BLA 761393

Condoliase Injection

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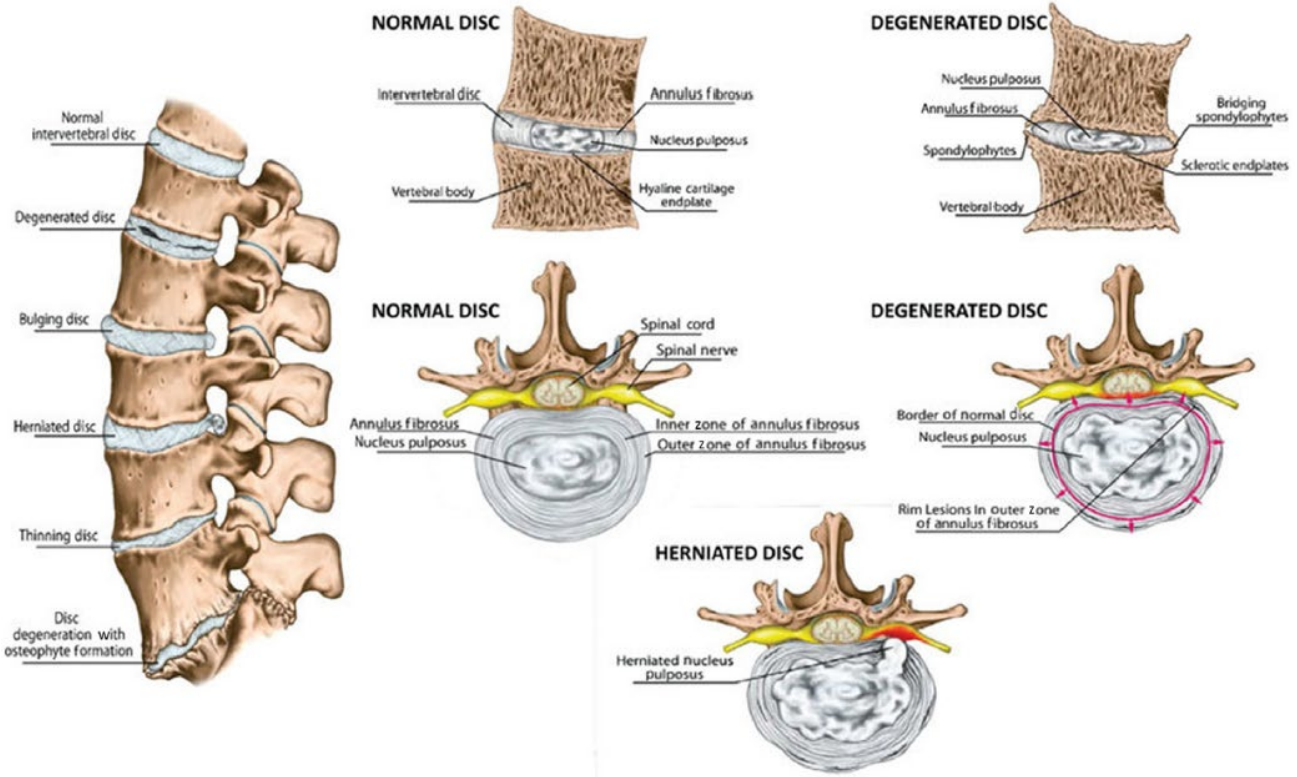
Outline

- Lumbar disc herniation (LDH) and radiculopathy
  - Anatomy and clinical aspects
- Efficacy
  - Agency approach to the three adequate and well-controlled studies
- Safety
  - Major safety findings, common adverse events (AEs)
  - Adverse events of special interest
- Summary

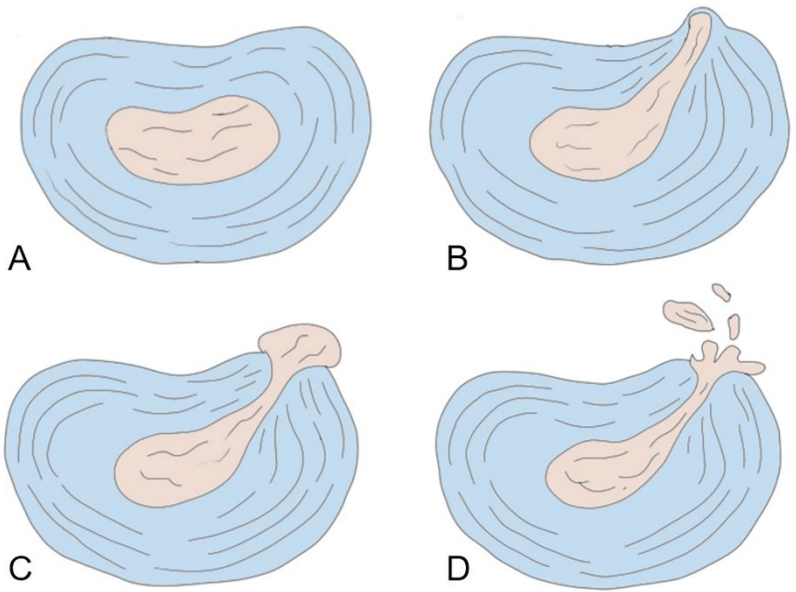
Lumbar Disc Herniation:
Background



Source: *Lumbar radicular pain,* Soar, H. et al., BJA Education.

