herniation. Study 1133 was conducted at 60 sites, all within the US, for a duration of 52 weeks.

All eligible patients were randomized 1:1 to either condoliase or sham injection (Figure 5). The randomization was balanced by randomly permuted blocks and stratified by site. The study duration for each patient was approximately 56 weeks in total. There was a screening period of up to 4 weeks, 1 day for treatment administration, and a follow-up period of 52 weeks.

7.5.1.2 Study 1133 Enrollment Criteria

Study 1133 included enrollment requirements to confirm root nerve root impingement, limit severity of underlying comorbid back pain, and restrict use of opioids and other medications. (See Section 7.4.3.2 for discussion of learnings from Study 1131 that informed design of the pivotal Phase 3 Study 1133.)

Eligible patients were males and females 30 to 70 years of age who had confirmed single-level LDH (L4 L5 or L5 S1 or L5 L6) and radicular nerve leg pain corresponding to root nerve root impingement who had shown inadequate improvement with conservative treatment prior to screening.

Enrolled patients had worst leg pain over the past 24 hours at bedtime corresponding to mean VAS scores ≥ 50 mm measured over 7 consecutive days, along with no change in dosage of current concomitant medication being used for pain relief.

Complete inclusion and exclusion criteria implemented in Study 1133 is provided in Appendix 13.5.1.

7.5.1.3 Study 1133 Endpoint Selection

Primary Endpoint: Mean change from baseline in average worst leg pain score at Week 13.

Key Secondary Endpoints:

- Change from baseline in average worst leg pain score at Week 52
- Change from baseline in herniation volume at Week 13
- Change from baseline in ODI score at Week 13

Other prespecified endpoints:

- Worst back pain over the past 24 hours (VAS)
- EuroQol visual analogue scale (EQ VAS)
- 36-item Short Form Health Survey (SF-36) scores
- Negative SLR test (yes/no)
- PGIC
- Incidence of posttreatment surgery for LDH at the same level of condoliase injection

7.5.1.4 Study 1133 Statistical Analysis Plan

Sponsor performed the primary efficacy analysis using both the MI (MNAR) and MMRM (MAR) to ensure interpretability of study results. All secondary and supportive analyses are presented using the FDA-recommended MI (MNAR) analysis. For completeness, MI (MNAR) results are provided in Appendix 13.3.2 (Study 1031) and Appendix 13.5.2 (Study 1133). MI (MNAR) can be problematic with small samples size. Therefore, subgroup analyses are consistently presented using the MMRM (MAR) approach.

(Additional details provided Section 1.5.1.4.)

7.5.2 Study 1133 Patient Disposition, Demographics, and Baseline Disease Characteristics

7.5.2.1 Study 1133 Disposition

Study 1133 enrolled 352 patients, all in the US. Of these patients, 341 patients received at least one dose of the study drug (169 condoliase vs 172 sham; Table 23). Of these, 311 patients completed the Week 13 Visit (156 condoliase vs 155 sham).

Table 23: Patient Disposition — Study 1133 (All Randomized Patients)

Disposition, n (%):	Condoliase (N=176)	Sham (N=176)
Modified ITT Population	169 (96.0)	172 (97.7)
Completed Week 13 Visit	156 (88.6)	155 (88.1)
Completed study	135 (76.7)	130 (73.9)
Discontinued study	41 (23.3)	46 (26.1)
Adverse event	2 (1.1)	2 (1.1)
Lost to follow-up	6 (3.4)	11 (6.3)
Pregnancy	1 (0.6)	0
Lack of efficacy	14 (8.0)	20 (11.4)
Physician decision	2 (1.1)	0
Withdrawal of patient consent	13 (7.4)	8 (4.5)
Protocol violation	1 (0.6)	0
Other	1 (0.6)	3 (1.7)

ITT: intent-to-treat; U: unit
Note: Percentages were based on the number of patients randomized. One patient in the condoliase group of Study 1133 died after all study visits were completed; this death was assessed as not treatment related.

7.5.2.2 Study 1133 Demographics

Patients in Study 1133 were representative of the overall US population expected to benefit from treatment with condoliase, and demographics were balanced between treatment groups (Table 24).

Table 24: Patient Demographics — Study 1133

	Study 1133 (US)	
Demographic, Statistic:	Condoliase (N=169)	Sham (N=172)
Age (years), median	46.0	45.0
Age group, n (%)		
30 – 49 years	105 (62.1)	103 (59.9)
50 – 59 years	42 (24.9)	54 (31.4)
≥ 60 years	22 (13.0)	15 (8.7)

Demographic, Statistic:	Study 1133 (US)	
	Condoliase (N=169)	Sham (N=172)
Sex, n (%)		
Male	95 (56.2)	89 (51.7)
Female	74 (43.8)	83 (48.3)
Race, n (%)		
American Indian or Alaska Native	1 (0.6)	0
Asian	6 (3.6)	9 (5.2)
Black or African American	18 (10.7)	14 (8.1)
White	137 (81.1)	142 (82.6)
Other	7 (4.1)	7 (4.1)
Ethnicity, n (%)		
Hispanic or Latino	47 (27.8)	43 (25.0)
Not Hispanic or Latino	122 (72.2)	129 (75.0)
Height (cm), median	172.7	172.1
Height group, n (%)		
< 170 cm	66 (39.1)	71 (41.3)
≥ 170 cm	103 (60.9)	101 (58.7)
Baseline weight (kg), median	84.8	84.1
BMI (kg/m^2), median	28.41	28.08
BMI category, n (%)		
< 18.5 kg/m^2	0	2 (1.2)
18.5 - < 25.0 kg/m^2	37 (21.9)	41 (23.8)
25.0 - < 35.0 kg/m^2	110 (65.1)	115 (66.9)
≥ 35.0 kg/m^2	22 (13.0)	14 (8.1)
Smoking history, n (%)		
Never smoked	106 (62.7)	103 (59.9)
Past smoker	34 (20.1)	36 (20.9)
Current smoker	29 (17.2)	33 (19.2)

BMI: body mass index; US: United States.

7.5.2.3 *Study 1133 Disease Characteristics*

Baseline disease characteristics of patients in Study 1133 are provided in Table 25.

Table 25: Baseline Disease Characteristics — Study 1133

Baseline Disease Characteristic, Statistic:	Study 1133 (US)	
	Condoliase (N=169)	Sham (N=172)
Occupation, n (%)		
Light labor	130 (76.9)	123 (71.5)
Heavy labor	39 (23.1)	49 (28.5)
Herniation site		
L4 – L5	70 (41.4)	71 (41.3)
L5 – S1	99 (58.6)	101 (58.7)
Days since onset of current radicular leg pain, median	139.0	153.5
VAS pain score for worst leg pain, median	73.14	71.93
VAS pain score for worst back pain, median	62.29	60.75
ODI score, median	48.0	49.0

ODI: Oswestry Disability Index; VAS: visual analog scale.

7.5.3 Study 1133 Efficacy Results

7.5.3.1 Study 1133 Primary Efficacy Results

7.5.3.1.1 Primary Efficacy Analysis — Worst Leg Pain over Past 24 Hours at 13 Weeks

Study 1133 met its primary efficacy endpoint, with condoliase demonstrating a statistically significant decrease in weekly average worst leg pain at Week 13, as compared to sham injection using the FDA-recommended MI (MNAR) analysis (Table 26). The LS mean (SE) treatment difference between condoliase and sham injection was -7.5 (3.28); p=0.0223. The MMRM (MAR) analysis confirmed these results with the same treatment difference (SE) between condoliase and sham: -7.5 (3.35); p=0.0263.

Table 26: Change from Baseline to Week 13 in Worst Leg Pain — Study 1133 (mITT)

	MI (MNAR)		MMRM (MAR)	
Worst Leg Pain, VAS:	**Condoliase (N=169)**	**Sham (N=172)**	**Condoliase (N=169)**	**Sham (N=172)**
Baseline, mean (SD)	72.0 (9.55)	71.8 (9.75)	72.0 (9.55)	71.8 (9.75)
Week 13, LS mean (SE)	30.7 (2.33)	38.2 (2.30)	29.9 (2.38)	37.4 (2.36)
Change in LS means	-41.2 (2.33)	-33.7 (2.30)	-41.7 (2.38)	-34.2 (2.36)
Treatment difference for condoliase vs sham				
Difference in LS means (SE)	-7.5 (3.28)		-7.5 (3.35)	
p-value	0.0223		0.0263	

LS: least squares; MAR: missing at random; MI: multiple imputation; mITT: modified intent to treat; MMRM: mixed model repeated measures; MNAR: missing not at random; SD: standard deviation; SE: standard error; VAS: visual analog scale.

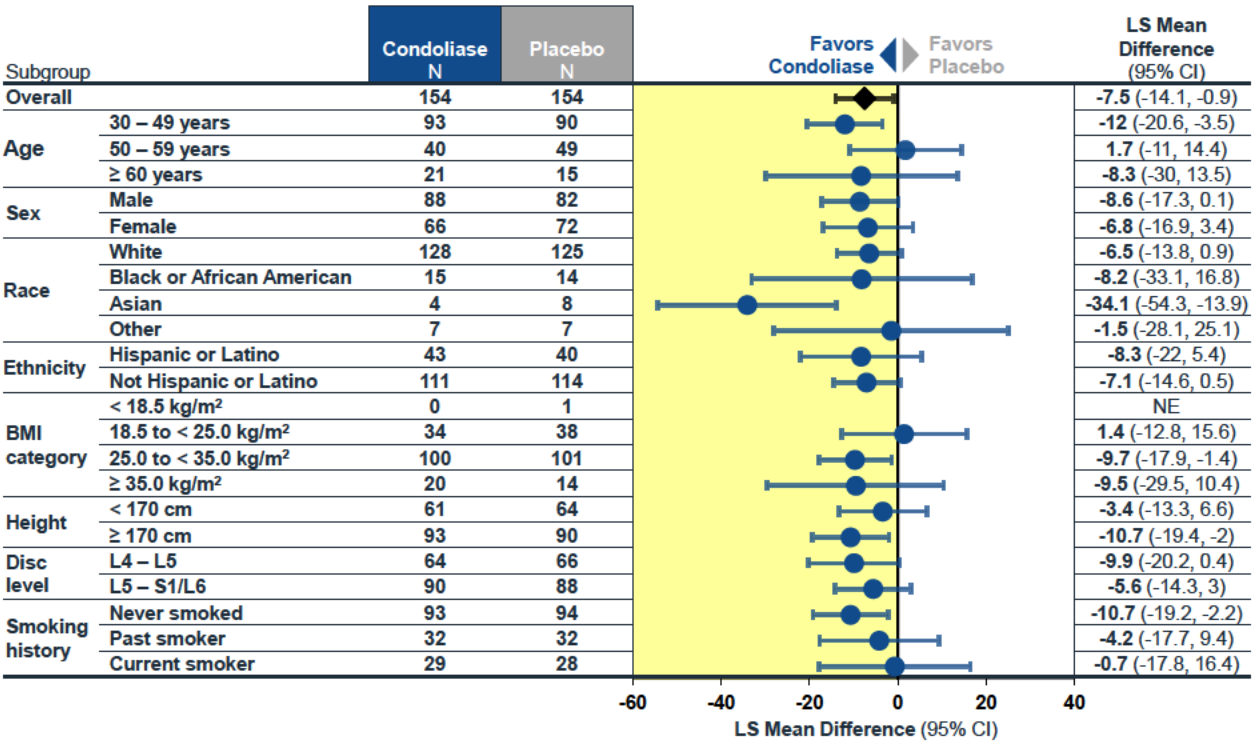
7.5.3.1.2 Additional Analyses of Primary Efficacy

7.5.3.1.2.1 Efficacy in Subgroups — Worst Leg Pain at Week 13 in Subgroups

Subgroup analyses show that single-dose condoliase provides meaningful reductions in leg pain, regardless of patient demographics or baseline disease characteristics.

In 19-of-21 subgroups assessed, patients who received condoliase showed a trend for improvement in weekly average worst leg pain at Week 13 compared to sham, with five subgroups demonstrating statistically significant results (Figure 25).

Figure 25: Forest Plot of Primary Efficacy in Subgroups — Study 1133 (mITT)



BMI: body mass index; CI: confidence interval; LS: least squares; mITT: modified intent to treat; NE: not evaluable.

7.5.3.1.2.2 Responder Analysis — Worst Leg Pain at 13 Weeks

Patients with a ≥ 30% improvement from baseline in worst leg pain were considered responders.

For 30% responders, statistically significant differences in responder rates occurred at Weeks 4 and 6 (Table 27). At all times, numerical treatment differences favored condoliase.

For 50% responders, statistically significant differences in responder rates occurred at Weeks 4 6, 13, and 26. At all times, numerical treatment differences favored condoliase.

Table 27: Responder Analysis for Weekly Average of Worst Leg Pain at Each Time Point — Study 1133 (mITT)

	30% Responders		50% Responders	
Timepoint Statistic, n (%):	Condoliase (N=169)	Sham (N=172)	Condoliase (N=169)	Sham (N=172)
Week 1				
Responder	43 (25.4)	37 (21.5)	23 (13.6)	23 (13.4)
Non-responder	126 (74.6)	135 (78.5)	146 (86.4)	149 (86.6)
Difference (95% CI)	3.9 (-5.1, 12.9)		0.2 (-7.0, 7.5)	
p-value	0.4436		1.000	
Week 2				

Timepoint Statistic, n (%):	30% Responders		50% Responders	
	Condoliase (N=169)	Sham (N=172)	Condoliase (N=169)	Sham (N=172)
Responder	64 (37.9)	50 (29.1)	40 (23.7)	32 (18.6)
Non-responder	105 (62.1)	122 (70.9)	129 (76.3)	140 (81.4)
Difference (95% CI)	8.8 (-1.2, 18.8)		5.1 (-3.6, 13.7)	
p-value	0.0869		0.2890	
Week 4				
Responder	90 (53.3)	71 (41.3)	73 (43.2)	53 (30.8)
Non-responder	79 (46.7)	101 (58.7)	96 (56.8)	119 (69.2)
Difference (95% CI)	12.0 (1.5. 22.5)		12.4 (2.2, 22.5)	
p-value	0.0302		0.0189	
Week 6				
Responder	108 (63.9)	86 (50.0)	86 (50.9)	67 (39.0)
Non-responder	61 (36.1)	86 (50.0)	83 (49.1)	105 (61.0)
Difference (95% CI)	13.9 (3.5, 24.3)		11.9 (1.4, 22.4)	
p-value	0.0118		0.0297	
Week 13				
Responder	114 (67.5)	98 (57.0)	105 (62.1)	84 (48.8)
Non-responder	55 (32.5)	74 (43.0)	64 (37.9)	88 (51.2)
Difference (95% CI)	10.5 (0.2, 20.7)		13.3 (2.8, 23.7)	
p-value	0.0575		0.0165	
Week 26				
Responder	112 (66.3)	97 (56.4)	105 (62.1)	87 (50.6)
Non-responder	57 (33.7)	75 (43.6)	64 (37.9)	85 (49.4)
Difference (95% CI)	9.9 (-0.4, 20.2)		11.5 (1.1, 22.0)	
p-value	0.0751		0.0380	
Week 39				
Responder	111 (65.7)	95 (55.2)	104 (61.5)	89 (51.7)
Non-responder	58 (34.3)	77 (44.8)	65 (38.5)	83 (48.3)
Difference (95% CI)	10.4 (0.1, 20.8)		9.8 (-0.7, 20.3)	
p-value	0.0596		0.0804	
Week 52				
Responder	109 (64.5)	99 (57.6)	107 (63.3)	93 (54.1)
Non-responder	60 (35.5)	73 (42.4)	62 (36.7)	79 (45.9)
Difference (95% CI)	6.9 (-3.4, 17.3)		9.2 (-1.2, 19.6)	
p-value	0.2220		0.0990	

CI: confidence interval.

Timepoint Statistic, n (%):	30% Responders		50% Responders	
	Condoliase (N=169)	Sham (N=172)	Condoliase (N=169)	Sham (N=172)

mITT: modified intent to treat.
Note: Responders are patients with a 30% or 50% improvement from baseline in worst leg pain score. All p-values are based on a Fisher's exact test.

7.5.3.2 Study 1133 — Secondary Efficacy Results

All secondary and supporting endpoints were analyzed by MI (MNAR), as recommended by FDA and agreed by Sponsor as the appropriate method. For completeness, results of the MMRM (MAR) analyses are provided in Appendix 13.5.2. Additional discussion of analysis methods is presented in Section 1.5.1.4.

7.5.3.2.1 Change in Worst Leg Pain through Week 52

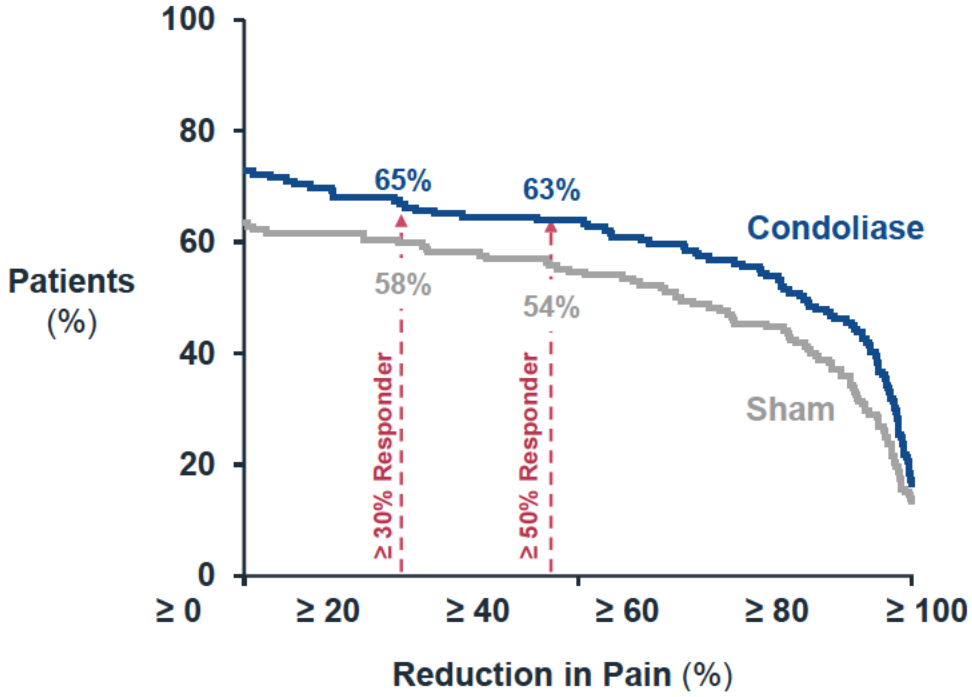
Starting four weeks after treatment, condoliase led to statistically significant reductions in worst leg pain that were reported at each subsequent timepoint and sustained for at least a year (Table 28; Figure 26).

Table 28: Change from Baseline in Weekly Average Worst Leg Pain at Each Time Point through Week 52 — Study 1133 (mITT)

Visit:	Difference in LS Means Compared to Placebo (95% CI)	p-value (Nominal)
Week 1	-1.7 (-5.8, 2.4)	0.4081
Week 2	-3.9 (-8.9, 1.1)	0.1243
Week 4	-5.9 (-11.7, -0.2)	0.0420
Week 6	-7.6 (-13.5, -1.8)	0.0109
Week 13	-7.5 (-13.9, -1.1)	0.0223
Week 26	-8.5 (-15.0, -2.0)	0.0109
Week 39	-6.8 (-13.3, -0.2)	0.0426
Week 52	-6.9 (-13.5, -0.2)	0.0433

CI: confidence interval; LS: least squares; mITT: Modified Intent to Treat.

Figure 26: Cumulative Distribution of Percent Reductions in Weekly Averages of Worst Leg Pain from Baseline to Week 52 — Study 1133 (mITT)

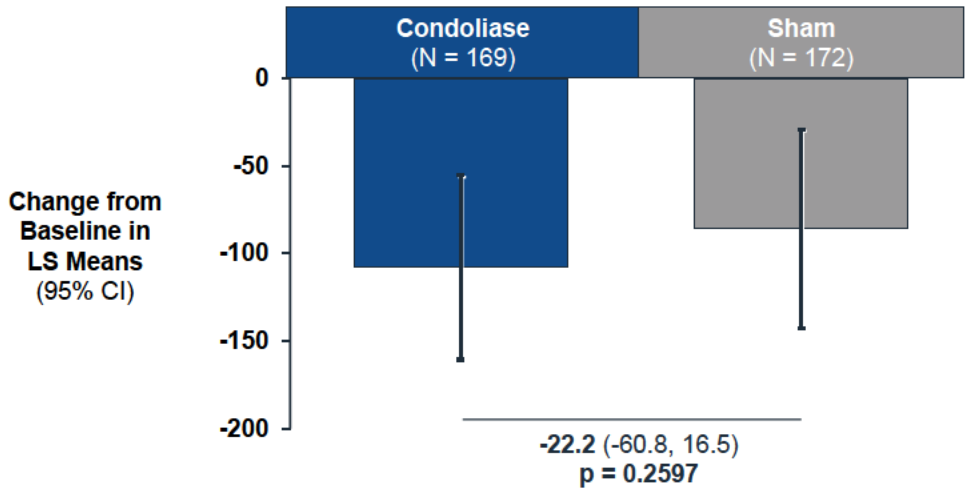


mITT: modified intent to treat.

7.5.3.2.2 Change in Herniation Volume at Week 13

On the key secondary endpoint change from baseline in herniation volume at Week 13, condoliase showed a trend for improvement over sham, but results were not statistically significant (p=0.2597; Figure 27).

Figure 27: Change from Baseline in Disc Herniation Volume at Week 13 — Study 1133 (mITT)



CI: confidence interval; LS: least squares; mITT: modified intent to treat.

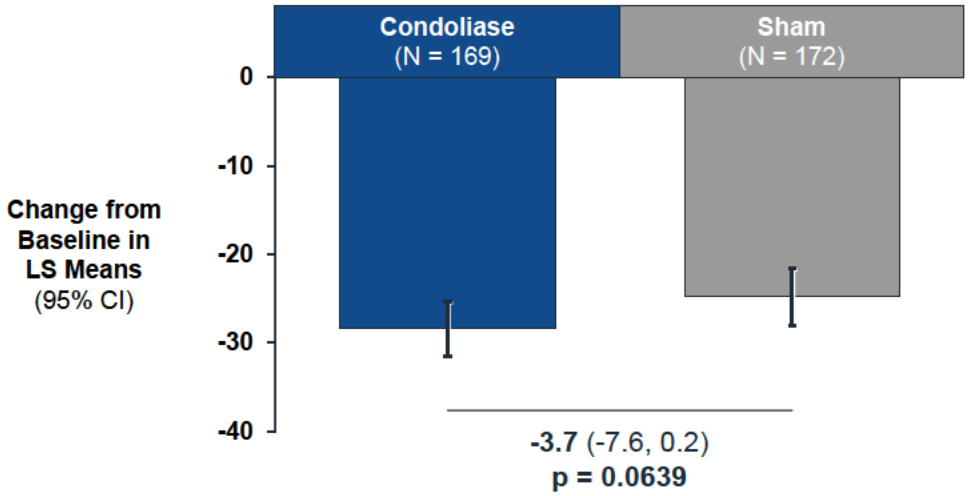
7.5.3.2.3 Change in Oswestry Disability Index

Change in ODI at Week 13

On the secondary endpoint of change in Oswestry Disability Index at Week 13, condoliase showed a trend for improvement over sham, but results were not statistically significant (p=0.0639; Figure 28).

Higher numbers reflect greater disability, and the maximum score is 50 points, with responses ranging from 0 to 5 points on each of 10 questions. (Additional details on the ODI are provided in Section 7.1.3; an example ODI questionnaire is provided in Appendix 13.7.)

Figure 28: Change from Baseline in ODI Score at Week 13 — Study 1133 (mITT)

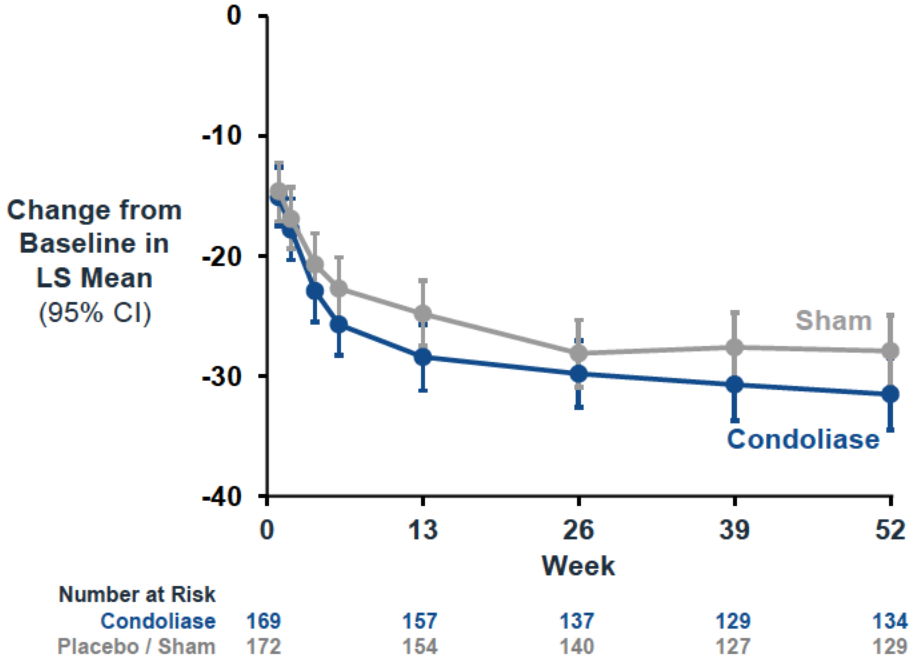


CI: confidence interval; LS: least squares; mITT: modified intent to treat; ODI: Oswestry Disability Index.

Change in ODI over Time, through Week 52

At Week 52, the LS mean change from baseline in ODI score was -31.5 (95% CI: -34.5, -28.5) for condoliase vs -27.9 (95% CI: -30.9, -24.9) for sham control. The LS means treatment group difference from sham was -3.6 (95% CI: -7.8, 0.6; p=0.0965) (Figure 29).

Figure 29: Change from Baseline in ODI over Time through Week 52 — Study 1133 (mITT)



CI: confidence interval; LS: least-squares; mITT: modified intent to treat; ODI: Oswestry Disability Index.

7.5.3.2.4 Patient Global Impression of Change (PGIC) at Week 13

Table 29 presents a summary of patient responses at Week 13 to their own perceptions of how well they had responded to treatment with condoliase or sham. A statistically significant greater proportion of patients (p=0.0103) treated with condoliase reported "very much improved" or "much improved" pain than sham, supporting the efficacy of condoliase in reducing radicular leg pain associated with nerve root impingement.

Table 29: Patient Global Impression of Change (PGIC) and Responder Analysis at Week 13 — Study 1133 (mITT)

PGIC, n (%):	Condoliase (N=169)	Sham (N=172)
Patient response		
Very much improved	57 (33.7)	38 (22.1)
Much improved	46 (27.2)	43 (25.0)
Minimally improved	32 (18.9)	37 (21.5)
No change	12 (7.1)	18 (10.5)
Minimally worse	6 (3.6)	12 (7.0)
Much worse	4 (2.4)	4 (2.3)
Very much worse	0	2 (1.2)
Missing	12 (7.1)	18 (10.5)
Responder analysis[1]		
Responder	103 (60.9)	81 (47.1)
Non-responder	66 (39.1)	91 (52.9)
Difference (95% CI)[2]	13.9% (3.4%, 24.3%)	
p-value for difference[2]	0.0103	

CI: confidence interval; mITT: modified intent to treat; PGIC=patient global impression of change.
1. Responders are those who reported "very much improved" or "much improved;" all other responses (including missing) were counted as non-responders.
2. Wald confidence interval is reported; p-value is based on the difference in proportions in proportions z test (identical to the Pearson chi-squared test).

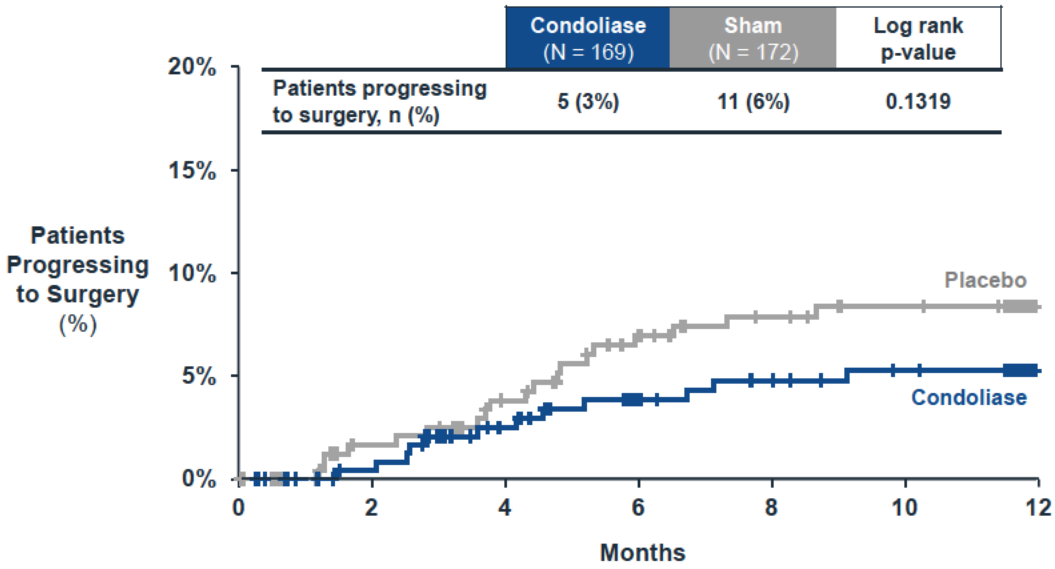
7.6 Rates of Surgery from Study 1133 and Survey of 1021 and 1031

In Study 1133, the incidence of post-treatment surgery for LDH at the same disc level of condoliase or sham group were recorded up to 52 weeks. Patients were less likely to undergo surgery for LDH a year after treatment with condoliase vs sham: 5/169 (3.0%) vs 11/172 (6.4%) patients progressed to surgery at any time during the year after condoliase vs sham, respectively (Kim et al, 2024) (Figure 30).

Additionally, a long-term follow-up survey of patients from studies 1021 and 1031 recorded incidence of post-treatment surgery for LDH at the same level of condoliase or placebo group. This long-term comparison of surgical rates among patients who participated in clinical trials in Japan (Studies 1021 or 1031) showed condoliase reduced rate of surgery by approximately half. Among patients treated with the 1.25 U dose in Japan, 10.8% vs 20.7% of condoliase-treated patients vs placebo had surgery for LDH (p=0.0448), with a median follow-up duration of

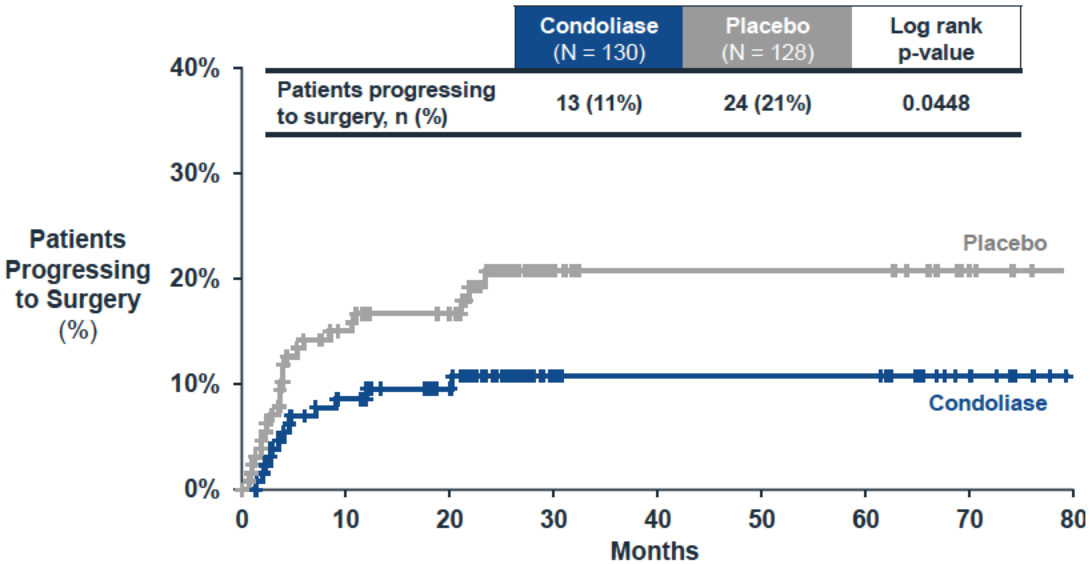
2 years for Study 1031 patients and 5 years for Study 1021 patients (Figure 31). Limitations of this survey include non-randomized follow-up, and heterogeneous patient cohort. (Matsuyama et al, 2023).

Figure 30: Time to Surgery during First Year after Injection with Condoliase vs Sham — Study 1133 (mITT)



mITT: Modified Intent to Treat.

Figure 31: Time to Surgery up to 5 Years after Injection with Condoliase Placebo (Published Results of Follow-up Survey to Clinical Trials in Japan)



Source: Adapted from Matsuyama, Seo, & Chiba (2023); Supplemental Figure 2.

7.7 Persistence of Efficacy and/or Tolerance Effects

Condoliase was shown to decrease worst leg pain by Week 13; furthermore, there was no worsening of leg pain after Week 13, and the treatment differences were maintained through Week 52. For Studies 1031 and 1133, statistically significant demonstrations of decreasing worst leg pain ended by Week 26, using the primary analysis method (MMRM [MAR]). However, statistical significance in decreased worst leg pain continued through Week 52 using the sensitivity analysis method (MI [MNAR]).

Together, these data demonstrate the persistence of efficacy, which remains sustained over long-term periods. There are no known indications of tolerance effects, as condoliase is proposed as a single injection.

7.8 Summary of Efficacy and Conclusions

Results from the condoliase program demonstrated that, in patients with LDH, treatment with 1.25 U administered as a single intradiscal injection significantly reduced radicular leg pain associated with LDH compared with control (placebo or sham).

Pivotal Studies 1133 and 1031 met the criteria for adequate and well-controlled as defined in the CFR, title 21, section 314.126. Statistically significant results favored treatment with condoliase vs control for the treatment of LDH. This was demonstrated in both Pivotal Phase 3 studies, based on the primary efficacy endpoint of change from baseline in average worst leg pain at Week 13. Results were consistent, regardless of both the statistical analysis methods used or patient subgroup population. Efficacy was further supported for each study by the results of other secondary analyses at Week 13 and Week 52.

These clinical efficacy results were consistently supported by other prespecified endpoints that measure response to treatment (50% responder, SLR, PGIC) or quality of life measures. These measures were either nominally statistically significant or favored condoliase therapy (Figure 16).

In conclusion, these data support that single dose of 1.25 U condoliase is effective as a treatment for radicular leg pain associated with LDH.

8 SIMILARITY OF LDH EPIDEMIOLOGY, CLINICAL PRESENTATION, AND TREATMENT IN US AND JAPAN

8.1 LDH Disease Epidemiology, Clinical Presentation, and Diagnosis Comparable in US and Japan

Lumbar disc herniation is diagnosed and treated similarly throughout the developed world, based on the following 4 characteristics: epidemiology, clinical symptomatology, diagnostic criteria, and methods of treatment.

Although the prevalence of lumbar disc herniation in the general population has not been reported, this information can be deduced from the results of studies in patients who have visited medical institutions and undergone treatment (Haro et al, 2022). For example, a study in the United Kingdom has analyzed 390 patients who underwent surgery after dividing them into age-based groups. Of 233 cases (59.7%) in young patients aged 25–45 years, 97% had herniation at L4/5 or L5/S. Meanwhile, 29 cases (7.4%) were in patients aged ≥ 65 years; among them, the male-female ratio was 1:1, only 12 cases (40%) were herniation of the L4/5 or L5/S disc, and more than half had upper levels of lumbar disc herniation (Haro et al, 2022). An analysis of 1,431 cases from the Netherlands has shown a relationship between the affected level and mean age; mean patient ages in cases of herniation at L2-3, L3-4, L4-5, and L5-S1 were 59.6, 59.5, 49.5, and 44.1 years, respectively, showing that lumbar disc herniation at upper levels than L4/5 increased with age (Haro et al, 2022). A longitudinal observation study from Norway (described in Section 2.2) reported an average of 50 lumbar disc operations per 100,000 Norwegian residents throughout the course of the study (Fjeld et al, 2019). A study in 15,631 cases registered with a surgery case registration system in Sweden has reported that about 20 surgeries per 100,000 population were performed annually in Sweden between 2000 and 2010 (Strömqvist et al, 2016) and a report from the US has estimated that lumbar disc herniation affects about 1% of the population, 2.8 million people annually (Haro et al, 2022).

When comparing the US and Japan, specifically, the prevalence of LDH is approximately 1% of the population in both countries, with the onset of LDH being about 40 years of age. Surgical intervention is slightly more common in patients between 20 and 40 years of age (Table 6). Lumbar disc herniation is seen more often in men than women in both countries, with slightly larger male predominance in Japan (3.3 to 1 versus 1.75 to 1; Kirita, 1975; Davis, 1994). Men are also more likely to undergo surgical treatment. The most commonly affected vertebral levels are L4-L5 and L5-S1. Not surprisingly, the most common symptoms are consistent and include low back pain, radiating or radicular leg pain, and sciatica, along with bowel and bladder dysfunction.

8.2 Standard of Care Comparable in US and Japan

The same diagnostic criteria are used to diagnose LDH in most industrialized countries (including Japan and the US) and include detailed history, neurological exam for motor and sensory abnormalities, SLR test, and imaging (Section 2.1.3), including MRI and/or CT/CT myelography (Table 7). A similar approach is taken in both countries with conservative treatment. This includes the use of analgesic agents, NSAIDs, and nerve or epidural blocks. While progression to surgery is on the order of twice as common in the US (National Database of Health Insurance Claims and Specific Health Checkups of Japan Ministry of Health, Labour and Welfare, 2022; Al Qaraghli, 2023) compared to Japan, surgical approaches are similar

between the countries and include discectomy and nucleotomy. Key references for these comparisons include The Clinical Practice Guideline on the Management of LDH (Haro et al, 2022), which globally reviewed the studies in patients who visited medical institutions or patients who underwent surgery for LDH and summarized epidemiological characteristics of Japan, as well as the US and Diagnosis and Treatment of LDH with Radiculopathy 2012 by NASS (Kreiner et al, 2012).