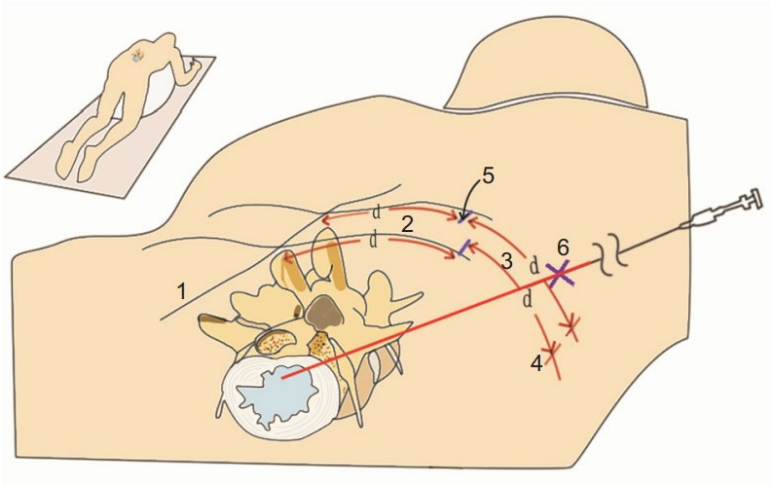
Lumbar Disc Herniation:
Background

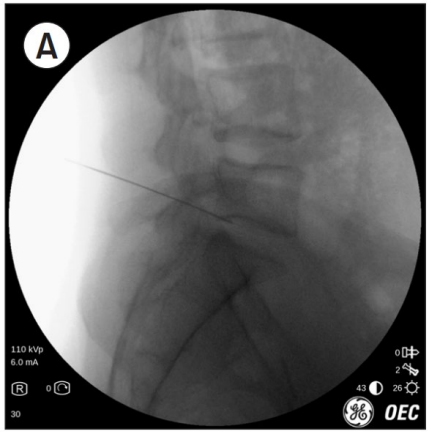
- The nucleus pulposus is a physiologically hydrated structure
- Herniation occurs through the annulus fibrosis
- Herniation can cause inflammation and lead to radicular symptoms
- Condoliase is a chondroitin sulfate degrading enzyme
- This can reduce intradiscal pressure and volume

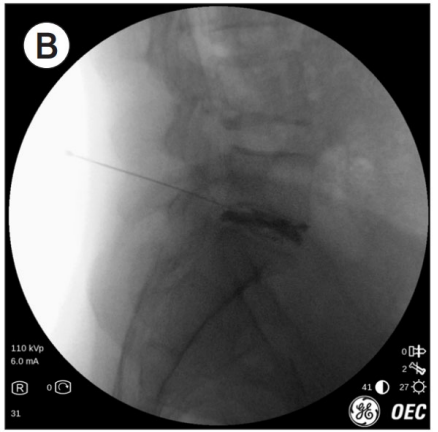


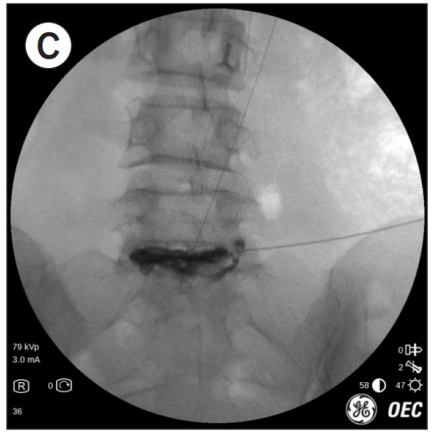
Source: Chen, Chien-Min, et al., 2020

Disc Access Procedure









www.fda.gov

Source: *Predictors of discogenic pain in magnetic resonance imaging,* Jain A et al., Korean J Pain 2021

Interventional Pain Practice

- Disc access requires detailed anatomic knowledge
- Multiple procedural variables
- Condoliase would commonly be administered by Interventional Pain Management (IPM) physicians
- IPM has a wide array of practice patterns

Efficacy

Summary of Phase 3 Studies

- The Applicant submitted three adequate and well-controlled studies:
  - Two studies were positive (1031 [Japan] and 1133 [US])
  - One study was negative (1131 [US])
- The negative study informed the eligibility criteria for Study 1133.
- We interrogated the causes of the failure for Study 1131.

Summary of Phase 3 Studies:

Primary Efficacy Endpoint

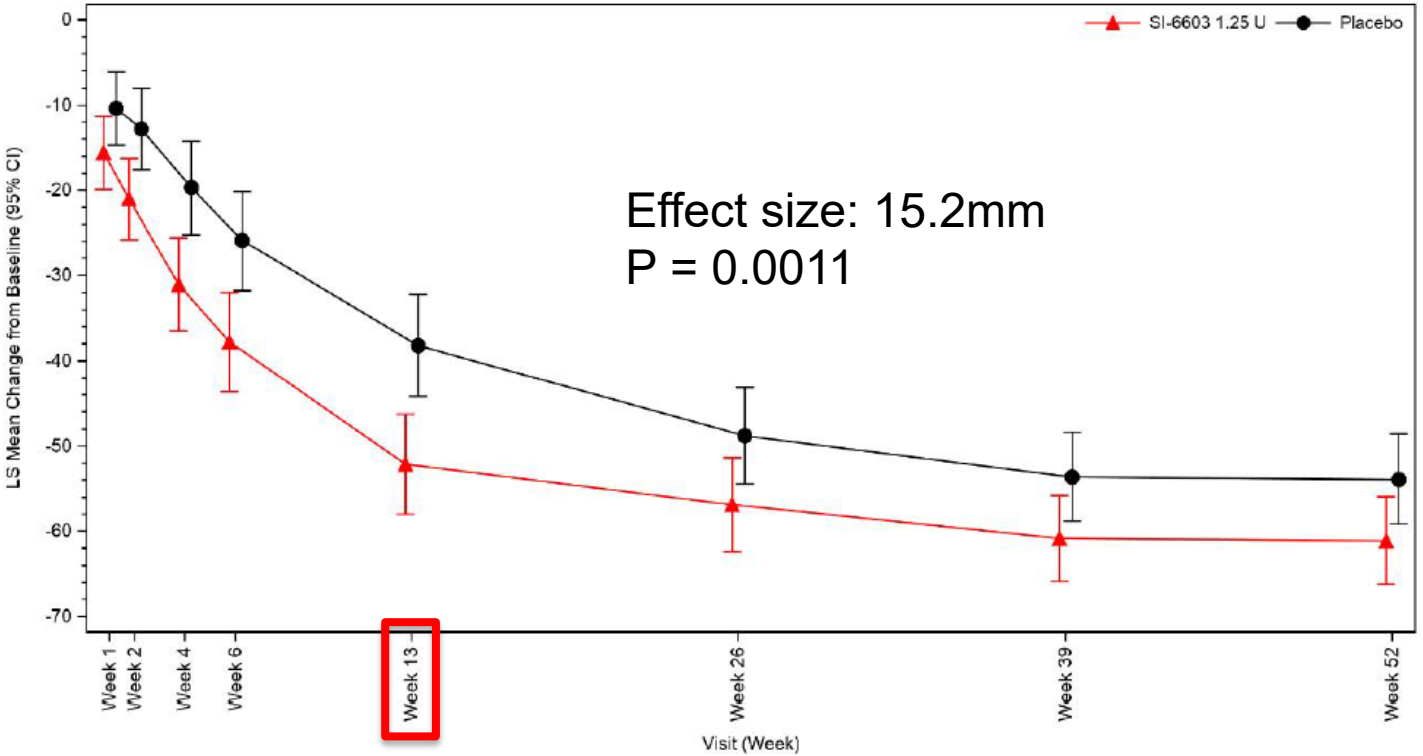
Study Characteristic	Study 1031 (Positive)	Study 1131 (Negative)	Study 1133 (Positive)
Location	Japan	USA	USA
Dates Conducted	3/2012-2/2014	9/2013 – 8/2017	11/2018–3/2023
Treatment LS Mean	-49.5mm	-37.7mm	-41.7mm
Control LS Mean	-34.3mm (placebo)	-39.6mm (sham)	-34.2mm (sham)
Estimated Treatment Effect (95% CI)	-15.2 (-24.2, -6.2)	+1.9 (-5.6, 9.4)	-7.5 (-14.1, -0.9)
p-value	p = 0.0011	p = 0.6212	p = 0.0263

Baseline Characteristics

- In general, the mean age of patients was 40 to 50 years with no consistent sex predominance.
- In the US studies, approximately 80% of patients were White and 10% Black or African American.
- The rate of baseline comorbidities ranged from 70% to 91%.
- Patients in the Japanese study were younger, had lower body mass index (24 versus ~28), and higher proportions of persons engaged in heavy labor (62% versus <26%).

Primary Endpoint Study 1031

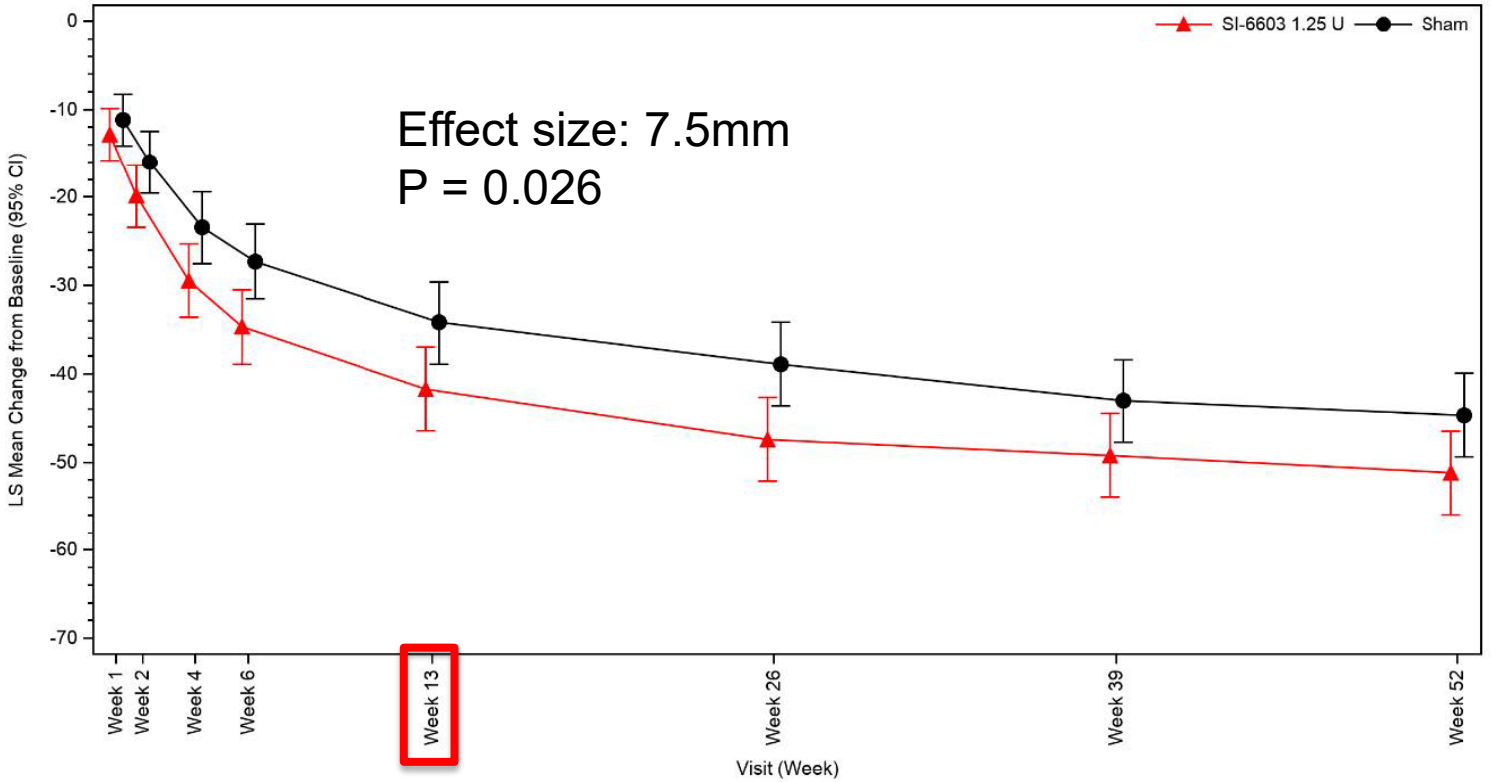
(Worst Leg Pain at Week 13, Modified Intent-To-Treat [mITT] Population)