Based on these factors, the Sponsor believes that data collected from studies conducted in Japan can be extrapolated to the US population. The general difference in body size between Japan and the US is likely to be reflected in hernia patients, but the impact of this difference is discussed based on the results in the submission.

8.3 Comparable Demographics and Disease Characteristics in Enrolled US and Japan Patients

Similar percentages of patients comprised the treated and mITT Population between Study 1031 (Japan) and Study 1133 (US), as well as the percentage of patients who completed the Week 13 visit and completed the study overall. A similar percentage of patients discontinued from the study in the Japanese and US studies, and the reasons for discontinuation including death, pregnancy, lack of efficacy, physician decision, withdrawal of patient consent, protocol violation, and Sponsor decision were similar between the studies, as well. The reasons for discontinuation that occurred at a 1.5-fold higher rate between Study 1031 and Study 1133 were AE (3.0% for Study 1031 and 1.1% for Study 1133, respectively), lost to follow-up (0% and 4.8%, respectively), and “other” (7.2% and 1.1%, respectively).

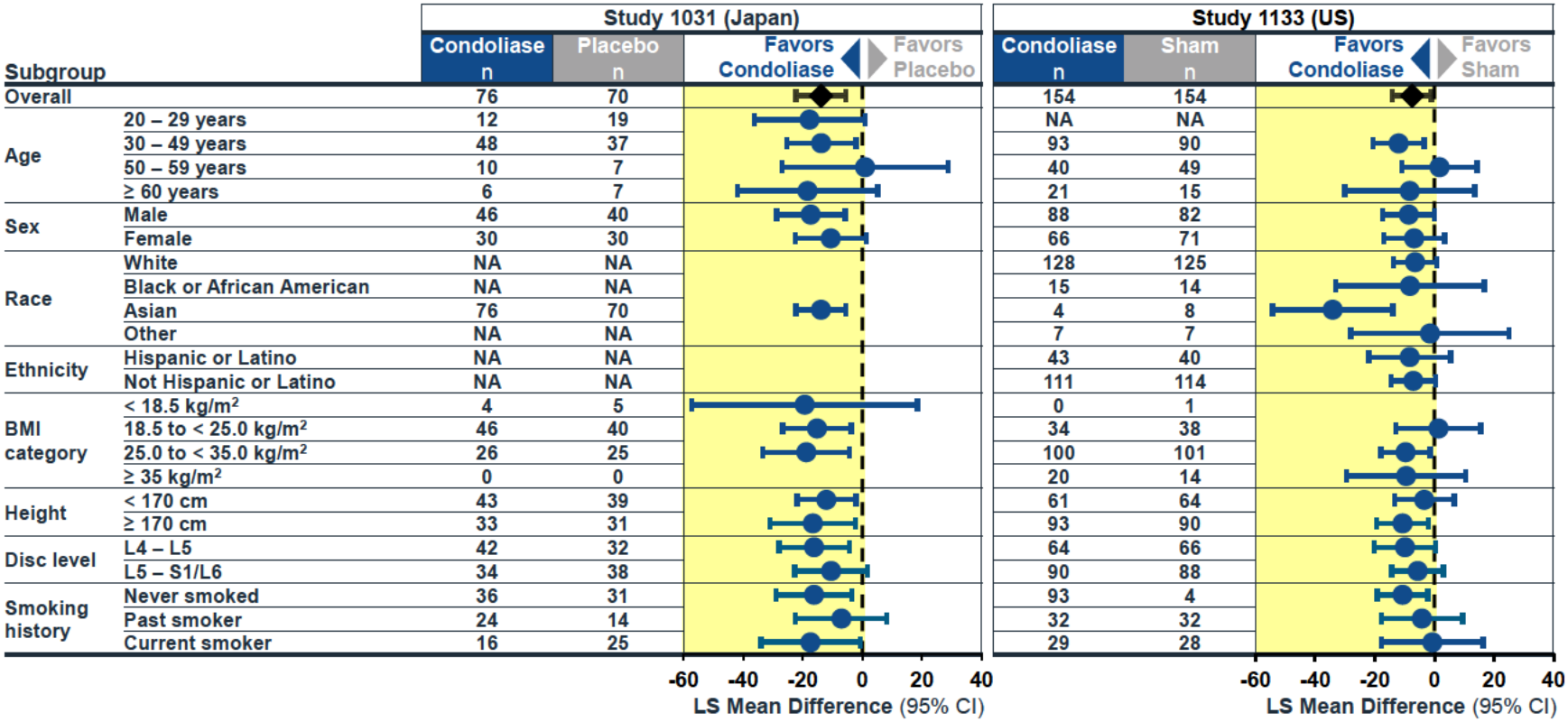
Regarding demographics and other baseline characteristics (Table 2, Table 3), none of the differences between patients in Study 1031 or 1133 were expected to or found to impact the efficacy of condoliase.

8.4 Efficacy Results from Studies Conducted in Japan Applicable to US Population

Efficacy data from Japanese patients in Study 1031 can be extrapolated to the US population based on the relevant comparisons described below.

Study 1133 and Study 1031 demographics (Table 2) and baseline disease characteristics (Table 3) were similar and representative of the overall population with radicular leg pain caused by nerve root impingement from LDH (Section 1.5.2.2). Comparison of primary efficacy results by subgroup shows that condoliase benefits patients in the proposed indication, regardless of age, sex, race/ethnicity, BMI, height, herniation location, or smoking history (Figure 32).

Figure 32: Comparison of Primary Efficacy Results in Subgroups — Pivotal Phase 3 Studies (mITT)



BMI: body-mass index; CI: confidence interval; LS: least squares; mITT: modified intent to treat; NA: not applicable.

As noted, Study 1031 was conducted in Japan, while Study 1133 was conducted in the US. Study 1031 met the criteria for adequate and well-controlled as defined in the CFR, title 21, section 314.126. There were no significant differences between the US population and non-US population that may have affected the efficacy profile of condoliase. In accordance with the International Conference for Harmonisation E5 guidance Ethnic Factors in the Acceptability of Foreign Clinical Data and as advised by the Agency at the End-of-Phase 2 meeting and presented in the Type B Pre-BLA Meeting briefing package, the following data were evaluated to demonstrate consistency between the study populations:

- Because plasma concentrations are undetectable, PK comparisons are not possible. Therefore, Sponsor examined serum concentration of keratan sulfate, which is considered to be a key component of nucleus pulposus tissue.
- The medical care setting, including standards of medical care and standards of supportive care, are not different between US and Japanese hospitals.

9 CLINICAL SAFETY

Summary

- The primary safety analysis of all patients from four Phase 2 and 3 randomized, controlled studies included 578 patients who received condoliase and 396 patients who received placebo/sham.
- Condoliase was well-tolerated with an acceptable safety profile from a single administration for patients with radicular leg pain associated with LDH.
- The incidence of serious AEs reported for the condoliase group and placebo/sham control group was similar across all time intervals.
- The safety profile observed in the clinical trials is supported by postmarketing surveillance and clinical use of condoliase in approximately 27,000 patients.

9.1 Safety Exposures

A total of 1,679 unique patients have been treated with condoliase in 6 completed clinical studies (1031, 1133, 1131, 1021, 1121, 1132).

To ensure sufficient capture of potential AEs of concern, agreement was reached with the FDA to obtain a total of 1,500 patients exposed to a single dose of study drug, where 1000 patients must be followed for 6-months, 300 patients for 1-year, and 150 patients for 2-years.

The number of condoliase exposed patients in the Safety Population was summarized by study and follow-up time. This summary was for all studies in the Secondary Safety Pool and included counts of exposed patients to condoliase at any dose group ≥ 1.25 U. The counts were presented overall and also for the number of exposed patients by follow-up times: ≥ 26 weeks, ≥ 52 weeks, and ≥ 104 weeks. The cut-off for ≥ 104 weeks was based on whether Study 1131 patients completed the Week 104 visit.

A total of 1679 patients were exposed to condoliase (≥ 1.25 U; Table 30). Of these, 1,301 patients were followed for ≥ 26 weeks, 438 patients were followed for ≥ 52 weeks, and 204 patients were followed for ≥ 104 weeks.

Table 30: Exposures to Condoliase ≥ 1.25 U and Follow-up Durations in Clinical Studies

Study/Phase (Country):	Study Design (Control)	Number Exposed	Number with Follow-up Duration	
			≥ 26 Weeks	≥ 52 Weeks
Study 1121/Phase 2 (US)	Open-label (n/a)	12	-	-
Study 1021/Phase 2/3 (Japan)	Double-blind (placebo)	147	-	-
Study 1031/Phase 3 (Japan)	Double-blind (placebo)	82	-	-
Study 1131/Phase 3 (US)	Double-blind (sham injection)	280	253	231

Study/Phase (Country):	Study Design (Control)	Number Exposed	Number with Follow-up Duration	
			≥ 26 Weeks	≥ 52 Weeks
Study 1132/Phase 3 (US & Europe)	Open-label (n/a)	991	703	-
Study 1133/Phase 3 (US)	Double-blind (sham injection)	167	145	95
Total	-	1,679	1,101	326
FDA Requirement	-	1,500	1,000	300

FDA: Food and Drug Administration; n/a: not applicable.
Note: For ≥ 26 and ≥ 52 weeks follow-up categories, only studies with full safety monitoring are included (Studies 1131, 1132, and 1133).

9.2 Primary Safety Dataset: Pooled Phase 2/3 RCTs (Studies 1031, 1133, 1131, 1021)

The condoliase safety profile is represented by the Pooled Phase 2/3 RCT Safety dataset. This pool consists of all patients from Phase 2 and Phase 3 randomized, controlled studies (1031, 1133, 1131, 1021). Because Study 1021 included treatment groups with dose levels of 2.5 and 5 U, those treatment groups were pooled and summarized as dose group > 1.25 U.

9.3 Safety Reporting from Pooled Phase 2/3 RCTs (Studies 1031, 1133, 1131, 1021)

In all studies, full safety monitoring data were collected up to Week 13 of the study. After Week 13, all studies continued collecting SAEs and AEs related to the disc and surrounding areas — AEs evaluated included leg pain, back pain, and other AEs related to neurological tests or the stability of the intervertebral disc and its surrounding tissues. Study 1131 collected all AEs through Week 104.

(The AE collection windows for each study are provided in Table 8, Section 1.6.1.)

9.4 Overall Safety

Most AEs were mild or moderate in severity, and rates of SAEs were consistent among patients who received condoliase vs sham/placebo controls (Table 31).

During each study interval (ie, Baseline to Week 13, Weeks 13 to 26, and Weeks 26 to 52), rates of patients with any AE were similar between treatment groups. Importantly, rates of serious and severe AEs were both low and consistent across treatment groups over time. Two patients who received condoliase vs one control died during the study period. No death was considered as related to study treatment.

Table 31: Summary of Adverse Events (Pooled Phase 2/3 RCT Safety)

Patients with, n (%):	Day 0 to Week 13		> 13 to 26 Weeks		> 26 to 52 Weeks	
	Condoliase (N=578)	Control (N=396)	Condoliase (N=421)	Control (N=252)	Condoliase (N=388)	Control (N=233)
Any AE	381 (65.9)	215 (54.3)	94 (22.3)	41 (16.3)	113 (29.1)	67 (28.8)
Mild	191 (33.0)	110 (27.8)	57 (13.5)	22 (8.7)	70 (18.0)	42 (18.0)
Moderate	157 (27.2)	86 (21.7)	28 (6.7)	12 (4.8)	35 (9.0)	21 (9.0)
Severe[a]	33 (5.7)	19 (4.8)	9 (2.1)	7 (2.8)	8 (2.1)	4 (1.7)

Patients with, n (%):	Day 0 to Week 13		> 13 to 26 Weeks		> 26 to 52 Weeks	
	Condoliase (N=578)	Control (N=396)	Condoliase (N=421)	Control (N=252)	Condoliase (N=388)	Control (N=233)
AE leading to study discontinuation	3 (0.5)	9 (2.3)	3 (0.7)	2 (0.8)	0	1 (0.4)
Treatment-related	8 (2.1)	4 (2.7)	6 (1.4)	2 (0.8)	11 (2.8)	3 (1.3)
Any SAE	15 (2.6)	13 (3.3)	9 (1.7)	6 (1.7)	14 (2.8)	6 (1.8)
Treatment-related	1 (0.2)	0	0	0	0	0
Death	0	0	1 (0.2)	1 (0.4)	1 (0.3)	0
Treatment-related	0	0	0	0	0	0

AE: adverse event; RCT: randomized, controlled trial; SAE: serious AE.
Note: For Any rows (serious or non-serious events), after Week 13 to Week 26 and after Week 26 to Week 52 includes only studies 1131 and 1133 in both numerator and denominator of patients at risk.
a. Patients are reported once at the highest severity. Missing severity is imputed as Severe.
Note: Up to Week 13 includes any AEs that start up until study day 98, inclusive. Percentages based on Safety Population. After Week 13 to Week 26 includes any AEs that start between study day 99 and study day 189, inclusive. Percentages are based on patients who were still in the study up until the start of the interval. After Week 26 to Week 52 includes any AEs that start between study day 190 and study day 379, inclusive. Percentages are based on patients who were still in the study up until the start of the interval. Control includes placebo and sham injections.

9.5 Common Adverse Events

Table 32 presents an overview of AEs by PT that were reported in ≥ 2% of patients in any treatment group at all time intervals in the Pooled Phase 2/3 RCT Safety. Up to Week 13, the most common (> 10% of patients) AEs in the condoliase group were back pain, MRI spinal abnormal, and pain in extremity. Back pain, the most commonly reported PT, was reported as first occurring for a greater percentage of patients in the condoliase group compared with the placebo/sham control at ≤ 1 day (7.4% [43 patients] and 3.8% [15 patients], respectively) or 2 to 7 days (7.3% [42 patients] and 2.3% [9 patients], respectively) postinjection; however, this difference did not persist to 8 days to 13 weeks (8.3% [48 patients] and 8.8% [35 patients]) or > 13 weeks (3.5% [20 patients] and 5.8% [23 patients]) post injection.

After Week 13 to Week 26 the most common (≥ 2% of patients) PTs of AEs in the condoliase group were MRI spinal abnormal and spinal X-ray abnormal, and after Week 26 to Week 52 the most common (>2% of patients) PTs of AEs in the condoliase group were MRI spinal abnormal, spinal X-ray abnormal, and back pain.

Table 32: Most Common Adverse Events (≥ 2% of Patients in Any Group), by Preferred Term (Pooled Phase 2/3 RCT Safety)

Patients with, n (%):	Baseline to Week 13		Week 13 to Week 26		Week 26 to Week 52	
	Condoliase (N=578)	Control (N=396)	Condoliase (N=421)	Control (N=252)	Condoliase (N=388)	Control (N=233)
Any AE	381 (65.9)	215 (54.3)	94 (22.3)	41 (16.3)	113 (29.1)	67 (28.8)
Back Pain	133 (23.0)	59 (14.9)	4 (1.0)	7 (2.8)	9 (2.3)	7 (3.0)
Spinal MRI abnormality	107 (18.5)	12 (3.0)	17 (4.0)	3 (1.2)	29 (7.5)	10 (4.3)
Pain in extremity	65 (11.2)	48 (12.1)	5 (1.2)	3 (1.2)	4 (1.0)	3 (1.3)

Patients with, n (%):	Baseline to Week 13		Week 13 to Week 26		Week 26 to Week 52	
	Condoliase (N=578)	Control (N=396)	Condoliase (N=421)	Control (N=252)	Condoliase (N=388)	Control (N=233)
Nasopharyngitis	34 (5.9)	16 (4.0)	2 (0.5)	2 (0.8)	2 (0.5)	5 (2.1)
Spinal X-ray abnormality	29 (5.0)	7 (1.8)	10 (2.4)	1 (0.4)	11 (2.8)	1 (0.4)
Injection site pain	27 (4.7)	16 (4.0)	0	0	0	0
Arthralgia	24 (4.2)	12 (3.0)	4 (1.0)	2 (0.8)	4 (1.0)	7 (3.0)
CRP increased	16 (2.8)	9 (2.3)	1 (0.2)	0	0	0
Headache	13 (2.2)	11 (2.8)	2 (0.5)	1 (0.4)	2 (0.5)	0
Hypoesthesia	13 (2.2)	11 (2.8)	1 (0.2)	1 (0.4)	0	1 (0.4)
Sciatica	11 (1.9)	9 (2.3)	2 (0.5)	1 (0.4)	1 (0.3)	3 (1.3)
Nausea	9 (1.6)	8 (2.0)	1 (0.2)	1 (0.4)	0	0
Blood triglycerides increased	5 (0.9)	8 (2.0)	0	0	0	0
Neutrophil count decreased	5 (0.9)	8 (2.0)	0	0	0	0
Pyrexia	4 (0.7)	9 (2.3)	0	0	1 (0.3)	0
COVID-19	5 (0.9)	5 (1.3)	4 (1.0)	4 (1.6)	3 (0.8)	8 (3.4)

AE: adverse event; MRI: magnetic resonance imaging; RCT: randomized, controlled trial.
Note: AEs were defined as adverse events that begin or that worsen in severity after the investigational drug has been administered. In system organ class and preferred term summarization, a patient was counted once if he/she reported one or more events. Adverse events were classified according to MedDRA version 24.0. Percentages are based on patients who were still in the study up until the start of the interval. Control includes placebo and sham injections.

9.6 Severe Adverse Events

Across treatment groups and time periods, the majority of AEs were similar and mild or moderate in severity (Table 33). Rates of severe AEs were similar between treatment groups over time.

Table 33: Summary of Severe AEs Affecting ≥ 0.5% in Either Treatment Group, by Preferred Term (Pooled Phase 2/3 RCT Safety)

Severe AE, n (%):	Baseline to Week 13		Week 13 to Week 26		Week 26 to Week 52	
	Condoliase (N=578)	Control (N=396)	Condoliase (N=421)	Control (N=252)	Condoliase (N=388)	Control (N=233)
Patients with any severe AE	33 (5.7)	19 (4.8)	9 (2.1)	7 (2.8)	8 (2.1)	4 (1.7)
Back pain	9 (1.6)	3 (0.8)	1 (0.2)	1 (0.4)	0	1 (0.4)
Pain in extremity	6 (1.0)	2 (0.5)	1 (0.2)	1 (0.4)	1 (0.3)	0
Intervertebral disc protrusion	1 (0.2)	3 (0.8)	2 (0.5)	2 (0.8)	2 (0.5)	0
Presyncope	0	2 (0.5)	0	0	0	0
Sciatica	0	2 (0.5)	0	0	0	0

Severe AE, n (%):	Baseline to Week 13		Week 13 to Week 26		Week 26 to Week 52	
	Condoliase (N=578)	Control (N=396)	Condoliase (N=421)	Control (N=252)	Condoliase (N=388)	Control (N=233)

AE: adverse event; RCT: randomized, controlled trial\.
Note: AEs were defined as adverse events that begin or that worsen in severity after the investigational drug has been administered. In system organ class and preferred term summarization, a patient was counted once if he/she reported one or more events. Adverse events were classified according to MedDRA version 24.0. Percentages are based on patients who were still in the study up until the start of the interval. Control includes placebo and sham injections.

9.7 Serious Adverse Events

Across all treatment groups and time periods, the rates of SAEs were low and consistent between treatment groups (Table 34). Over the full 52-Week study period, only one SAE was considered related to treatment: one patient in the condoliase group reported a single event of serious back pain, which occurred before Week 13. A complete list of all SAEs up to Week 52 is provided in Appendix 13.8.1.

Table 34: Summary of Most Common SAEs (≥ 2 Events in Any Group), by Preferred Term (Pooled Phase 2/3 RCT Safety)

SAE, n (%):	Baseline to Week 13		Week 13 to Week 26		Week 26 to Week 52	
	Condoliase (N=578)	Control (N=396)	Condoliase (N= 538)	Control (N=359)	Condoliase (N=493)	Control (N=333)
Any SAE	15 (2.6)	13 (3.3)	9 (1.7)	6 (1.7)	14 (2.8)	6 (1.8)
Back pain	2 (0.3)	0	0	0	0	1 (0.3)
Intervertebral disc protrusion	2 (0.3)	3 (0.8)	2 (0.4)	2 (0.6)	2 (0.4)	0
Lumbar radiculopathy	2 (0.3)	0	0	0	0	0
Pain in extremity	0	2 (0.5)	0	0	0	0
Sciatica	0	2 (0.5)	0	0	0	0

RCT: randomized, controlled trial; SAE: serious adverse event.
Note: Adverse events were defined as adverse events that begin or that worsen in severity after the investigational drug has been administered. In system organ class and preferred term summarization, a patient was counted once if he/she reported one or more events. Adverse events were classified according to MedDRA version 24.0. Percentages are based on patients who were still in the study up until the start of the interval. Control includes placebo and sham injections.

9.8 Safety Topics of Interest

Prespecified safety topics of interest were events that warranted additional investigations due to identified or potential risk. Queries to identify these Safety Topics of Interest were agreed to with FDA. See Appendix 13.8.4 for a list of Safety Topics of Interest search criteria. Rationale for Safety Topics of Interest is described below:

- Because protein-based drugs are known to carry risks for anaphylaxis and hypersensitivity, these conditions were investigated.
- A comprehensive search of spinal abnormalities potentially related to the mechanism of action of chemonucleolysis was undertaken.

- Discitis, osteomyelitis, and hematoma were investigated to better characterize these potential/identified procedural risks.
- While condoliase is highly specific for the nucleus pulposus, paresis and paralysis were searched for potential off target effects
- For any new medication, it is important to characterize the potential risks of medication errors.

For the Pooled Phase 2/3 RCT Safety, all Safety Topics of Interest were summarized. All time intervals together were considered, and percentages were unadjusted for study size.

9.8.1 Discitis, Osteomyelitis, Paresis, Paralysis, and Medication Errors

The following categories were identified through customized queries and had an incidence of only 1 event or 0 events:

- One event (0.2%) for discitis and one event (0.2%) for osteomyelitis was reported in the same patient and classified as an SAE in the condoliase group. No events were reported for patients in the placebo/sham control. One event (0.2%) for hematoma was reported for one patient in the condoliase group, with no events reported for placebo/sham control.
- No events of paresis or paralysis were reported in either treatment group.
- One event (0.2%) for medication error was reported in the condoliase group vs none for placebo/sham control. It is noted that two additional cases were identified through manual review of protocol deviations, one in condoliase group and one in placebo/sham control.

9.8.2 Spinal Abnormality

Spinal Abnormality AEs were identified through a customized query designed to capture events that could potentially be linked to the mechanism of action. In the Pooled Phase 2/3 RCT Safety, the incidence of spinal abnormality AEs was 0.9% (5 patients) vs 1.3% (5 patients) for the condoliase vs placebo/sham control groups, respectively (Table 11). The only PT reported for > 1 patient in the condoliase group was spinal osteoarthritis: 3 (0.5%) vs 1 (0.3%) for condoliase vs control. Two patients in the placebo/sham control group reported a serious event (spinal osteoarthritis and vertebral foraminal stenosis). Most events occurred more than 13 weeks after injection.

9.8.3 Hypersensitivity

Hypersensitivity related AEs were identified through SMQs. For the Pooled Phase 2/3 RCT Safety, the overall incidence of events from Hypersensitivity SMQ-narrow was greater in condoliase vs placebo/sham control: 22 (3.8%) vs 13 (3.3%) patients for condoliase vs control, respectively (Table 35). Time to onset is shown in Table 36. The most common (> 2participants) AEs were Rash, Dermatitis contact, Urticaria and Toxic skin eruption. No AEs reported from the Hypersensitivity (SMQ narrow) were serious.

(A list of all Hypersensitivity from an SMQ broad search is provided in Table 53 of Appendix 13.8.2.)

Table 35: Incidence of Hypersensitivity (SMQ Narrow) AEs (Pooled Phase 2/3 RCTs)

Preferred Term, n (%):	Condoliase (N=578)	Placebo/Sham Pooled (N=396)
Rash	11 (1.9)	3 (0.8)
Dermatitis contact	3 (0.5)	1 (0.3)
Urticaria	3 (0.5)	1 (0.3)
Toxic skin eruption	2 (0.3)	0
Conjunctivitis allergic	1 (0.2)	0
Contract media allergy	1 (0.2)	0
Drug hypersensitivity	1 (0.2)	0
Eczema nummular	1 (0.2)	0
Hand dermatitis	1 (0.2)	0
Allergic cough	0	1 (0.3)
Angioedema	0	1 (0.3)
Drug eruption	0	0
Eczema	0	2 (0.5)
Injection site dermatitis	0	1 (0.3)
Injection site rash	0	1 (0.3)
Rash maculo-papular	0	1 (0.3)
Rhinitis allergic	0	1 (0.3)

AE: adverse event; RCT: randomized, controlled trial; SMQ: standardized MedDRA query.

Table 36: Incidence of Hypersensitivity (SMQ Narrow) AEs, by First Occurrence (Pooled Phase 2/3 RCTs)

Preferred Term, n (%):	Condoliase (N=578)	Placebo/Sham Pooled (N=396)
Rash	11 (1.9)	3 (0.8)
2 – 7 days	8 (1.4)	2 (0.5)
8 days – 13 weeks	3 (0.5)	0
> 13 weeks	0	1 (0.3)
Dermatitis contact	3 (0.5)	1 (0.3)
2 – 7 days	1 (0.2)	0
8 days – 13 weeks	2 (0.3)	1 (0.3)
Urticaria	3 (0.5)	1 (0.3)
2 – 7 days	2 (0.3)	1 (0.3)
8 days – 13 weeks	1 (0.2)	0
Toxic skin eruption	2 (0.3)	0
2 – 7 days	2 (0.3)	0
> 13 weeks	0	0
Conjunctivitis allergic	1 (0.2)	0
2 – 7 days	1 (0.2)	0

Preferred Term, n (%):	Condoliase (N=578)	Placebo/Sham Pooled (N=396)
Contract media allergy	1 (0.2)	0
> 13 weeks	1 (0.2)	0
Drug hypersensitivity	1 (0.2)	0
≤ 1 day	1 (0.2)	0
Eczema nummular	1 (0.2)	0
> 13 weeks	1 (0.2)	0
Hand dermatitis	1 (0.2)	0
> 13 weeks	1 (0.2)	0

AE: adverse event; RCT: randomized, controlled trial; SMQ: standardized MedDRA query.

9.8.4 Anaphylactic Reactions

Anaphylactic reaction related AEs were searched with a standardized MedDRA queries (SMQ). No events from Anaphylactic reaction (SMQ narrow) were reported in either treatment group.

9.8.5 Prespecified Imaging Findings

In addition to monitoring spinal abnormality AEs, the Sponsor also prospectively conducted periodic imaging in the clinical studies to further evaluate the potential for incremental long-term disc degradation following a single injection of condoliase. Imaging evaluations consisted of x-rays and MRI. For x-ray, the following 3 prespecified changes were assessed that could be signs of disc degeneration or spinal instability:

- ≥ 30% decrease in disc height from baseline (disc degeneration)
- Vertebral posterior angle flexion ≥ 5° (spinal instability)
- Vertebral body translation of ≥ 3 mm (spinal instability)

For MRI, the Modic Type changes were assessed, as described in Table 37.

Table 37: Modic Type Changes

Change Type:	Imaging Criteria
Modic Type 1	Decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images indicating the presence of inflammation
Modic Type 2	Increased signal intensity on T1-weighted images and isointense or slightly increased signal intensity on T2-weighted images indicating conversion of red to yellow marrow and increase marrow fat
Modic Type 3	Hypointense on T1- and T2-weighted images indicating bony sclerosis adjacent to the endplates

9.8.5.1 Summary of Imaging Findings

In the development program for condoliase, imaging findings of disc height decrease and Modic Type 1 and 2 changes were observed more frequently with condoliase as compared to control, but no clear evidence suggests that these imaging observations are related to increased leg/back pain (Table 38 and Table 39).

Table 38: Disc-Related Imaging Changes on X-ray (Pooled Phase 2/3 RCT Safety)

	Week 13		Week 26		Week 52	
Imaging Change, %:	Condoliase (N=578)	Control (N=396)	Condoliase (N=421)	Control (N=252)	Condoliase (N=388)	Control (N=233)
≥ 30% decrease in disc height	4%	0	6%	0	6%	0.3%
Vertebral posterior angle flexion ≥ 5°	1%	0.6%	2%	2%	3%	2%
Vertebral body translation of ≥ 3 mm	0.2%	1%	0.9%	1%	0.9%	0.3%

RCT: randomized clinical trial.
Note: Control includes placebo and sham injections.

Table 39: Disc-related Imaging Changes by Modic Type (Pooled Phase 2/3 RCT Safety)

	Week 13		Week 26		Week 52	
Imaging Change, %:	Condoliase (N=578)	Control (N=396)	Condoliase (N=421)	Control (N=252)	Condoliase (N=388)	Control (N=233)
Change to Type 1	27%	5%	30%	10%	32%	15%
Change to Type 2	0.5%	0	2%	0	4%	0.9%
Change to Type 3	0	0	0	0	0	0

RCT: randomized clinical trial.
Note: Control includes placebo and sham injections.

To further evaluate the risk for imaging changes after condoliase administration, an expert neurosurgeon independently reviewed the imaging findings. The expert reviewer was unable to identify a clear association between the imaging findings and clinical outcomes because disc height loss and new Modic changes are known to occur with natural history of LDH and there is individual variation regarding the association of these changes with patient outcomes. (Additional discussion of expert report provided in Section 9.8.5.2.)

Imaging findings usually had no effect on leg pain or ability to function. There were no differences in leg pain scores or ODI through 1 year follow up when comparing patients that met the prespecified imaging change thresholds compared to those that did not. However, there was a weak association of new Modic Type 1 with mild to moderate back pain.

The expert also noted a trend that patients who met imaging finding thresholds either had no increased back pain or brief period of increased back pain with improvement in leg pain.

The overall conclusion was that the observed imaging changes align with expected age-related changes in disc dimensions and structure.

9.8.5.2 Long-Term Spinal Safety — Discussion of Clinical Studies and Medical Expert Opinion

In clinical studies, prespecified image findings from MRI and X-ray of disc height decrease ≥ 30% compared to baseline and Modic Type 1 and Type 2 change from baseline occurred more frequently in condoliase group than in control group. Mean disc height decreased rapidly following condoliase injection, stabilizing by Week 26 with no or little further change

at Week 52 and Week 104. The proportion of patients with new Modic Type 1 increased through Week 26 and then remained stable. New Modic Type 2 changes were much less common than disc height loss and Modic Type 1 changes during 52 weeks of follow-up and published reports indicate Modic Type 2 changes are an expected finding following Modic Type 1 and are less likely to be associated with clinical symptoms and are not discussed further. Condoliase and control groups showed less frequent and similar rates for vertebral body angle flexion and translation AEs.

To ascertain whether the higher rate of disc height decrease of ≥ 30% and increased rate of new Modic Type 1 affected clinical symptoms, the correlation between imaging and symptoms was evaluated. Worst leg and back pain VAS and increase in leg or back pain VAS had no clear association with disc height decrease ≥ 30% or new Modic Type 1. Disc height decrease had no clear association with leg or back pain AEs in study patients. New Modic Type 1 had no clear association with leg pain AE's but showed an inconsistent association with back pain AEs.

To further evaluate the risk of imaging changes that are frequently observed after condoliase administration, medical expert opinion was sought. From the neurosurgeon's expert report, "Disc height loss (DHL) and new Modic changes are known to occur with natural history. As expected from condoliase's mechanism of action, DHL and Modic changes occurred more often in condoliase group. Not surprisingly, much individual variations exist regarding DHL and Modic changes and patient outcome." Moreover, patients with Imaging AEs did not reveal clear association with clinical outcomes (leg pain scores, ODI, neurological testing) by the expert review. The expert reviewer did note that patients with new Modic Type 1 tended to be more likely to report back pain.

While more condoliase-treated patients exhibited disc height loss of at least 30%, leg symptoms improved in that group, suggesting no increase in foraminal narrowing. Mean disc height loss was -15% in the condoliase group and -7% in the placebo/sham group, consistent with DHL following discectomy according to a recent meta-analysis (Chen et al, 2021).

Radiographic signs of spinal instability were rare and roughly equal in the condoliase and placebo/sham groups.

New Modic Type 1 changes were more frequent in the condoliase group but seemed to stabilize after Week 26 with a cumulative incidence of 32% at Week 52. The placebo group showed a steady increase to 15% at Week 52. Modic Type 1 changes are also common following discectomy. Bostelmann et al (2019) reported 25% of patients had new Modic Type 1 changes 12 months after surgery and 13% had new Modic Type 2 changes. Feng et al (2024) found that 37% of subjects without Modic change before surgery developed Modic Type 1 or 2 at 12 months.

9.8.5.3 Background on Radiological Methods

These imaging findings were investigated for several reasons. First, while the method of action of condoliase predicts for disc volume reduction and associated disc height loss, these changes could hypothetically lead to spine segment instability and possible increased back pain. Flexion angle and translation exceeding the predefined thresholds are established radiographic criteria to detect segmental instability. In addition, excessive disc height loss could potentially result in foraminal narrowing leading to bony impingement of the exiting nerve root at the target level and worsening of leg symptoms. Therefore, the incidence of disc height loss ≥ 30% was monitored.

Second, the non-clinical studies of condoliase documented changes in the disc and adjacent endplates that, if present in patients, would manifest as increased incidence of Modic findings on MRI. Therefore, these changes were prospectively investigated.

Modic changes are a common finding in patients with degenerative disc disease and are frequently reported in patients with LDH. The published literature contains mixed reports on the association of Modic changes with back pain and a large meta-analysis reported no association exists (Chen et al, 2019).

The etiology and pathophysiology of Modic changes are not entirely clear but suspected causes are biomechanical loading (leading to disc injury), autoimmune response or infection (Viswanathan et al, 2020; Dudli et al, 2016). It is known that disc degeneration leads to disruption of the cartilaginous and bony endplate of the vertebral body. The damaged disc tissue can cause an immune response or possibly an autoimmune response to the nucleus pulposus, which is an immune privileged tissue. Hydraulic pressure can cause proinflammatory mediators in the disc to migrate through the disrupted endplate to the bone marrow leading to an immune response there causing formation of granulation tissue, fibrosis, increased vascularization and sensory neoinnervation in the adjacent endplate. These acute changes are detected as Modic Type 1 change on MRI. Modic Type 2 is a consequence of chronic inflammation without edema and conversion of red to yellow marrow. Modic Type 3 change represents bony sclerosis as a result of increased bone turnover and thickening of bony trabeculae. Modic 1 changes are “unstable” and may convert to Modic 2 or revert to normal. Modic 2 changes are more stable and may not change for years although conversion to Modic 3 or regression to Modic 1 has been reported. Albert and Manniche (2007) reported in a study of 166 non-operated subjects with sciatica that 9% had prevalent Modic Type 1 changes at baseline and 29% developed new Modic Type 1 changes after 14 months.

9.9 Summary of Safety and Conclusions

The Safety Population for the primary safety analysis (Pooled Phase 2/3 RCT Safety) consisted of all patients from four Phase 2 and Phase 3 randomized, controlled studies. This pool included 578 patients who received condoliase and 396 patients who received placebo/sham control. These clinical data, along with postmarketing data (reported through March 11, 2024; Section 10) support that condoliase treatment was well tolerated with an acceptable safety profile in patients with radicular leg pain associated with LDH in adults.

10 POSTMARKETING EXPERIENCE

Since the March 2018 approval in Japan, there have been an estimated an estimated 27,000 exposures of condoliase,[3] Note that the method of estimating patient exposure described in this section provides a gross approximation of actual exposure and therefore should not be used to determine the AE incidence.

Sources of the postmarketing data are from unsolicited reports including cases reported spontaneously to SKK, cases published in literature and solicited reports which are cases from SKK post-marketing commitment surveys. The post-marketing commitment surveys are ongoing. Results from these surveys are reviewed as part of routine pharmacovigilance and no regulatory action has resulted from these reviews. In some post-marketing reports, clinical information (such as medical history, use of concomitant drugs) is limited and follow-up information may not be available. Thus, post-marketing data is best suited for signal detection.

Postmarketing safety data is generally consistent with the safety profile observed in clinical trials, with most events related to pain or hypersensitivity (Table 40).

(Complete listings of postmarketing Safety Topics of Interest by SMQ narrow (Table 54) and SMQ broad (Table 55) searches are provided in Appendix 13.8.2.)

Table 40: Summary of Postmarketing Safety (≥ 5 Events)

	Unsolicited		Solicited	
Preferred Term (≥ 5 Events), n:	**Non-serious**	**Serious**	**Non-serious**	**Serious**
Any Adverse Drug Reaction	176	77	336	80
Rash	45	2	21	1
Back pain	24	7	107	11
Urticaria	21	3	32	2
Pruritus	11	1	4	0
Drug eruption	10	6	13	0
Pain in extremity	9	8	36	12
Erythema	6	1	3	0
Pyrexia	5	2	2	0
Nausea	4	2	3	1
Intervertebral discitis	1	8	3	4
Intervertebral disc protrusion	1	3	23	20
Lumbar spinal stenosis	1	1	4	2
Musculoskeletal pain	0	1	6	1
MRI abnormal	0	1	5	0
Intervertebral disc disorder	0	0	11	2
Intervertebral disc space narrowing	0	0	9	2
Vertebral osteophyte	0	0	6	0

[3] Estimate based on units shipped.

	Unsolicited		Solicited	
Preferred Term (≥ 5 Events), n:	**Non-serious**	**Serious**	**Non-serious**	**Serious**

MRI: magnetic resonance imaging.
Note: Data compiled from 6 years of postmarketing pharmacovigilance in Japan from approval in March 2018 through data cutoff date of March 11, 2024. Estimated 27,000 exposures, based on number of units shipped.

As of March 2024, the postmarketing data contained several AE terms that were not seen in clinical trials based on the searches for hypersensitivity and anaphylactic reaction SMQs. As part of the hypersensitivity SMQ search, there were several reported events known as severe cutaneous adverse reactions (SCAR). SCAR are life-threatening, T-cell mediated, delayed drug hypersensitivity reactions. There are 3 main clinical types of SCAR: acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome, and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (Gibson et al, 2023). The reports of SCAR in the condoliase postmarketing experience included only AGEP.