Source: Integrated Summary of Efficacy, Page 78

Primary Endpoint Study 1133

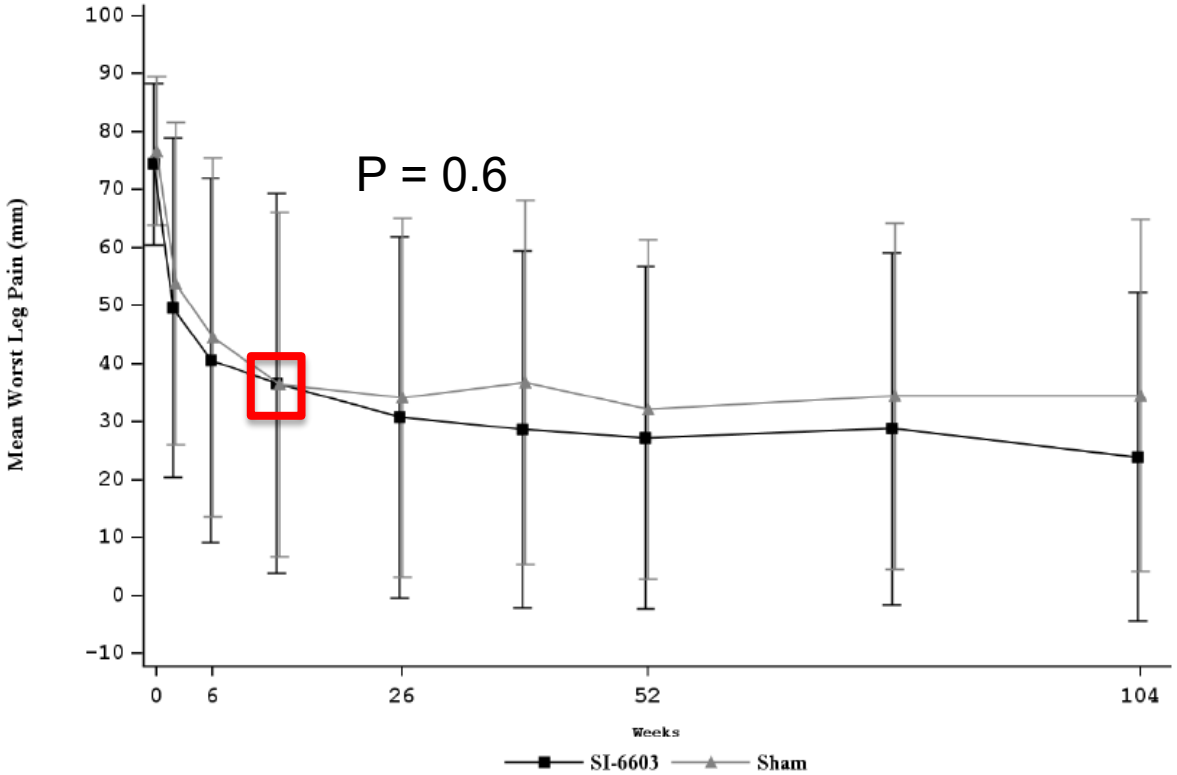
(Worst Leg Pain at Week 13, mITT Population)



Source: Integrated Summary of Efficacy, Page 78

Primary Endpoint Study 1131

(Worst Leg Pain at Week 13, Intent-To-Treat [ITT] Population)



Source: Study 1131 Clinical Study Report, Page 81

Negative Study:
Applicant's Explanation

- "In Study 1131, a majority of enrolled subjects had radiologic evidence showing non-definitive impingement of the nerve root by their herniation. These findings are in contrast to the findings in Study 1031."
  - "Based on these findings, the inclusion/exclusion criteria of Study 1133 were modified to identify subjects with demonstrable nerve root impingement by definitive appearance of herniation assessed by magnetic resonance imaging (MRI)"
- Study 1131 enrolled patients with higher baseline low back pain

Source: Integrated Summary of Efficacy, Page 57

Strategy to Interrogate Failed Study

- Compare/contrast design differences (selection criteria, comparator, etc.)
- Compare/contrast results
  - Baseline characteristics
  - Protocol compliance
  - Subgroup analyses
  - Quantity of missing data/imputation
- Hypothesis generation
- Request/conduct analyses to explore hypothesis(es)
- Decide whether the failure of Study 1131 is explicable
- Determine whether substantial evidence of efficacy was met

Study Eligibility Criteria

Selection Criteria	Study 1031 (Positive)	Study 1131 (Negative)	Study 1133 (Positive)
MRI Confirmed Nerve Root Impingement Criteria	None	None	Enrolled only patients **WITH** MRI confirmed nerve root impingement

Baseline Characteristics

Baseline Characteristic	Study 1031 (Positive)	Study 1131 (Negative)	Study 1133 (Positive)
Percentage of Patients With MRI Confirmed Nerve Root Impingement	88%	27%	100%

Source: Information Request (IR) Response received July 19, 2024, Tables IR17.3.1a.1 – IR 17.3.2

Key Differences in Eligibility Criteria

Study 1131 (Negative) Enrolled Patients With:	Study 1133 (Positive)
Low Back Pain > Radicular Leg Pain (20%) • Baseline mean back pain VAS: 74.8mm	Excluded LBP > Radicular Leg Pain and patients with back pain not due to lumbar disc herniation (LDH) • Baseline mean back pain VAS: 53.1mm
Comorbid Chronic Pain Disorders (7.2%)	Excluded potential confounding lower extremity diagnoses
Comorbid Chronic Spine Comorbidities (3.5%)	Excluded patients with other potential lumbar spine pain generators

Source: IR Response received July 19, 2024, Tables IR17.3.1a.1 – IR 17.3.2

Study 1131 Findings

- Statistical interrogation for causes of Study 1131 failure
- Results inconclusive, cannot identify specific cause(s)
- Confirmation of nerve root impingement has clinical validity

Efficacy Conclusions

- The Applicant has fulfilled the requirement to show substantial evidence of effectiveness
- The effect size ranges from 7.5 mm to 15.2 mm
- The indication of treatment of radicular leg pain associated with confirmed nerve root impingement caused by LDH is supported by the evidence

Safety

Condoliase Safety

- General Safety
  - Exposure and sources of data
  - Major safety findings
  - Common, non-serious adverse events
- Adverse events of special interest
  - “Spine-related adverse events”
  - Hypersensitivity
- Summary

General Safety

Data Sources and Exposure

Clinical Study Data

Phase/Countries	Study/Design	Subjects with Exposure to SI-6603 ≥ 1.25 U	Subjects Followed for ≥26 Weeks	Subjects Followed for ≥52 Weeks	Subjects Followed for ≥104 Weeks [1]
Phase 2 / United States	Study1121/ Open-label	12	NA	NA	NA
Phase 2/3 / Japan	Study1021/ Double-blind Placebo-control	147	NA	NA	NA
Phase 3 Pivotal / Japan	Study1031/ Double-blind Placebo-control	82	NA	NA	NA
Phase 3 Pivotal / United States	Study1131/ Double-blind sham injection control	280	253	231	204
Phase 3 / United States and Europe	Study1132/ Open-label	991	703	NA	NA
Phase 3 Pivotal / United States	Study1133/ Double-blind sham injection control	167	145	95	NA
Total		1679	1101	326	204
FDA Requirement		1500	1000	300	150

Source: Integrated Summary of Safety (ISS), Table 7

Condoliase Safety – AE Collection Periods

Primary Safety Pool

Study	Phase/ Country	13-weeks	26-weeks	52-weeks	104-weeks
Double-Blind, Randomized, Sham- or Placebo-Controlled, Phase 2/3 or Phase 3 Studies					
Study 1021	Phase 2/3 / Japan	Full Safety Monitoring	SAEs and AEs related to intervertebral disc and surrounding tissues		NA
Study 1031	Phase 3 Pivotal Study/ Japan	Full Safety Monitoring	SAEs and AEs related to intervertebral disc and surrounding tissues		NA
Study 1131	Phase 3 Pivotal Study/ US	Full Safety Monitoring			
Study 1133	Phase 3 Pivotal Study/ US	Full Safety Monitoring			NA
Open-Label Phase 2 or Phase 3 Studies					
Study 1121	Phase 2/ US	Full Safety Monitoring	SAEs and AEs related to intervertebral disc and surrounding tissues		NA
Study 1132	Phase 3/ US and EU	Full Safety Monitoring		NA	
Open-Label Phase 1/2 Study					
SKK6603J01	Phase 1/2 / Japan	Full Safety Monitoring	NA		

Source: Integrated Summary of Safety, Table 5

SAE: Serious Adverse Event, **AE:** Adverse Event

Japanese Postmarketing Data Summary

- Condoliase was approved in Japan in 2018.
- Data sources for postmarketing data include Unsolicited and Solicited reports.
- Multiple periodic safety update reports have been submitted to the Japanese Pharmaceuticals and Medical Devices Agency.