All post-marketing patients identified from hypersensitivity and anaphylactic reaction SMQs had recovered or were recovering. These AEs have been reported in unsolicited and solicited reports as follows:

- Anaphylactic reactions (1 unsolicited and 1 solicited). Both patients recovered.
- Anaphylactic shock (1 unsolicited). Patient recovered.
- Erythema multiforme (1 unsolicited). The patient was recovering.
- Dermatitis exfoliative generalized (1 solicited). Patient recovered.
- AGEP (1 unsolicited and 1 solicited). Both patients recovered. One of these patients also reported Dermatitis exfoliative generalized (see above)
- SJS (1 solicited). This case met the criteria of serious. On follow-up review, the case of SJS lacked seminal characteristics; therefore, the diagnosis has been updated by the reporter to anaphylaxis. Patient recovered.

While hypersensitivity and anaphylactic reactions AEs were infrequently reported, the Sponsor acknowledges that protein-based injected products, like condoliase, carry inherent risk of hypersensitivity and has proposed that hypersensitivity including anaphylaxis be included in the label as a warning and precaution.

11 BENEFIT-RISK CONCLUSIONS

11.1 Clinical Meaningfulness of Outcomes

Studies 1031 and 1133 were adequate and well-controlled trials in Japan and the US, respectively. A total of 518 patients were randomized to receive condoliase (N=260) or placebo/sham control (N=258). Enrolled patients were representative of the US population of patients with radicular leg pain associated with LDH in terms of age, gender, hernia pathology, and disease characteristics. Furthermore, treatment guidelines, prior therapies and access to standard of care were also similar for these patients, supporting that results are relevant to the US population. The condoliase and placebo/sham treatment arms had similar baseline demographics and disease characteristics, thus supporting comparisons between treatment arms (Table 2).

Studies 1031 and 1133 showed that condoliase reduced radicular leg pain by Week 13, meeting the primary endpoint with statistical significance (Figure 6) — results that were sustained through Week 52 (Table 20 [Study 1031]; Table 28 [Study 1133]). The condoliase treatment benefit in worst radicular leg pain was clinically meaningful, statistically significant, and consistent across a majority of subgroups (Figure 20 [Study 1031]; Figure 25 [Study 1133]). The benefits were corroborated by patient reports of increased functionality. The overall benefit risk of condoliase was further supported by smaller herniation volumes observed in the treatment group compared to the control groups.

Overall, Studies 1031 and 1133 demonstrated substantial evidence of efficacy as shown across key measures of efficacy, response to treatment and quality of life. All measures were either nominally statistically significant or favored condoliase therapy, as shown in Figure 16.

11.2 Ability to Manage Risks

The integrated analyses show that condoliase was well tolerated, with an acceptable safety profile that was consistent for the targeted population and no evidence for increased and non-manageable safety risk. To manage/mitigate the safety risk identified in the condoliase development program, instructions for proper administration will be detailed in labeling (proposed USPI).

As an injected protein, condoliase carries a risk for hypersensitivity and anaphylaxis. There were no anaphylactic AEs in the clinical trials, and the few hypersensitivity events were all mild or moderate in severity. In the postmarketing setting in Japan, there have been 24 reports of serious hypersensitivity events and 15 reports of serious anaphylaxis, from among an estimated 27,000 exposures over the 6 years since its approval (Section 10). While a single injection will possibly minimize immune related risks, the proposed label will include a warning so that clinicians can monitor patients for the risk of hypersensitivity and anaphylaxis.

No unexpected safety signals emerged during long-term treatment of up to 2 years. In the safety topics of interest, no clinically meaningful AE signals or imbalance in AE reporting were observed suggestive of increased and non-manageable safety risk with condoliase. An increased risk for disc-related findings detected by imaging was observed in patients treated with condoliase during the earlier time intervals; however, after Week 26 similar trends were observed in both the condoliase and placebo/sham groups. These imaging findings were not associated with symptoms or detrimental effect on leg pain.

11.3 Benefit-Risk Conclusion

Although guidelines state that neural impingement is of obvious importance when evaluating LDH, clinical studies including Study 1031, 1131 and 1133 showed the need to confirm nerve root impingement by the herniation. Without impingement, shrinking the herniation with condoliase is unlikely to alleviate the radicular leg pain. As shown in Appendix 13.5.1, nerve root impingement by the herniation is readily identifiable on imaging. This information will be communicated to clinicians and patients, enabling an informed decision to use condoliase.

Condoliase has a favorable benefit-risk profile for patients with radicular leg pain caused by LDH. Treatment resulted in consistently beneficial effects across multiple clinically important endpoints. Condoliase reduced radicular leg pain early and with a durable effect up to 52 weeks. The treatment benefit extended to improvements in functionality, as assessed by the ODI. Condoliase is well tolerated, with a clinical safety profile bolstered by more than 6 years of postmarketing exposure data in Japan. Condoliase provides a safe and effective therapeutic option for patients who do not respond to conservative treatment and who seek non-surgical options.

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13 APPENDICES

13.1 Standard of Care and Treatment Guidelines in Japan (Evidence Supporting Similarities of Studies and Patient Populations in US and Japan)

Haro, 2022. Japanese Orthopaedic Association (JOA) Clinical Practice Guidelines on the Management of Lumbar Disc Herniation.

13.2 Summary of Other Supportive Endpoints and Results from Pivotal Phase 3 Studies 1031 and 1133

Table 41: Summary of Other Supportive Endpoints and Results — Pivotal Phase 3 Studies 1031 and 1133

	Treatment Group Difference	
Endpoint	**Study 1031**	**Study 1133**
Change from Baseline in Worst Back Pain	Week 13 -7.1 (95% CI -15.0, 0.8) p=0.0765 Week 52 -9.4 (95% CI -17.6, -1.3) p=0.0227	Week 13 -4.9 (95% CI -10.9, 1.1) p=0.1098 Week 52 -4.6 (95% CI -11.4, 2.2) p=0.1827
Change from Baseline in ODI Score	Week 52 -6.7 (95% CI -12.6, -0.9) p=0.0250	Week52 -3.1 (95% CI -6.9, 0.6) p=0.1016
Percentage of Subjects with Negative SLR Test	Week 13 condoliase: 65 (79.3), placebo: 46 (56.8) p=0.0024 Week 52 condoliase:66 (80.5), placebo: 53 (65.4) p=0.0320	Week 13 condoliase: 98 (62.8), sham: 72 (46.8); 16.1 (95% CI 5.1, 27.0); p=0.0045 Week 52 condoliase:108 (81.2), sham: 79 (60.8); 20.4 (95% CI 9.7, 31.1); p=0.0003
Percentage of Subjects without Hypoesthesia, Muscle Weakness, or Hyporeflexia	No nominally significant differences were found, though the percentage of subjects without symptom favored condoliase, except for hypoesthesia at Week 52 (condoliase: 69 (84.1), sham: 56 (69.1), p=0.0347).	No nominally significant differences were found, though the percentage of subjects without symptom favored condoliase, except for hypoesthesia at L5 at Week 52 (condoliase: 128 (96.2), sham: 116 (89.2), 7.0 (95% CI 0.8, 13.2); p=0.0281).

	Treatment Group Difference	
Endpoint	**Study 1031**	**Study 1133**
Change from Baseline in SF-36 Score	Physical Component Score Week 13 5.5 (95% CI 1.1, 10.0) p=0.0139 Week 52 6.1 (95% CI 1.0, 11.1) p=0.0186 Mental Component Score Week 13 0.8 (95% CI -1.7, 3.3) p=0.5301 Week 52 1.3 (95% CI -1.1, 3.8) p=0.2861	Physical Component Score Week 13 1.1 (95% CI -1.0, 3.1) p=0.3149 Week 52 2.4 (95% CI 0.2, 4.6) p=0.0341 Mental Component Score Week 13 1.3 (95% CI -0.6, 3.2) p=0.1851 Week 52 0.3 (95% CI -1.6, 2.1) p=0.7693
Change from Baseline in Intervertebral Disc Volume	Week 13 -1176.7 (95% CI -1434.9, -918.6) p < 0.0001 Week 52 -1158.9 (95% CI -1451.4, -866.4) p < 0.0001	Week 13 -1030.7 (95% CI -1172.3, -889.2) p < 0.0001 Week 52 -758.0 (95% CI -911.9, -604.2) p < 0.0001
Change from Baseline in Herniation Volume	Week 52 -117.1 (95% CI -202.6, -31.6) p=0.0076	Week 52 -14.8 (95% CI -53.7, 24.1) p=0.4533
Percentage of 30% Responders for Weekly Average Worst Leg Pain	Week 13 condoliase: 64 (78.0), placebo: 49 (60.5) p=0.0194 Week 52 condoliase:66 (80.5), placebo: 57 (70.4) p=0.1421	Week 13 condoliase: 114 (67.5), placebo: 98 (57.0); 10.5 (95% CI 0.2, 20.7); p=0.0575 Week 52 condoliase:109 (64.5), placebo: 99 (57.6); 6.9 (-3.4, 17.3); p=0.2220
Percentage of 50% Responders for Weekly Average Worst Leg Pain	Week 13 condoliase: 59 (72.0), placebo: 41 (50.6) p=0.0077 Week 52 condoliase:65 (79.3), placebo: 51 (63.0) p=0.0244	Week 13 condoliase: 105 (62.1), placebo: 84 (48.8); 13.3 (95% CI 2.8, 23.7); p=0.0165 Week 52 condoliase:107 (63.3), placebo: 93 (54.1); 9.2 (95% CI -1.2, 19.6); p=0.0990

	Treatment Group Difference	
Endpoint	**Study 1031**	**Study 1133**
Percentage of Subjects with Posttreatment Surgery for LDH at the Same Level of Investigational Product Injection	condoliase: 8 (9.8), placebo: 8 (9.9)	condoliase: 5 (3.0), sham: 11 (6.4) p=0.1319

CI: confidence interval; LDH: lumbar disc herniation; mITT: modified intent to treat; ODI: Oswestry Disability; SLR: straight leg raise Index; SF36: 36-item Short Form Health Survey.

13.3 Study 1031 Supplementary Information

13.3.1 Study 1031 Inclusion/Exclusion Criteria

Inclusion Criteria

- Patients with lumbar disc herniation (ie, without rupture of the posterior longitudinal ligament) at L4-L5 or L5-S1 as confirmed by MRI, and clinical symptoms corresponding to the position of the impaired nerve root. If L6 was present, patients with an impaired L5 or S1 nerve root and corresponding clinical symptoms.
- Patients with sciatica in either lower leg for ≥ 6 weeks prior to the time of informed consent.
- Patients with a positive (≤ 70º) straight leg raising (SLR) test on the symptomatic side.
- Patients with no improvement on drug therapy (NSAIDs) or drug therapy combined with nerve root block for ≥ 6 weeks prior to the time of informed consent.
- Patients whose worst leg pain over the past 24 hours (VAS) at bedtime for the 7 consecutive days up to the day before registration satisfied both a) and b) below in at least 3 VAS scores during baseline.
    a) No additional concomitant medication or change in dosage or administration of current concomitant medication being used for pain relief
    b) Mean of VAS scores satisfying a) above is ≥ 50 mm, and the range of fluctuation in VAS scores (ie difference between minimum and maximum scores) is ≤ 25 mm
- Adults ages 20-70 years at the time of informed consent
- Patients who voluntarily gave their written, informed consent to participate in the study after being given a thorough explanation of the study using the written information for patients and after confirming that he or she fully understood the contents of the form.

Exclusion Criteria

- Patients with ≥ 2 lumbar disc herniations on MRI
- Patients with extrusion-type or sequestration-type herniation based on MRI-confirmed rupture into the posterior longitudinal ligament
- Patients who had participated in a previous clinical study of condoliase
- Patients who were pregnant, breast-feeding, or possibly pregnant based on pregnancy tests

- Patients who had been administered a nerve root block (local anesthetic agent, steroid, opioid analgesic) for the lumbar disc herniation within 3 weeks prior to the time of informed consent
- Patients who had undergone lumbar surgery (lumbar discectomy, chemonucleolysis, percutaneous nucleotomy, etc)
- Patients with the following symptoms and diseases that could affect the result of this study:
  - Posterior intervertebral angle ≥ 5º during flexion on X-ray
  - Severe or rapidly progressive neurological disorder, cauda equina syndrome (neurologic bladder and bowel dysfunction)
  - Lumbar spine disorder other than lumbar disc herniation, eg spinal osteoarthritis, spondylolisthesis (≥ 3 mm vertebral body translation), spinal column stenosis, osteophytes (Nathan's classification: Grade III/IV), spinal tumor, ankylosing spondylitis, intervertebral discitis, etc
  - Osteoporosis, rheumatoid arthritis
  - Cancer (patients with a history of cancer within 5 years prior to the time of informed consent, with the exception of complete recovery by surgical or local treatment)
  - Serious disorders such as cerebrovascular disorder, pulmonary infarction, ischemic heart disease, arrhythmia, myocardial infarction, and cardiac failure
  - Respiratory disorders that could interfere with daily activities or sleeping as a result of persistent cough or paroxysmal dyspnoea (asthma, etc)
  - Drug dependence, alcohol dependency
- Patients who met any of the following criteria
  - Platelet count: < lower limit of normal (LLN) of the laboratory
  - AST (GOT), ALT (GPT): ≥ 2.5× upper limit of normal (ULN) of the laboratory
  - Total bilirubin: ≥ 1.5× ULN of the laboratory
  - Serum creatinine: ≥ 1.5× ULN of the laboratory
  - HCV antibody, HBV antibody: Positive
- Patients with BMI ≥ 35.0 kg/m^2
- Patients receiving compensation under the Industrial Accident Compensation Insurance Act, Automobile Liability Security Act, etc
- Patients who participated in another clinical study within 4 months prior to the time of informed consent
- Patients who, for any other reason, are deemed by the investigator or sub-investigator to be unsuitable for the safe conduct of the study

13.3.2 Study 1031 Efficacy Results Using MMRM (MAR) Analysis

Table 42: Change from Baseline in Weekly Averages of Worst Leg Pain at Week 52 Using MMRM (MAR) Analysis — Study 1031 (mITT)

	MMRM (MAR)	
Worst Leg Pain, VAS:	**Condoliase (N=82)**	**Placebo (N=81)**
Baseline, mean (SD)	72.4 (12.29)	74.6 (12.48)
Week 52, LS mean (SE)	12.1 (2.59)	19.3 (2.69)
Change from Baseline, LS Mean (SE)	-61.1 (2.59)	-53.9 (2.69)
95% CI	(-66.2, -55.9)	(-59.2, -48.6)

Worst Leg Pain, VAS:	MMRM (MAR)	
	Condoliase (N=82)	Placebo (N=81)
Treatment difference for condoliase vs placebo		
Difference in LS means (SE)	-7.2 (3.74)	
95% CI	(-14.6, 0.2)	
p-value (nominal)	0.0575	

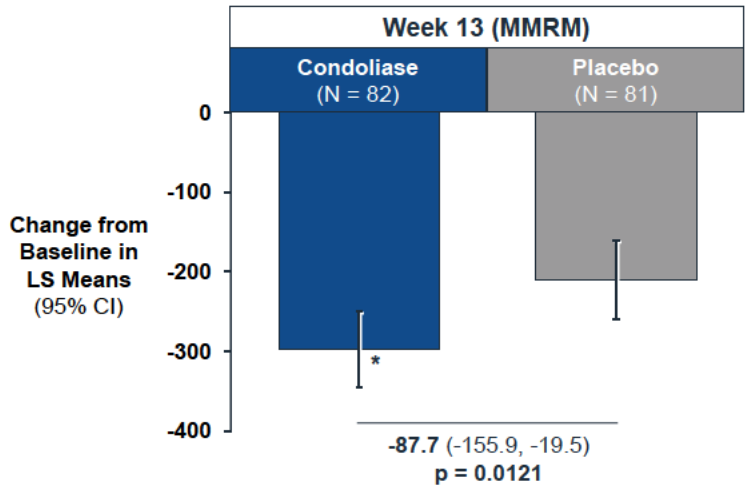
CI: confidence interval; LS: least squares; MAR: missing at random; mITT: modified intent to treat; MMRM: mixed methods repeat measures; SD: standard deviation; SE: standard error; VAS: visual analog scale.

Table 43: Change from Baseline in Weekly Average Worst Leg Pain at Each Time Point through 52 Weeks Using MMRM (MAR) Analysis — Study 1031 (mITT)

Visit:	MMRM (MAR)	
	Difference in LS Means (95% CI)	p-value (Nominal)
Week 1	-5.2 (-11.3, 0.9)	0.0929
Week 2	-8.3 (-15.0, -1.5)	0.0171
Week 4	-11.3 (-19.1, -3.6)	0.0043
Week 6	-11.9 (-20.1, -3.6)	0.0050
Week 13	-13.9 (-22.3, -5.5)	0.0013
Week 26	-8.2 (-16.1, -0.3)	0.0432
Week 39	-7.2 (-14.5, 0.0)	0.0505
Week 52	-7.2 (-14.6, 0.2)	0.0575

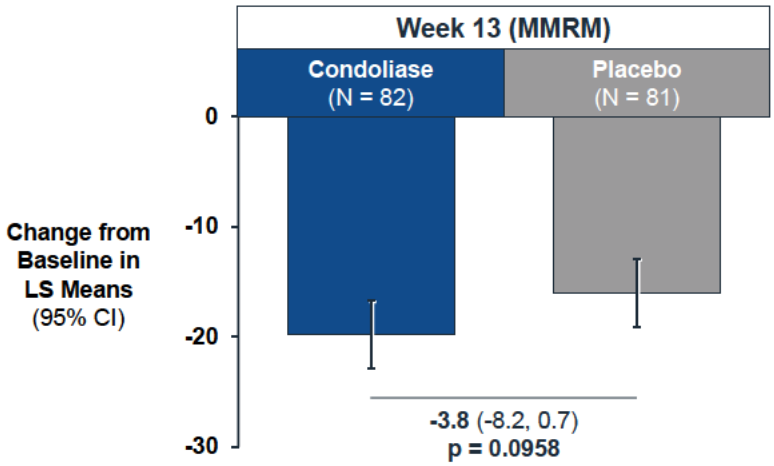
CI: confidence interval; LS: least squares; MAR: missing at random; mITT: Modified Intent to Treat; MMRM: mixed methods repeat measures.

Figure 33: Change from Baseline in Disc Herniation Volume at Week 13 Using MMRM (MAR) Analysis — Study 1031 (mITT)



* nominal p-value < 0.05.
CI: confidence interval; LS: least squares; MAR: missing at random; mITT: modified intent to treat; MMRM: mixed methods repeat measures.

Figure 34: Change from Baseline in ODI Score at Week 13 Using MMRM (MAR) Analysis — Study 1031 (mITT)



CI: confidence interval; LS: least-squares; MAR: missing at random; mITT: modified intent to treat; MMRM: mixed methods repeat measures; ODI: Oswestry Disability Index.