Summary of Treatment-Emergent Adverse Events (TEAEs) – All Time Intervals (Primary Safety Pool)

			Pooled		
	SI-6603 1.25 U (N=578) n (%)	SI-6603 >1.25 U (N=98) n (%)	Placebo (N=128) n (%)	Sham Control (N=268) n (%)	Placebo/Sham Pooled (N=396) n (%)
Treatment-emergent AEs					
Total number of events	1377	178	273	491	764
Subjects with events	450 (77.8)	83 (84.7)	99 (76.5)	167 (63.3)	266 (67.7)
Subjects who died	3 (0.4)	0	0	1 (0.6)	1 (0.4)
Subjects with events leading to study discontinuation	7 (1.0)	0	6 (4.0)	7 (2.8)	13 (3.2)
Serious treatment-emergent AEs					
Total number of Serious events	54	3	9	23	32
Subjects with Serious events	43 (6.7)	3 (3.1)	9 (6.9)	17 (7.8)	26 (7.5)

Source: 74-Day Letter Response received June 13, 2024, Table D74.10a (Page 8-9)

TEAE: Treatment Emergent Adverse Event

Summary of TEAEs From Weeks 0-13 (>2% of Patients by PT) (Primary Safety Pool)

			Pooled		
Preferred Term	**SI-6603 1.25 U (N = 578) n (%)**	**SI-6603 >1.25 U (N = 98) n (%)**	**Placebo (N = 128) n (%)**	**Sham Control (N = 268) n (%)**	**Placebo/ Sham Pooled (N = 396) n (%)**
Subjects with at least one TEAE	381 (65.9)	75 (76.5)	88 (68.8)	127 (47.4)	215 (54.3)
Back pain	133 (23.0)	22 (22.4)	33 (25.8)	26 (9.7)	59 (14.9)
Magnetic resonance imaging spinal abnormal	107 (18.5)	17 (17.3)	3 (2.3)	9 (3.4)	12 (3.0)
Pain in extremity	65 (11.2)	14 (14.3)	31 (24.2)	17 (6.3)	48 (12.1)
Nasopharyngitis	34 (5.9)	8 (8.2)	14 (10.9)	2 (0.7)	16 (4.0)
Spinal X-ray abnormal	29 (5.0)	13 (13.3)	6 (4.7)	1 (0.4)	7 (1.8)
Injection site pain	27 (4.7)	5 (5.1)	10 (7.8)	6 (2.2)	16 (4.0)
Arthralgia	24 (4.2)	0	0	12 (4.5)	12 (3.0)
C-reactive protein increased	16 (2.8)	3 (3.1)	2 (1.6)	7 (2.6)	9 (2.3)
Headache	13 (2.2)	1 (1.0)	5 (3.9)	6 (2.2)	11 (2.8)
Hypoaesthesia	13 (2.2)	1 (1.0)	6 (4.7)	5 (1.9)	11 (2.8)
Sciatica	11 (1.9)	0	0	9 (3.4)	9 (2.3)
Nausea	9 (1.6)	0	2 (1.6)	6 (2.2)	8 (2.0)

Summary of TEAEs From Weeks 13-26 (>2% of Patients by PT) (Primary Safety Pool)

			Pooled		
Preferred Term	**SI-6603 1.25 U (N = 421) n (%)**	**SI-6603 >1.25 U (N = 0) n (%)**	**Placebo (N = 0) n (%)**	**Sham Control (N = 252) n (%)**	**Placebo/ Sham Pooled (N = 252) n (%)**
Subjects with at least one TEAE	94 (22.3)	NA	NA	41 (16.3)	41 (16.3)
Magnetic resonance imaging spinal abnormal	17 (4.0)			3 (1.2)	3 (1.2)
Spinal X-ray abnormal	10 (2.4)			1 (0.4)	1 (0.4)
Back pain	4 (1.0)			7 (2.8)	7 (2.8)

Source: Integrated Summary of Safety, Table 16

TEAE: Treatment Emergent Adverse Event, **PT**: Preferred Term

Summary of TEAEs From Weeks 26-52 (>2% of Patients by PT) (Primary Safety Pool)

			Pooled		
Preferred Term	**SI-6603 1.25 U (N = 388) n (%)**	**SI-6603 >1.25 U (N = 0) n (%)**	**Placebo (N = 0) n (%)**	**Sham Control (N = 233) n (%)**	**Placebo/ Sham Pooled (N = 233) n (%)**
Subjects with at least one TEAE	113 (29.1)	NA	NA	67 (28.8)	67 (28.8)
Magnetic resonance imaging spinal abnormal	29 (7.5)			10 (4.3)	10 (4.3)
Spinal X-ray abnormal	11 (2.8)			1 (0.4)	1 (0.4)
Back pain	9 (2.3)			7 (3.0)	7 (3.0)
Arthralgia	4 (1.0)			7 (3.0)	7 (3.0)
COVID-19	3 (0.8)			8 (3.4)	8 (3.4)
Nasopharyngitis	2 (0.5)			5 (2.1)	5 (2.1)

Source: Integrated Summary of Safety, Table 17

TEAE: Treatment Emergent Adverse Event, **PT**: Preferred Term

Summary of TEAEs (Weeks 0-52)
(>2% of Patients by PT)
(Phase 3 Studies)

Preferred Term	Condoliase 1.25 U N=529 n (%)	Placebo or Sham Control N=349 n (%)
Any AE	405 (76.6)	223 (63.9)
Magnetic resonance imaging spinal abnormal	151 (28.5)	36 (10.3)
Back pain	129 (24.4)	63 (18.1)
Pain in extremity	69 (13.0)	46 (13.2)
Spinal X-ray abnormal	53 (10.0)	10 (2.9)
Arthralgia	30 (5.7)	18 (5.2)
Nasopharyngitis	30 (5.7)	19 (5.4)
Injection site pain	23 (4.3)	16 (4.6)
C-reactive protein increased	15 (2.8)	9 (2.6)
Hypoaesthesia	15 (2.8)	12 (3.4)
Headache	14 (2.6)	8 (2.3)
Sciatica	14 (2.6)	14 (4.0)
COVID-19	11 (2.1)	17 (4.9)
Rash	11 (2.1)	2 (0.6)

Source: CDS Tables (adae.xpt; Software: R)

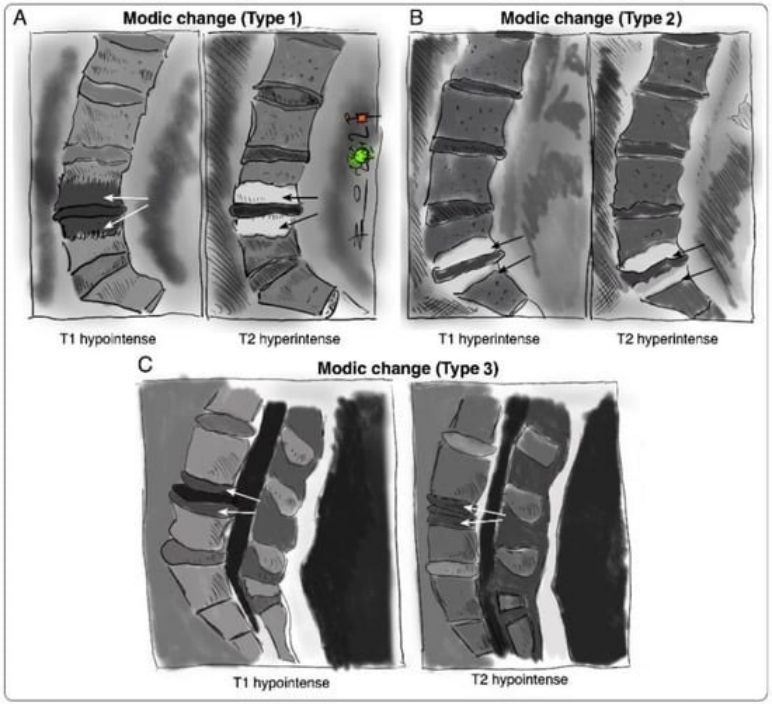
TEAE: Treatment Emergent Adverse Event, **PT**: Preferred Term

Adverse Events of Special Interest

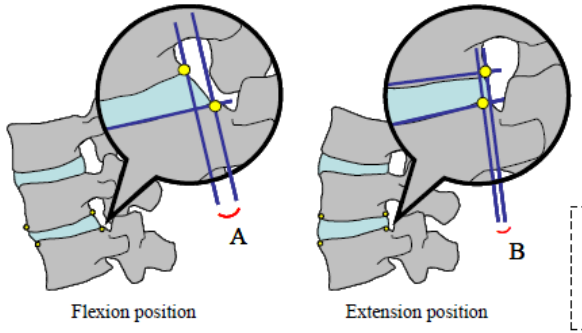
“Spine-Related Adverse Events”

Spine-Related Adverse Event Measures

Modic Changes (MRI)



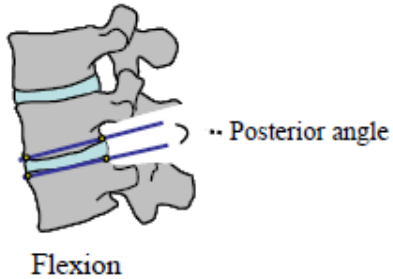
Vertebral Translation (X-ray)



Translation = | A – B |

When, of the vertebral bodies adjacent to the target intervertebral disc, the upper is behind the lower, the measured value becomes negative.

Vertebral Posterior Angle (X-ray)



Source: *Herger, Nick et al.*(left) and Study 1131 Protocol, Page 96 (right)

Placebo and Sham Controls

- Placebo and sham procedures are different
- Acceleration of disc degeneration and poorer clinical outcomes have been observed after discography
- The Agency advised the Sponsor to use a sham control
- Higher adverse event rates in placebo

Disc Height Loss

- Model and Mechanism of Action
- Disc Height Loss Sequelae
- Post-Operative Disc Height Loss

Back Pain Onset

(Primary Safety Pool)

(All Time Points)

Preferred Term Time of First Occurrence	SI-6603 1.25 U (N=578) n (%)	SI-6603 >1.25 U (N=98) n (%)	Pooled Placebo (N=128) n (%)	Pooled Sham Control (N=268) n (%)	Pooled Placebo/Sham Pooled (N=396) n (%)
Back pain	153 (26.5)	27 (27.6)	42 (32.8)	40 (14.9)	82 (20.7)
≤1 day	43 (7.4)	8 (8.2)	9 (7.0)	6 (2.2)	15 (3.8)
2-7 days	42 (7.3)	11 (11.2)	4 (3.1)	5 (1.9)	9 (2.3)
8 days-13 weeks	48 (8.3)	3 (3.1)	20 (15.6)	15 (5.6)	35 (8.8)
>13 weeks	20 (3.5)	5 (5.1)	9 (7.0)	14 (5.2)	23 (5.8)

Source: Integrated Summary of Safety, Appendix 15-2-1, Table: 3.19.1

Back Pain Severity

(Primary Safety Pool)

(All Time Points)

System Organ Class Preferred Term Maximum Severity	SI-6603 1.25 U (N=578) n (%)	SI-6603 >1.25 U (N=98) n (%)	Pooled Placebo (N=128) n (%)	Pooled Sham Control (N=268) n (%)	Pooled Placebo/Sham Pooled (N=396) n (%)
Back pain	153 (27.4)	27 (27.6)	42 (34.3)	40 (16.0)	82 (22.1)
Mild	77 (15.9)	18 (18.4)	27 (22.9)	21 (7.7)	48 (12.8)
Moderate	66 (10.1)	9 (9.2)	14 (10.9)	15 (6.4)	29 (7.9)
Severe	10 (1.4)	0	1 (0.6)	4 (1.9)	5 (1.5)