13.4 Study 1131 Supplementary Information

13.4.1 Study 1131 Inclusion/Exclusion Criteria

Inclusion Criteria

Patients must have met all of the following criteria for inclusion in the study:

- Patients who had given their written informed consent to participate in a clinical study based on voluntary agreement after a thorough explanation of the patient's participation was provided to them. Patients were required to have adequate reading and writing abilities such that they were able to comprehend and answer the questions on the patient-completed assessments and ICF.
- Patients with lumbar disc herniation (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 position of the impaired nerve root; if the 6th lumbar vertebra (L6) was present, patients with impaired L5 or S1 nerve root and corresponding clinical symptoms
- Patients with positive SLR ≤ 70° on the symptomatic side.
- Patients with sciatica in either leg for ≥ 6 weeks and ≤1 year prior to the time of informed consent.
- Patients with no improvement from adequate conservative treatment* for ≥ 6 weeks prior to the time of informed consent.
  *Adequate conservative treatment included pharmacotherapy (eg, nonsteroidal anti-inflammatory drugs, opiate preparations, or nonopioid analgesics). Physical therapy and/or spinal injection, epidural injection, or nerve block were also allowed to be included.
- Patients with the worst leg pain (by VAS ≥ 50 mm) during the past 24 hours at the time of informed consent and at the time of enrollment (Day -1 or Day 0).
- Patients with ≥ 30% on ODI at the time of enrollment (Day -1 or Day 0).
- Male or female patients 30 to 70 years of age at the time of informed consent.
- Female patients who were not pregnant and did not plan to become pregnant during the study. Females of childbearing potential had to provide a negative serum

pregnancy test during the Screening period, and had to use reliable contraception, and continue to use reliable contraception until Week 104 (reliable methods of contraception are defined in Exclusion Criterion below). Non-childbearing potential was defined as postmenopausal for at least 2 years or surgical sterilization or hysterectomy at least 3 months before study start.

Exclusion Criteria

Patients who met any of the following exclusion criteria were not included in the study:

- Patients who had 2 or more symptomatic lumbar disc herniations as assessed by MRI. Two or more level symptomatic lumbar disc herniations were 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.
- Patients with a contraindication to receiving an MRI.
- Patients in whom a rupture into the posterior longitudinal ligament was assessed by MRI (that is, those with transligamentous extrusion or sequestration [free fragment] type lumbar disc herniation).
- Patients who had previously received condoliase administration at any time.
- Patients who were pregnant, breast-feeding, or women of childbearing potential with positive pregnancy tests. Female patients post-hysterectomy and/or bilateral tubal ligation or postmenopausal who had not menstruated within past 2 years did not need to take the pregnancy tests.
- Sexually active female patients of childbearing potential who were not willing to use adequate contraceptive measures to avoid pregnancy until Week 104 of the study. Sexually active male patients who were not willing to use adequate contraceptive measures until Week 13 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 included the following: diaphragm plus a spermicidal agent or condoms (male or female) plus a spermicidal agent.
  - Vasectomy, intrauterine device, and/or exclusive sexual partner for whom one of the above acceptable methods applied.
- Patients who had received a spinal injection, epidural injection, or nerve block for lumbar disc herniation within 3 weeks prior to the time of informed consent.
- Patients who had undergone lumbar operation, lumbar percutaneous nucleotomy or lumbar intradiscal therapies (eg, chemonucleolysis or intradiscal electrothermal treatment) at any level of lumbar spine.
- Patients with the following medical conditions or diseases:
  - Vertebral body angle formed by flexion ≥ 5.
  - Neurological disorders including cauda equina syndrome that was considered severe or that demonstrated rapid progression.
  - Spondylosis deformans, spondylolisthesis (translation of vertebral body ≥ 3 mm), spinal deformity (scoliosis: Cobb angle > 10°; kyphosis: Cobb angle (T5-T12) < 10° or > 40°; or lordosis (L1-S1): Cobb angle < 35°), spinal canal stenosis (except for complication of lumbar disc herniation), spinal tumor, ankylosing spondylitis, diskitis, or other than disc herniation clinically significant disorders of the lumbar spine.
  - Osteophyte at lumbar spine (Nathan's classification ≥ 3rd degree).

  - Cancer: patients who had 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 had evidence of major psychiatric disease, mental disorder, drug dependency, alcohol dependency, or substance use disorders.
  - Patients who had a tendency to bleed.
- Patients with medical conditions and/or diseases that the investigator believed could affect the study results or the safe conduct of the study.
- Patients who met any of the following criteria:
  - Hepatic function: AST or ALT: ≥ 2.5× ULN
  - Total-bilirubin: ≥ 1.5 x ULN
  - Renal function: serum creatinine: ≥ 1.5× ULN
  - Hepatitis C virus or hepatitis B surface antigen: positive
- BMI ≥ 35.
- Patients who were receiving compensation according to the Workers' Compensation Act or were involved in personal injury litigation due to a lumbar-related injury.
- Patients who participated in another clinical study within 4 months prior to the time of informed consent, or who were expected to participate in another study during the period of this study.

13.4.2 Study 1131 Disposition, Demographics, and Baseline Disease Characteristics

Table 44: Patient Disposition — Study 1131

	Screened (N=955)	
Disposition, n (%):	**Condoliase (N=290)**	**Sham (N=95)**
Randomized	290 (100)	95 (100)
Injected	238 (96.6)	94 (98.9)
Evaluated at Week 13	256 (88.3)	88 (92.6)
Evaluated at Week 25	215 (74.1)	78 (82.1)
Completed Week 104	204 (70.3)	71 (74.7)
Discontinued	86 (29.7)	24 (25.3)
Withdrew consent	45 (15.5)	13 (13.7)
Adverse event	3 (1.0)	3 (3.2)
Poor response to study drug	4 (1.4)	0
Investigator's decision	3 (1.0)	0
Other	31 (10.7)	8 (8.4)

Disposition, n (%):	Screened (N=955)	
	Condoliase (N=290)	Sham (N=95)

Note: Denominators for percentages are based on the number of patients randomized in each treatment group.

Table 45: Patient Demographics — Study 1131 (ITT)

Demographic, Statistic:	Condoliase (N=280)	Sham (N=94)
Age group, n (%)		
≤ 50 years	161 (57.5)	46 (48.9)
> 50 years	119 (42.5)	48 (51.1)
Age (years)		
Mean (SD)	48.7 (9.46)	49.3 (9.63)
Median (min – max)	48.0 (30 – 70)	51.0 (30 – 68)
Sex, n (%)		
Female	144 (51.4)	50 (53.2)
Male	136 (48.6)	44 (46.8)
Race, n (%)		
Asian	4 (1.4)	1 (1.1)
White	240 (85.7)	75 (79.8)
Black	32 (11.4)	16 (17.0)
Other	4 (1.4)	2 (2.1)
BMI, n (%)		
< 25 kg/m^2	61 (21.8)	27 (28.7)
25 – 30 kg/m^2	115 (41.1)	34 (36.2)
> 30 kg/m^2	104 (37.1)	33 (35.1)
BMI (kg/m^2)		
Mean (SD)	28.4 (4.15)	28.0 (4.20)
Median (min – max)	28.5 (17 – 37)	28.0 (18 – 35)
Smoking history, n (%)		
Never smoked	147 (52.5)	53 (56.4)
Past smoker	66 (23.6)	19 (20.2)
Current smoker	67 (23.9)	22 (23.4)

BMI: body mass index; ITT: Intent-to-Treat; SD: standard deviation.

Table 46: Patient Baseline Disease Characteristics — Study 1131 (ITT)

Baseline Characteristic, Statistic:	Condoliase (N=280)	Sham (N=94)
Occupation, n (%)		
Heavy labor	55 (19.6)	22 (23.4)
Light labor	225 (80.4)	72 (76.6)

Baseline Characteristic, Statistic:	Condoliase (N=280)	Sham (N=94)
Leg pain (VAS)		
n	280	94
Mean (SD)	74.4 (14.01)	76.7 (12.75)
Median (min – max)	74.5 (17 – 100)	77.0 (52 – 100)
Leg pain (VAS), n (%)		
50 to ≤ 70 mm	109 (38.9)	31 (33.0)
> 70 to 100 mm	168 (60.0)	63 (67.0)
Back pain (VAS)		
n	280	94
Mean (SD)	74.3 (18.99)	76.5 (18.14)
Median (min – max)	77.5 (2 – 100)	78.0 (2 – 100))
ODI		
n	280	94
Mean (SD)	48.3 (13.67)	49.1 (13.92)
Median (min – max)	46.0 (8 – 100)	48.0 (24 – 94)
		N=95
Days of onset of current leg pain, (%)		
< 90	58 (20.0)	24 (25.3)
≥ 90	232 (80.0)	71 (74.7)
Days of onset of current leg pain		
n	290	95
Mean (SD)	181.3 (93.95)	168.3 (90.06)
Median (min – max)	163.0 (43 – 377)	160.0 (-12 – 360)
Herniation site, n (%)		
L4-L5	116 (40.0)	45 (47.4)
L5-S1	173 (59.7)	50 (52.6)
L5-L6	1 (0.3)	0
Location of current leg pain, n (%)		
Left leg	161 (55.5)	43 (45.3)
Right leg	129 (44.5)	52 (54.7)
Back pain, n (%)		
Yes	286 (98.6)	92 (96.8)
No	4 (1.4)	3 (3.2)

ITT: Intent-to-Treat; ODI: Oswestry disability index; SD: standard deviation; VAS: visual analog scale.
Note: Denominator for percentages is based on the number of patients in each treatment group.

13.5 Study 1133 Supplementary Information

13.5.1 Study 1133 Inclusion/Exclusion Criteria

Inclusion Criteria

Patients were allowed to participate in this study only if they met all the following criteria:

- Patients who had given their written informed consent to participate in the clinical study based on voluntary agreement after a thorough explanation of subject participation is provided to them. Subjects should have been willing and able to provide written informed consent, adhere to the study visit schedule, and answer the questions on subject-completed assessments.
- Ages 30 to 70 (inclusive) at the time of informed consent
- Have contained posterolateral LDH at either L4-L5 or L5-S1 (or L5-L6):
  - with the presence of demonstrable nerve root impingement, as assessed by MRI;
  - chief complaint of unilateral radiculopathy and/or radicular leg pain corresponding to the ipsilateral leg and distribution of the affected nerve root; and
  - positive result of SLR test (≤70°) only on the ipsilateral leg having chief complaint of radiculopathy corresponding to the pain and distribution of the affected nerve root.
- Symptoms of radiculopathy and/or radicular leg pain only in the unilateral leg corresponding to the distribution of the affected nerve root for 6 weeks or more but 1 year or less, and which is still ongoing at the time of informed consent.
- Patients with inadequate improvement in pain caused by LDH despite 6 weeks or more of conservative treatment,* which was still ongoing at the time of informed consent.
  * Conservative treatment was pharmacotherapy (eg, steroids, NSAIDs, or non-opioid analgesics), physical therapy, chiropractic, acupuncture, spinal injection, epidural injection, or nerve block. For spinal injection, an inadequate response over a 4-week period can be counted toward the required ≥ 6 weeks of conservative treatment.
- Patients whose worst leg pain (100 mm VAS) for the 7 consecutive days up to the day before randomization met following conditions:
  - at least 5 worst leg pain scores on the days when not using any rescue medications or increasing or adding non-prohibited concomitant medications to treat LDH;
  - the mean of the worst leg pain scores is 50 to 90 mm; and
  - the range of fluctuation in worst leg pain scores over the 7 days (difference between minimum and maximum scores) is ≤ 25 mm.
- Subjects who could comply with the rules of rescue medication usage as defined in the protocol and, for those who qualified to receive rescue medication 2 (hydrocodone/acetaminophen), were not at high risk of opioid abuse, as determined by the investigator.
- Patients with ≥ 30% on the ODI at the time of randomization.

Exclusion Criteria

Patients were not allowed to participate in this study if they met any of the following criteria:

- Subjects who had LDHs demonstrating clear impingement to the nerve root* at 2 or more levels as assessed by MRI and possessed symptoms corresponding to the distribution of the affected nerve root.
  *Judged first by the investigator, then confirmed by assessment of independent central image readers.
- Subjects with a contraindication to receive MRIs (eg, pacemaker or other metallic implants not compatible with MRI).
- Subjects that demonstrated LDH as described below in the disc to be treated, as assessed by MRI*:
  - Rupture into the posterior longitudinal ligament (those with transligamentous extrusion or sequestration [free fragment]-type LDH);
  - Isolated central herniation;
  - Anterolateral herniation; and/or
  - Extraforaminal herniation.
    *Judged first by the investigator, then confirmed by assessment of independent central image readers.
- Subjects that demonstrated clinical symptoms of radiculopathy (eg, sciatica, weakness, sensory loss, or positive result of SLR test [≤70°]) caused by LDH on the contralateral leg.
- Subjects who, within 28 days prior to randomization, had:
  - Received a block procedure (eg, spinal injection, epidural injection or nerve block) for treatment of LDH; and/or
  - Received oral or injectable corticosteroids to the back, buttock, or posterior/lateral aspects of the affected leg. Note: Inhaled, nasal, or topical steroids used over small areas of skin (eg, <100 cm^2) was permitted.
- Subjects who, within 7 days prior to randomization, had:
  - Taken opioids (including tramadol, tapentadol, meperidine, or opioid-containing combination products) by any route of administration;
  - Taken cannabis by any route of administration; and/or
    Note: Use of cannabidiol oil that contains regulated quantities of tetrahydrocannabinol (ie, psychoactive cannabidiol oil preparations) was prohibited; amounts of tetrahydrocannabinol resulting in a positive drug test would be disqualifying.
  - Received local anesthesia to the back, buttock, or posterior/lateral aspects of the affected leg (local anesthesia to the back during SI-6603 injection procedure was permitted). If the local anesthesia was part of a block procedure, exclusion criterion 5 applies.
    Note: The protocol permitted enrollment of otherwise qualifying subjects who were on opioids immediately prior to screening and who were willing to switch to hydrocodone/acetaminophen as an on-study rescue medication. However, it was possible and permissible that some sites may have elected not to enroll such subjects for logistical or other reasons.
- Subjects who currently had any of the following conditions:
  - Low back pain caused by disorders other than LDH;

  - Mean of worst low back pain assessed by VAS for 7 consecutive days up to the day before randomization was >90 mm; or;
  - Mean of worst low back pain assessed by VAS for 7 consecutive days up to the day before randomization was >10 mm higher than the mean of worst leg pain.
    Note: For low back pain assessment by VAS for 7 consecutive days up to the day before randomization, at least 5 out of 7 days needed to be entered.

- Subjects who were pregnant or breast-feeding, or women of childbearing potential with a positive serum or urine pregnancy test(s). Pregnancy tests were not required for female subjects who had undergone a hysterectomy and/or bilateral tubal ligation, or who were postmenopausal (had not menstruated within the past 2 years).
- Sexually active female subjects of childbearing potential who had a male partner and were not willing to use adequate contraceptive measures to avoid pregnancy until the end of the study. Sexually active male subjects with female partners who were not willing to use adequate contraceptive measures until Week 13 of the study. Adequate methods of birth control included the following:

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

    - Diaphragm plus a spermicidal agent; or
    - Condoms (male or female) plus a spermicidal agent.

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

  Female subjects who had undergone hysterectomy and/or bilateral tubal ligation, or were postmenopausal (had not menstruated within past 2 years) did not need to practice birth control.
- Subjects who had undergone a lumbar operation, lumbar percutaneous nucleotomy, or lumbar intradiscal therapies (eg, chemonucleolysis or intradiscal electrothermal treatment) at the affected level of lumbar spine, or surgery at any other lumbar spine level with persistent symptom(s) including failed back surgery syndrome.
- Subjects with any of the following:

  - X-ray imaging findings of vertebral body angle formed by flexion ≥5°, and/or spondylolisthesis (vertebral body translation ≥3 mm)* in the disc to be treated;
  - Any of the following spinal related disorders*: spondylosis deformans, degenerative spondylolisthesis, spinal deformity (scoliosis: Cobb angle >20° or lordosis [L1-S1]: Cobb angle <20°), spinal tumor, diskitis, vertebral fracture adjacent to the disc to be treated, bony stenosis with nerve root impingement at L3-L4, L4-L5 or L5-S1, or severe lumbar degenerative disc disease in the disc to be treated;
  - Any of the following spinal related disorders* associated with low back pain that would interfere with safety or efficacy evaluations: spinal canal stenosis (except for stenosis caused by LDH), spondyloarthritis, ankylosing spondylitis, vertebral fracture in the lumbar spine, significant degenerative disease of the facet joints, or other disorders of the lumbar spine;
  - Presence of osteophytes in the lumbar spine (Nathan's classification ≥3rd degree).*
    *Judged first by the investigator, then confirmed by assessment of independent central image readers.

- Subjects with history, diagnosis, signs or symptoms of disorders that, in the investigator's opinion, was likely to interfere with pain efficacy assessments. Examples may have included: chronic pain disorders (eg, fibromyalgia, restless legs syndrome), peripheral neuropathy caused by certain disorders (eg, diabetes), Parkinson's disease, complex regional pain syndrome, osteoarthritis (unless symptoms are only in the upper extremities), osteoporosis, spondyloarthritis, ankylosing spondylitis, rheumatoid arthritis, or gout.
- Subjects with any history of any psychosis or psychotic disorder (included schizophrenia and bipolar I disorder), or subjects with any nonpsychotic psychiatric disorder, including known personality disorders, that had been sufficiently severe to cause functional impairment within 6 months prior to screening. This latter exclusion was not intended to exclude subjects with depression or anxiety that did not cause functional impairment or who were adequately treated with antidepressant or anxiolytic medication at doses that were not expected to change during the course of the trial.
- Subjects with history within the last 5 years of substance abuse or dependency, including, but not limited to, alcohol, opioids, cannabis (even where legal), and prescribed central nervous system stimulants or depressants.
- Subjects with alcohol consumption in excess of an average of 2 drinks per day (1 unit=12 ounces of beer, 5 ounces of non-fortified wine, or 1.5 ounces of 80-proof liquor).
- Subjects who met either of the following conditions:
    - Subjects who could not wash-out opioids or cannabis for relief of pain, and could not remain free of these prohibited medications during the course of the trial; or
    - Subjects who had opioid withdrawal symptoms.
- Subjects who tested positive at screening or randomization for drugs of abuse, including (but not limited to) opioids, amphetamines (even when prescribed), cocaine, and cannabinoids (even where legal, prescribed, or possibly due to use of cannabidiol oil). A positive result for benzodiazepine may have been permissible if, in the investigator's opinion, it was the result of appropriate use of a prescribed medication. A positive result for opioids or cannabinoids at screening, but not baseline, was permissible if, in the investigator's opinion, the result was from opioids or cannabinoids taken before screening and which had since been stopped and would not be resumed during the study, except as specified for rescue medication. Exclusionary urine drug tests were considered conclusive and were not to be repeated.
  Note: Subjects should have been advised that they should not submit for urine drug testing if they had taken any opioids in the preceding 3 days or were using any of the prohibited drugs. Subjects should not have been urine drug tested if there was any reported or known prohibited drug use or opioid use within the preceding 3 days.
- Subjects who tested positive for alcohol on the blood alcohol test at screening. Subjects should have been informed that they must not drink alcohol within 12 hours of the screening blood test and should not have taken the test if they had done so. A positive blood alcohol test could not be repeated.
- Subjects who had 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.

- Subjects with neurological disorders, including cauda equina syndrome that was severe or that demonstrated rapid progression, and subjects who had a seizure in the past 5 years or who were taking anticonvulsant medications for any reason other than neuropathic pain.
- Subjects with motor weakness graded less than 4 (Medical Research Council Scale <4).
- Subjects with human immunodeficiency virus, or a current, active, clinically significant systemic infection that required treatment with antibiotics, antivirals, or antifungals.
- Subjects with the following medical conditions or diseases:
    - Clinically significant disorders, such as uncontrolled pulmonary disease (eg, asthma, chronic obstructive pulmonary disease), uncontrolled hypertension, type I or uncontrolled type II diabetes, or other serious heart, liver, kidney, or blood disease or immunodeficiency;
    - Clinically evident cerebrovascular disease, pulmonary infarction, congestive heart failure, or arrhythmia (eg, excludes normal sinus rate variations and atrial or ventricular ectopy ≤2/min); or
    - History or signs of coronary artery disease with or without angina pectoris or myocardial infarction within the last 6 months.
- Subjects who had difficulty receiving injection of investigational product, or subjects with a tendency to bleed or with bleeding disorders, such as (but not limited to) hemophilia, aplastic anemia, cirrhosis of the liver, leukemia, thrombocytopenia, and vitamin K deficiency. Subjects using medication for the purpose of anticoagulation, including heparin and warfarin, which cannot be reversed preoperatively, were also excluded.
- Subjects with medical conditions and/or diseases that the investigator believed could affect the study results or interfere with safe conduct of the study.
- Subjects who met any of the following criteria:
    - Aspartate aminotransferase or alanine aminotransferase ≥2.5x upper limit of normal (ULN);
    - Total bilirubin ≥1.5 x ULN, unless isolated Gilbert’s syndrome;
    - Serum creatinine ≥1.5 x ULN; or
    - Hepatitis C virus antibody or hepatitis B surface antigen positive. Subjects who had been successfully treated for hepatitis C and currently had undetectable hepatitis C virus RNA were eligible for study participation.
- Subjects with a body mass index (BMI) ≥40.
- Subjects who had difficulties securing an investigational product injection route by the investigator for anatomical reasons.
- Subjects who were currently hospitalized or had a planned hospitalization during the life of the study.
- Subjects who had a planned move that may have resulted in difficulty visiting a clinical site(s) during the life of the study.
- Subjects who previously participated in a clinical study of SI-6603.
- Subjects who were receiving compensation according to the Workers' Compensation Act or were involved in personal injury litigation due to a lumbar-related injury.
- Subjects who participated in another interventional clinical study within 30 days prior to the time of informed consent, or who were expected to participate in another study during the period of this study.

13.5.2 Study 1133 Efficacy Results Using MMRM (MAR) Analysis

Table 47: Change from Baseline in Weekly Averages of Worst Leg Pain at Week 52 Using MMRM (MAR) Analysis — Study 1133 (mITT)

	MMRM (MAR)	
Worst Leg Pain, VAS:	**Condoliase (N=169)**	**Sham (N=172)**
Baseline, mean (SD)	72.0 (9.55)	71.8 (9.75)
Week 52, LS mean (SE)	20.4 (2.40)	27.0 (2.41)
Change from Baseline, LS Mean (SE)	-51.2 (2.40)	-44.7 (2.41)
95% CI	(-55.9, -46.5)	(-49.4, -39.9)
Treatment difference for condoliase vs placebo		
Difference in LS means (SE)	-6.5 (3.40)	
95% CI	(-13.2, 0.2)	
p-value (nominal)	0.0558	

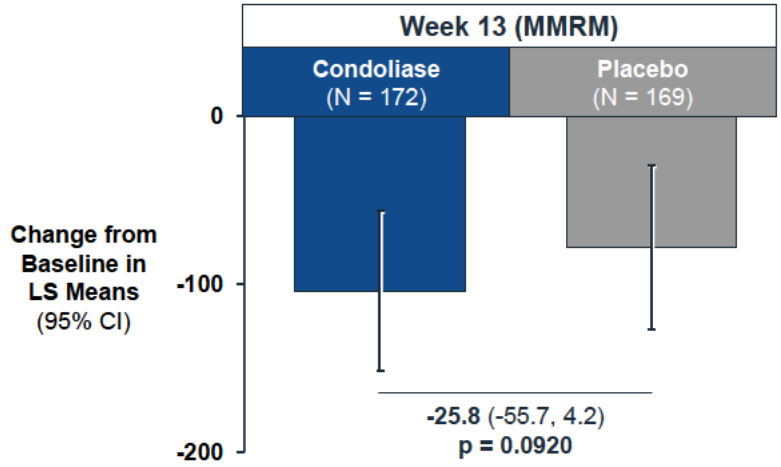
CI: confidence interval; LS: least squares; MAR: missing at random; mITT: modified intent to treat; MMRM: mixed methods repeat measures; SD: standard deviation; SE: standard error; VAS: visual analog scale.

Table 48: Change from Baseline in Weekly Average Worst Leg Pain at Each Time Point through Week 52 Using MMRM (MAR) Analysis — Study 1133 (mITT)

	MMRM (MAR)	
Visit:	**Difference in LS Means Compared to Placebo (95% CI)**	**p-value (Nominal)**
Week 1	-1.6 (-5.8, 2.5)	0.4311
Week 2	-3.8 (-8.8, 1.2)	0.1373
Week 4	-6.0 (-11.8, -0.2)	0.0418
Week 6	-7.4 (-13.3, -1.5)	0.0146
Week 13	-7.5 (-14.1, -0.9)	0.0263
Week 26	-8.5 (-15.1, -1.8)	0.0124
Week 39	-6.2 (-12.8, 0.5)	0.0689
Week 52	-6.5 (-13.2, 0.2)	0.0558

CI: confidence interval; LS: least squares; MAR: missing at random; mITT: Modified Intent to Treat; MMRM: mixed model repeated measures.

Figure 35: Change from Baseline in Disc Herniation Volume at Week 13 Using MMRM (MAR) Analysis — Study 1133 (mITT)



CI: confidence interval; LS: least squares; MAR: missing at random; mITT: modified intent to treat; MMRM: mixed methods repeat measures.
* Nominal p-value <0.05.

Table 49: Change from Baseline in ODI Score at Weeks 13 and 52 Using MMRM (MAR) Analysis — Study 1133 (mITT)

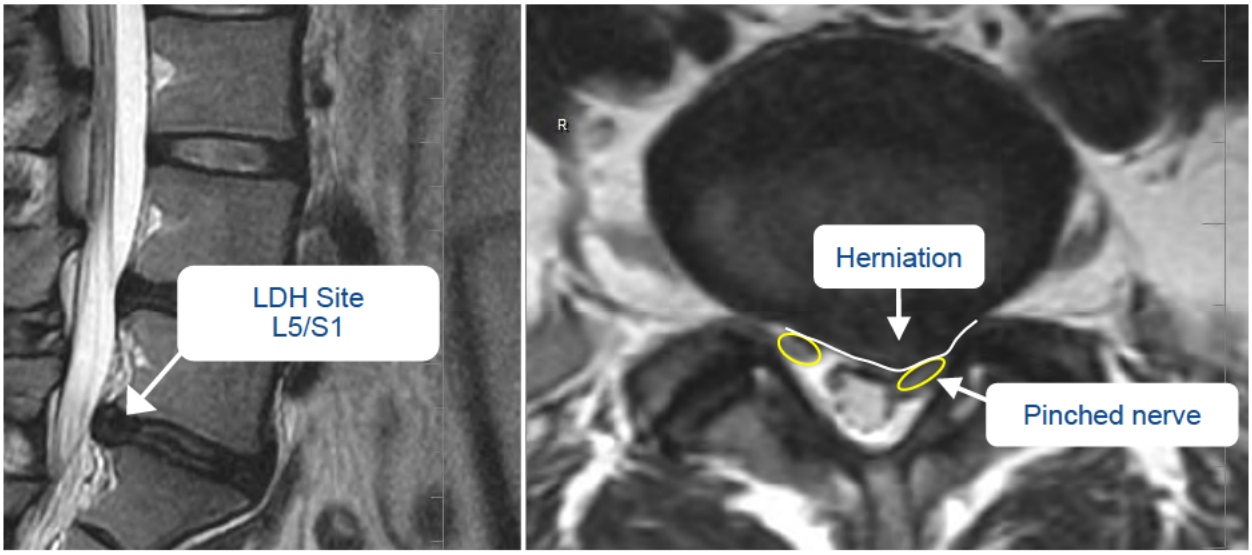
	MMRM (MAR)	
ODI Score:	**Condoliase (N=169)**	**Sham (N=172)**
Baseline, mean (SD)	48.2 (11.77)	49.1 (11.85)
Week 13, LS mean (SE)	19.1 (1.38)	23.2 (1.38)
Change from Baseline, LS mean (SE)	-29.6 (1.38)	-25.4 (1.38)
Treatment difference, LS mean (95% CI)	-4.2 (-8.0, -0.3)	
Nominal p-value	0.0336	
Week 52, LS mean (SE)	14.0 (1.34)	17.2 (1.34)
Change from Baseline, LS mean (95% CI)	-34.6 (1.34)	-31.5 (1.34)
Treatment difference, LS mean (95% CI)	-3.1 (-6.9, 0.6)	
Nominal p-value	0.1016	

CI: confidence interval; LS: least squares; MAR: missing at random; mITT: Modified Intent to Treat; MMRM: mixed model repeated measures; ODI: Oswestry disability index; SD: standard deviation.

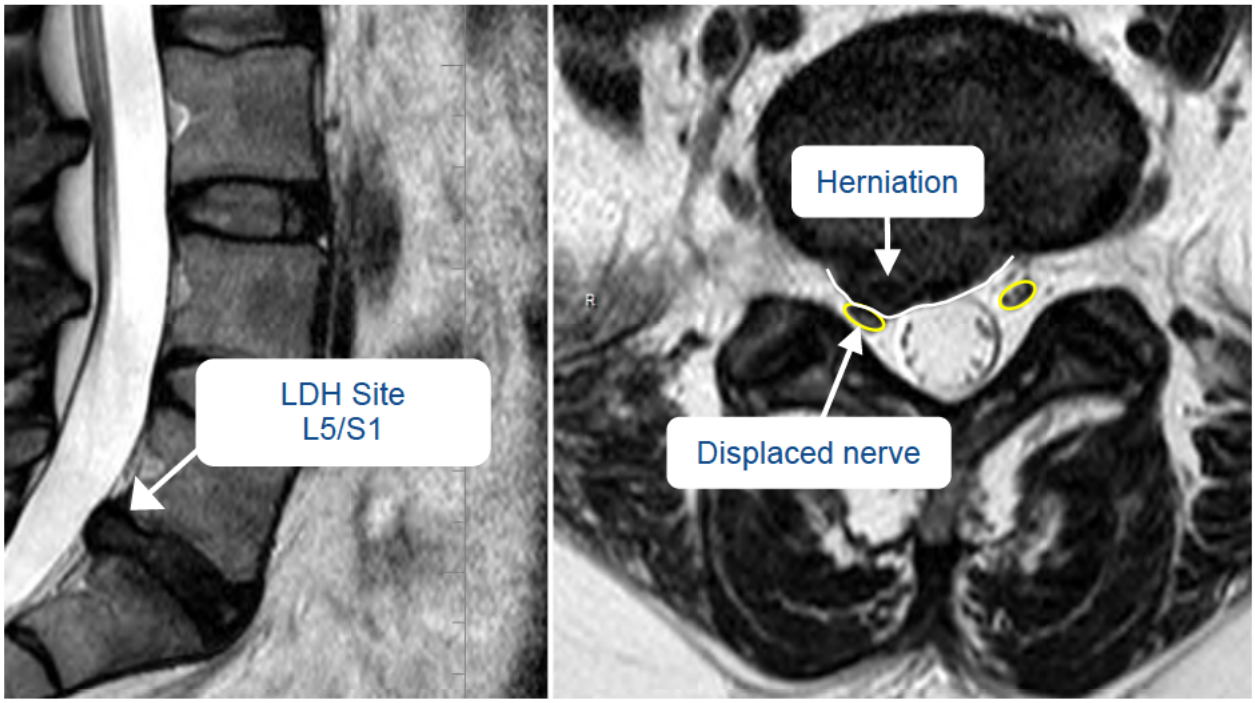
13.6 Imaging Examples of Nerve Root Impingement Appropriate for Treatment with Condoliase

Figure 36: Example Spine Images with Visible Nerve Root Impingement (Appropriate for Treatment with Condoliase)

Example of Pinched Nerve



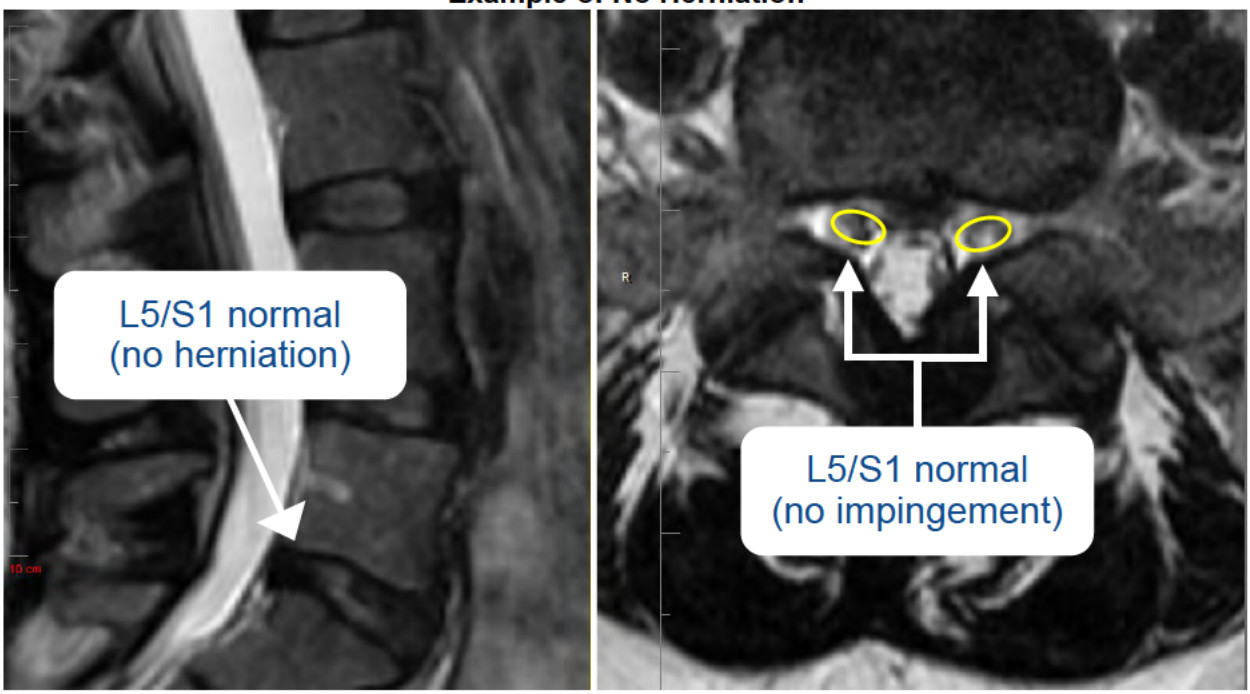
Example of Displaced Nerve



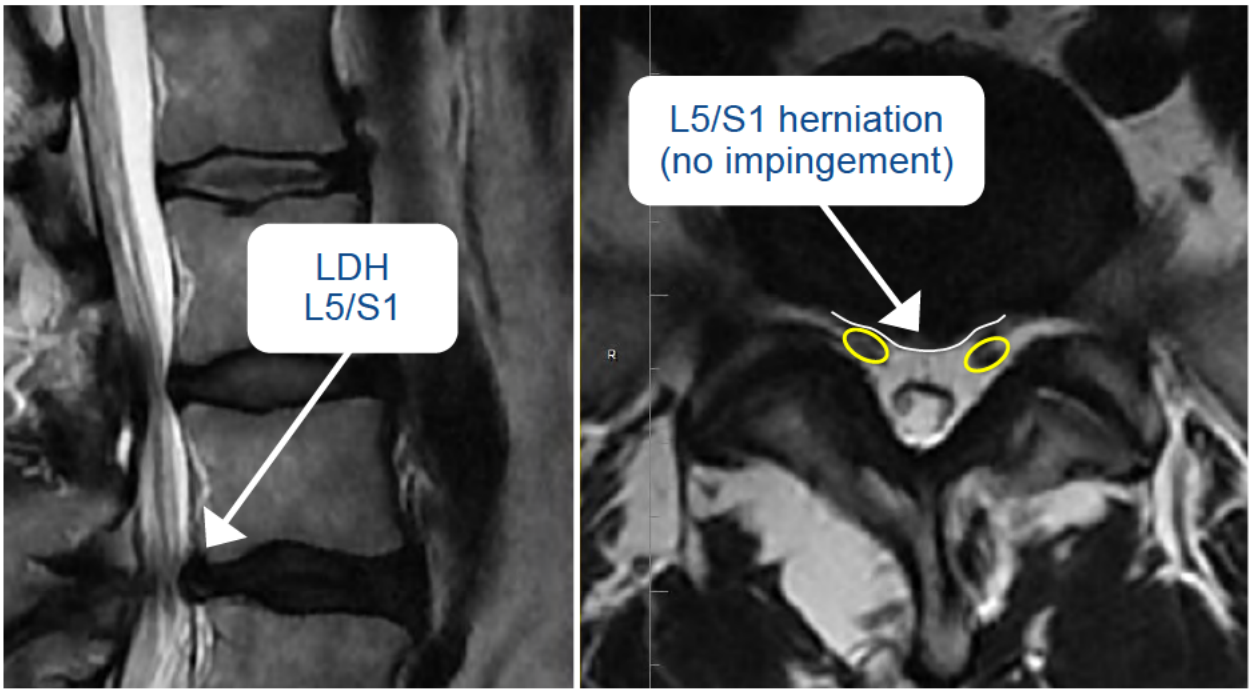
LDH: lumbar disc herniation.
Note: Deidentified patient images from Study 1133. Nerves encircled in yellow.

Figure 37: Example Spine Images without Visible Nerve Root Impingement (Inappropriate for Treatment with Condoliase)

Example of No Herniation



Example of Herniation without Nerve Root Impingement



LDH: lumbar disc herniation.
Note: Deidentified patient images from Study 1133. Nerves encircled in yellow.

13.7 Oswestry Disability Index (ODI) Questionnaire

Oswestry Low Back Pain Disability Questionnaire

Instructions

This questionnaire has been designed to give us information as to how your back or leg pain is affecting your ability to manage in everyday life. Please answer by checking ONE box in each section for the statement which best applies to you. We realise you may consider that two or more statements in any one section apply but please just shade out the spot that indicates the statement which most clearly describes your problem.

Section 1 – Pain intensity

- ☐ I have no pain at the moment
- ☐ The pain is very mild at the moment
- ☐ The pain is moderate at the moment
- ☐ The pain is fairly severe at the moment
- ☐ The pain is very severe at the moment
- ☐ The pain is the worst imaginable at the moment

Section 2 – Personal care (washing, dressing etc)

- ☐ I can look after myself normally without causing extra pain
- ☐ I can look after myself normally but it causes extra pain
- ☐ It is painful to look after myself and I am slow and careful
- ☐ I need some help but manage most of my personal care
- ☐ I need help every day in most aspects of self-care
- ☐ I do not get dressed, I wash with difficulty and stay in bed

Section 3 – Lifting

- ☐ I can lift heavy weights without extra pain
- ☐ I can lift heavy weights but it gives extra pain
- ☐ Pain prevents me from lifting heavy weights off the floor, but I can manage if they are conveniently placed eg. on a table
- ☐ Pain prevents me from lifting heavy weights, but I can manage light to medium weights if they are conveniently positioned
- ☐ I can lift very light weights
- ☐ I cannot lift or carry anything at all

Section 4 – Walking*

- ☐ Pain does not prevent me walking any distance
- ☐ Pain prevents me from walking more than 1 mile
- ☐ Pain prevents me from walking more than 1/2 mile
- ☐ Pain prevents me from walking more than 100 yards
- ☐ I can only walk using a stick or crutches
- ☐ I am in bed most of the time

(Continued on next page)

Section 5 – Sitting

- ☐ I can sit in any chair as long as I like
- ☐ I can only sit in my favourite chair as long as I like
- ☐ Pain prevents me sitting more than one hour
- ☐ Pain prevents me from sitting more than 30 minutes
- ☐ Pain prevents me from sitting more than 10 minutes
- ☐ Pain prevents me from sitting at all

Section 6 – Standing

- ☐ I can stand as long as I want without extra pain
- ☐ I can stand as long as I want but it gives me extra pain
- ☐ Pain prevents me from standing for more than 1 hour
- ☐ Pain prevents me from standing for more than 30 minutes
- ☐ Pain prevents me from standing for more than 10 minutes
- ☐ Pain prevents me from standing at all

Section 7 – Sleeping

- ☐ My sleep is never disturbed by pain
- ☐ My sleep is occasionally disturbed by pain
- ☐ Because of pain I have less than 6 hours sleep
- ☐ Because of pain I have less than 4 hours sleep
- ☐ Because of pain I have less than 2 hours sleep
- ☐ Pain prevents me from sleeping at all

Section 8 – Sex life (if applicable)

- ☐ My sex life is normal and causes no extra pain
- ☐ My sex life is normal but causes some extra pain
- ☐ My sex life is nearly normal but is very painful
- ☐ My sex life is severely restricted by pain
- ☐ My sex life is nearly absent because of pain
- ☐ Pain prevents any sex life at all

Section 9 – Social life

- ☐ My social life is normal and gives me no extra pain
- ☐ My social life is normal but increases the degree of pain
- ☐ Pain has no significant effect on my social life apart from limiting my more energetic interests eg, sport
- ☐ Pain has restricted my social life and I do not go out as often
- ☐ Pain has restricted my social life to my home
- ☐ I have no social life because of pain

Section 10 – Travelling

- ☐ I can travel anywhere without pain
- ☐ I can travel anywhere but it gives me extra pain
- ☐ Pain is bad but I manage journeys over two hours
- ☐ Pain restricts me to journeys of less than one hour
- ☐ Pain restricts me to short necessary journeys under 30 minutes
- ☐ Pain prevents me from travelling except to receive treatment

(End of Questionnaire)

13.8 Supplemental Safety Information

13.8.1 Serious Adverse Events up to Week 52

Table 50: Summary of Serious AEs by System Organ Class and Preferred Term — up to Week 13 (Pooled Phase 2/3 RCT Safety)

System Organ Class Preferred Term SAE, n (%):	Condoliase (N=578)	Placebo/Sham Pooled (N=396)
Patients with at least one SAE	15 (2.6)	13 (3.3)
Musculoskeletal and connective tissue disorders	5 (0.9)	6 (1.5)
Back pain	2 (0.3)	0
Intervertebral disc protrusion	2 (0.3)	3 (0.8)
Intervertebral disc disorder	1 (0.2)	0
Osteoarthritis	0	1 (0.3)
Pain in extremity	0	2 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.5)	0
Diffuse large B-cell lymphoma	1 (0.2)	0
Renal cell carcinoma	1 (0.2)	0
Uterine leiomyoma	1 (0.2)	0
Infections and infestations	2 (0.3)	1 (0.3)
Cellulitis	1 (0.2)	0
Intervertebral discitis	1 (0.2)	0
Osteomyelitis	1 (0.2)	0
Appendicitis	0	1 (0.3)
Nervous system disorders	2 (0.3)	4 (1.0)
Lumbar radiculopathy	2 (0.3)	0
Cervical radiculopathy	0	1 (0.3)
Radiculopathy	0	1 (0.3)
Sciatica	0	2 (0.5)
Seizure	0	1 (0.3)
Gastrointestinal disorders	1 (0.2)	2 (0.5)
Intestinal obstruction	1 (0.2)	0
Duodenal ulcer	0	1 (0.3)
Hemorrhoids	0	0
Lower gastrointestinal hemorrhage	0	1 (0.3)
General disorders and administration site conditions	1 (0.2)	0
Non-cardiac chest pain	1 (0.2)	0
Investigations	1 (0.2)	0
Liver function test increased	1 (0.2)	0

AE: adverse event; RCT: randomized, controlled trial; SAE: serious adverse event.
Note: Percentages based on Safety Population.

Table 51: Summary of Serious AEs by System Organ Class and Preferred Term — after Week 13 to Week 26 (Pooled Phase 2/3 RCT Safety)

System Organ Class Preferred Term SAE, n (%):	Condoliase (N=538)	Placebo/Sham Pooled (N=359)
Patients with at least one SAE	9 (1.7)	6 (1.7)
Infections and infestations	3 (0.6)	0
Abdominal abscess	1 (0.2)	0
Appendicitis	1 (0.2)	0
COVID-19	1 (0.2)	0
Musculoskeletal and connective tissue disorders	2 (0.4)	3 (0.8)
Intervertebral disc protrusion	2 (0.4)	2 (0.6)
Osteoarthritis	0	1 (0.3)
Eye disorders	1 (0.2)	0
Cataract	1 (0.2)	0
Gastrointestinal disorders	1 (0.2)	1 (0.3)
Abdominal hernia	1 (0.2)	0
Gastric ulcer	0	1 (0.3)
Injury, poisoning and procedural complications	1 (0.2)	2 (0.6)
Toxicity to various agents	1 (0.2)	0
Dural tear	0	1 (0.3)
Pseudomeningocele	0	1 (0.3)
Stab wound	0	1 (0.3)
Psychiatric disorders	1 (0.2)	1 (0.3)
Bipolar disorder	1 (0.2)	0
Suicide attempt	0	1 (0.3)

AE: adverse event; RCT: randomized, controlled trial; SAE: serious adverse event.
Note: Percentages are based on patients who were still in the study up until the start of the interval. For SAEs, after Week 13 to Week 26 includes all studies in the Pool (1021, 1031, 1131, and 1133).

Table 52: Summary of Serious AEs by System Organ Class and Preferred Term — after Week 26 to Week 52 (Pooled Phase 2/3 RCT Safety)

System Organ Class Preferred Term, n (%):	Condoliase (N=493)	Placebo/Sham Pooled (N=333)
Patients with at least one SAE	14 (2.8)	6 (1.8)
Musculoskeletal and connective tissue disorders	4 (0.8)	3 (0.9)
Intervertebral disc protrusion	2 (0.4)	0
Back pain	1 (0.2)	1 (0.3)
Neck pain	1 (0.2)	0
Arthralgia	0	1 (0.3)
Spinal osteoarthritis	0	1 (0.3)
Vertebral foraminal stenosis	0	1 (0.3)

System Organ Class Preferred Term, n (%):	Condoliase (N=493)	Placebo/Sham Pooled (N=333)
Infections and infestations	3 (0.6)	1 (0.3)
Clostridium difficile colitis	1 (0.2)	0
Urosepsis	1 (0.2)	0
Viral infection	1 (0.2)	0
Appendicitis	0	1 (0.3)
Injury, poisoning and procedural complications	2 (0.4)	0
Facial bones fracture	1 (0.2)	0
Pulmonary contusion	1 (0.2)	0
Rib fracture	1 (0.2)	0
Skin abrasion	1 (0.2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.4)	0
Metastases to spine	1 (0.2)	0
Parathyroid tumor	1 (0.2)	0
Reproductive system and breast disorders	2 (0.4)	0
Cervical dysplasia	1 (0.2)	0
Ovarian cyst	1 (0.2)	0
Cardiac disorders	1 (0.2)	0
Prinzmetal angina	1 (0.2)	0
Metabolism and nutrition disorders	1 (0.2)	0
Dehydration	1 (0.2)	0
Nervous system disorders	1 (0.2)	0
Cerebral haematoma	1 (0.2)	0
Renal and urinary disorders	1 (0.2)	0
Bladder perforation	1 (0.2)	0
Hepatobiliary disorders	0	2 (0.6)
Cholecystitis	0	1 (0.3)
Cholecystitis acute	0	1 (0.3)

AE: adverse event; RCT: randomized, controlled trial; SAE: serious adverse event.
Note: Percentages are based on patients who were still in the study up until the start of the interval. For SAEs, after Week 26 to Week 52 includes all studies in the Pool (1021, 1031, 1131, and 1133).

13.8.2 All Hypersensitivity and Anaphylactic Reaction AEs in Pooled Phase 2/3 Randomized Clinical Trials

Table 53: All Hypersensitivity and Anaphylactic Reaction (SMQ Broad) Adverse Events (Pooled Phase 2/3 RCT Safety)

SMQ Broad AE, n (%):	Condoliase (N=578)	Placebo/Sham Pooled (N=396)
Hypersensitivity (SMQ)	31 (5.4)	16 (4.0)
Rash	11 (1.9)	3 (0.8)
Asthma	3 (0.5)	1 (0.3)
Conjunctivitis	3 (0.5)	0
Dermatitis contact	3 (0.5)	1 (0.3)
Pruritus	3 (0.5)	0
Urticaria	3 (0.5)	1 (0.3)
Toxic skin eruption	2 (0.3)	0
Conjunctivitis allergic	1 (0.2)	0
Contrast media allergy	1 (0.2)	0
Cough variant asthma	1 (0.2)	0
Drug hypersensitivity	1 (0.2)	0
Eczema nummular	1 (0.2)	0
Eosinophilia	1 (0.2)	0
Erythema	1 (0.2)	0
Flushing	1 (0.2)	0
Hand dermatitis	1 (0.2)	0
Allergic cough	0	1 (0.3)
Angioedema	0	1 (0.3)
Drug eruption	0	0
Eczema	0	2 (0.5)
Eosinophil count increased	0	1 (0.3)
Injection site dermatitis	0	1 (0.3)
Injection site rash	0	1 (0.3)
Rash maculo-papular	0	1 (0.3)
Rhinitis allergic	0	1 (0.3)
Seasonal allergy	0	1 (0.3)
Anaphylactic reaction (SMQ)	27 (4.7)	10 (2.5)
Rash	11 (1.9)	3 (0.8)
Cough	4 (0.7)	2 (0.5)
Asthma	3 (0.5)	1 (0.3)
Pruritus	3 (0.5)	0
Urticaria	3 (0.5)	1 (0.3)
Cough variant asthma	1 (0.2)	0
Dyspnea	1 (0.2)	1 (0.3)
Erythema	1 (0.2)	0

SMQ Broad AE, n (%):	Condoliase (N=578)	Placebo/Sham Pooled (N=396)
Flushing	1 (0.2)	0
Hypotension	1 (0.2)	0
Swelling	1 (0.2)	0
Angioedema	0	1 (0.3)
Hyperventilation	0	1 (0.3)

AE: adverse event; RCT: randomized, controlled trial; SMQ: standardized MedDRA query.

13.8.3 Postmarketing Adverse Events of Interest by Preferred Term

Table 54: All Safety Topics of Interest Collected in Postmarketing Setting (SMQ Narrow Search) — Solicited and Unsolicited, Serious and Non-serious

SMQ (Narrow) Preferred Term, n:	Unsolicited		Solicited	
	Non-serious	Serious	Non-serious	Serious
Any adverse events	87	36	104	45
Anaphylaxis (SMQ narrow)	1	1	0	1
Anaphylactic reaction	0	1	0	1
Anaphylactic shock	1	0	0	0
Discitis	1	8	3	4
Intervertebral discitis	1	8	3	4
Hematomas	0	0	0	1
Spinal epidural hematoma	0	0	0	1
Hypersensitivity (SMQ narrow)	84	16	79	6
Acute generalized exanthematous pustulosis	0	1	0	1
Anaphylactic reaction	0	1	0	1
Anaphylactic shock	1	0	0	0
Dermatitis allergic	0	0	6	0
Dermatitis exfoliative generalized	0	0	0	1
Drug eruption	10	6	15	0
Drug hypersensitivity	1	0	1	0
Eczema	2	1	2	0
Erythema multiforme	1	1	0	0
Hypersensitivity	0	0	1	0
Rash	46	2	21	1
Rash pruritic	1	0	0	0
Stevens-Johnson syndrome[1]	0	1	0	0
Toxic skin eruption	1	0	1	0
Urticaria	21	3	32	2
Osteomyelitis	0	3	0	0

SMQ (Narrow) Preferred Term, n:	Unsolicited		Solicited	
	Non-serious	Serious	Non-serious	Serious
Osteomyelitis	0	3	0	0
Paresis and Paralysis	0	0	0	1
Monoplegia	0	0	0	1
Spinal abnormalities	1	8	22	32
Extradural abscess	0	2	0	1
Lumbar spinal stenosis	1	1	7	14
Myelopathy	0	0	0	1
Spinal compression fracture	0	0	3	3
Spinal instability	0	1	2	2
Spinal osteoarthritis	0	0	2	1
Spinal synovial cyst	0	1	2	3
Spondylolisthesis	0	1	4	4
Spondylolysis	0	0	0	1
Vertebral foraminal stenosis	0	2	1	2
Vertebral lateral recess stenosis	0	0	1	0

SJS: Stevens-Johnson Syndrome; SMQ: standardized MedDRA query.
1. On follow-up review, the case lacked seminal features of Stevens-Johnson Syndrome (SJS), eg, mucous membrane involvement, and therefore the diagnosis has been updated to anaphylaxis and not SJS. A follow-up report is in progress.
Note: Data compiled from 6 years of postmarketing pharmacovigilance in Japan from approval in March 2018 through data cutoff date of March 11, 2024. Estimated 27,000 exposures, based on number of units shipped. Preferred terms classified as Hypersensitivity SMQ (narrow) and Anaphylactic reaction SMQ (narrow), respectively, were tabulated.

Table 55: All Safety Topics of Interest Collected in Postmarketing Setting (SMQ Broad Search) — Solicited and Unsolicited, Serious and Non-serious

SMQ (Broad) Preferred Term, n:	Unsolicited		Solicited	
	Non-serious	Serious	Non-serious	Serious
AI safety topic of interest events	195	47	174	49
Anaphylaxis (SMQ broad)	91	10	62	5
Anaphylactic reaction	0	1	0	1
Anaphylactic shock	1	0	0	0
Blood pressure decreased	2	0	0	0
Cough	1	0	0	0
Dyspnea	0	2	1	1
Erythema	6	1	4	0
Hyperventilation	1	0	0	0
Pruritus	12	1	4	0
Rash	46	2	21	1
Rash pruritic	1	0	0	0
Urticaria	21	3	32	2

SMQ (Broad) Preferred Term, n:	Unsolicited		Solicited	
	Non-serious	Serious	Non-serious	Serious
Discitis	1	8	3	4
Intervertebral discitis	1	8	3	4
Hematomas	0	0	0	1
Spinal epidural hematoma	0	0	0	1
Hypersensitivity (SMQ broad)	102	18	87	6
Acute generalized exanthematous pustulosis	0	1	0	1
Anaphylactic reaction	0	1	0	1
Anaphylactic shock	1	0	0	0
Dermatitis allergic	0	0	6	0
Dermatitis exfoliative generalized	0	0	0	1
Drug eruption	10	6	15	0
Drug hypersensitivity	1	0	1	0
Eczema	2	1	2	0
Erythema	6	1	4	0
Erythema multiforme	1	1	0	0
Hypersensitivity	0	0	1	0
Pruritus	12	1	4	0
Rash	46	2	21	1
Rash pruritic	1	0	0	0
Stevens-Johnson syndrome[1]	0	1	0	0
Toxic skin eruption	1	0	1	0
Urticaria	21	3	32	2
Osteomyelitis	0	3	0	0
Osteomyelitis	0	3	0	0
Paresis and Paralysis	0	0	0	1
Monoplegia	0	0	0	1
Spinal abnormalities	1	8	22	32
Extradural abscess	0	2	0	1
Lumbar spinal stenosis	1	1	7	14
Myelopathy	0	0	0	1
Spinal compression fracture	0	0	3	3
Spinal instability	0	1	2	2
Spinal osteoarthritis	0	0	2	1
Spinal synovial cyst	0	1	2	3
Spondylolisthesis	0	1	4	4
Spondylolysis	0	0	0	1
Vertebral foraminal stenosis	0	2	1	2
Vertebral lateral recess stenosis	0	0	1	0

SMQ (Broad) Preferred Term, n:	Unsolicited		Solicited	
	Non-serious	Serious	Non-serious	Serious

SJS: Stevens-Johnson Syndrome; SMQ: standardized MedDRA query.
1. On follow-up review, the case lacked seminal features of Stevens-Johnson Syndrome (SJS), eg, mucous membrane involvement, and therefore the diagnosis has been updated to anaphylaxis and not SJS. A follow-up report is in progress.
Note: Data compiled from 6 years of postmarketing pharmacovigilance in Japan from approval in March 2018 through data cutoff date of March 11, 2024. Estimated 27,000 exposures, based on number of units shipped. Preferred terms classified as Hypersensitivity SMQ (broad) and Anaphylactic reaction SMQ (broad), respectively, were tabulated.

13.8.4 MedDRA Queries Used for Safety Topics of Interest

Table 56: MedDRA Queries Used for Safety Topics of Interest

Safety Topic of Interest	Means of Identification
Discitis	Preferred Term: Intervertebral discitis
Osteomyelitis	Preferred Terms: Candida osteomyelitis Chronic recurrent multifocal osteomyelitis Osteomyelitis Osteomyelitis acute Osteomyelitis bacterial Osteomyelitis blastomyces Osteomyelitis chronic Osteomyelitis drainage Osteomyelitis fungal Osteomyelitis salmonella Osteomyelitis viral Staphylococcal osteomyelitis
Hematomas	Preferred Terms: Administration site hematoma Application site hematoma Hematoma Hematoma infection Hematoma muscle Injection site hematoma Intra-abdominal hematoma Post procedural hematoma Puncture site hematoma Spinal cord hematoma Spinal epidural hematoma Spinal subdural hematoma Subcutaneous hematoma Traumatic hematoma Spinal subarachnoid haemorrhage Spinal subdural haemorrhage Spinal stroke
Hypersensitivity	Hypersensitivity SMQ (broad and narrow)
Anaphylaxis	Anaphylactic reaction SMQ (broad and narrow)
Paresis and Paralysis	All Preferred Terms under the High Level Term: Paralysis and paresis (excluding cranial nerve)
Spinal Abnormalities	Preferred Terms: Extradural abscess

Safety Topic of Interest	Means of Identification
	Ligamentum flavum hypertrophy Lumbar spinal stenosis Myelopathy Spinal retrolisthesis Spinal compression fracture Spinal instability Spinal deformity Spinal fracture Spinal cord abscess Spinal cord disorder Spinal synovial cyst Spondylolisthesis Spondylolysis Spinal osteoarthritis Vertebral foraminal stenosis Vertebral lateral recess stenosis
Medication error	Preferred Terms: Product administered at inappropriate site Medication Error Product Administration Error

MedDRA: Medical Dictionary for Regulatory Activities; SMQ: standardized MedDRA query.