Source: 74-Day Letter Response received June 13, 2024, Table D74.10c

Imaging Findings – Radiographic Instability
(Primary Safety Pool)

(Condoliase 1.25U vs. Sham/Placebo Pooled)	Percent With Posterior Angle ≥5 Degrees		Vertebral Body Translation of ≥3 mm	
	Active	Pooled Control	Active	Pooled Control
Week 6	2.0%	1.9%	0.3%	0.5%
Week 13	1.4%	0.6%	0.2%	1.4%
Week 26	2.4%	2.3%	0.9%	1.1%
Week 52	2.5%	2.4%	0.9%	0.3%

Source: Modified from Integrated Summary of Safety (ISS), Table 35

Imaging Findings – Disc and Endplates
(Primary Safety Pool)

(Condoliase 1.25U vs. Sham/Placebo)	Disc Height Loss (Percentage)		Percent With ≥30% Disc Height Loss	
	Active	Pooled Control	Active	Pooled Control
Week 6	10.8%	3.9%	1.3%	0%
Week 13	13.6%	3.9%	3.9%	0%
Week 26	15.8%	6%	6.4%	0%
Week 52	15.4%	6.6%	6.2%	0.3%

Source: Modified from ISS Table 35 and Table 6.3.1 from Appendix 15.2.1

Imaging Findings – Disc and Endplates
(Primary Safety Pool)

(Condoliase 1.25U vs. Sham/Placebo)	Progressed to M1 Changes		Progressed to M2 Changes		Progressed to M3 Changes	
	Active	Pooled Control	Active	Pooled Control	Active	Pooled Control
Week 6	20.3%	2.3%	0.3%	0%	0%	0%
Week 13	26.6%	4.5%	0.5%	0%	0%	0%
Week 26	29.6%	9.5%	2.2%	0%	0%	0%
Week 52	31.7%	14.7%	4.2%	0.9%	0%	0%

Source: Modified from ISS Table 35 and Table 6.3.1 from Appendix 15.2.1

Spine-Related Adverse Event Findings

- Condoliase is associated with disc height loss and endplate changes
- Link between discectomy and Modic Changes
- Link between Modic Changes and back pain
- Condoliase Phase 3 studies and Modic Change associations

Spine-Related Adverse Events

(Primary Safety Pool)

(All Time Points)

	Condoliase (1.25U) n=578	Placebo/Sham Pooled n=396
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%)
Total Spinal Abnormalities	**5 (0.9%)**	**5 (1.3%)**

Discitis	1 (0.2%)	0

Source: Integrated Summary of Safety, Table 31

Post-Treatment Lumbar Surgery Requirement

(Primary Safety Pool)

(All Time Points)

	Pooled				
	SI-6603 1.25 U (N = 578) n (%)	SI-6603 >1.25 U (N = 98) n (%)	Placebo (N = 128) n (%)	Sham Control (N = 268) n (%)	Placebo/ Sham Pooled (N = 396) n (%)
Subjects with follow-up contact	476	0	76	242	318
Any surgery	27 (5.7)	0	8 (10.5)	16 (6.6)	24 (7.5)
LDH at the target level	26 (5.5)	0	8 (10.5)	15 (6.2)	23 (7.2)
LDH at a non-target level	1 (0.2)	0	0	1 (0.4)	1 (0.3)
Surgery not for LDH	3 (0.6)	0	0	3 (1.2)	3 (0.9)
Onset time interval for any surgery [1]					
Up to Week 13	10 (2.1)	0	3 (3.9)	4 (1.7)	7 (2.2)
After Week 13 to Week 26	7 (1.5)	0	5 (6.6)	7 (2.9)	12 (3.8)
After Week 26 to Week 52	6 (1.3)	0	0	4 (1.7)	4 (1.3)
After Week 52	4 (0.8)	0	0	1 (0.4)	1 (0.3)

Source: Integrated Summary of Safety, Table 36

Long Term Follow-Up Studies
(Study 10r2 and 10r3)

	Study 10r2	Study 10r3
Sample Size	n=179	n=37
Groups Followed	Placebo & Active	Active Only
Duration of Follow-up	Study 1031 ~2 years Study 1021 ~5 years	Study 1031 ~10 years
Evaluations	Interviews and Imaging	Interviews and Imaging
Lumbar Surgery Rate	Active = 10.8% Placebo = 20.7%	Active=13.5%

Source: Study 10r2 and Study 10r3 Clinical Study Reports

Hypersensitivity

Hypersensitivity Adverse Event Summary

(Primary Safety Pool)
(All Time Points)

	SI-6603 1.25 U (n=578)	Pooled PBO/Sham (n=396)
Rate of any AE in the hypersensitivity SMQ*	31 (5.4%)	16 (4.0%)
Rash	11 (1.9%)	3 (0.8%)
Urticaria	3 (0.5%)	1 (0.3%)
Asthma	3 (0.5%)	1 (0.3%)
Conjunctivitis	3 (0.5%)	0
Contact Dermatitis	3 (0.5%)	1 (0.3%)
Pruritus	3 (0.5%)	0

Source: Integrated Summary of Safety, Table 31

*__SMQ__ = Standardized MedDRA Query

Hypersensitivity – By Onset

(Primary Safety Pool)

(All Time Points)

	SI-6603 1.25 U (n=578)	Pooled PBO/Sham (n=396)
Hypersensitivity (SMQ*)	31 (5.4%)	16 (4.0%)
≤ 1 day	3 (0.5%)	1 (0.3%)
2 to 7 days	12 (2.1%)	5 (1.3%)
8 days to 13 weeks	11 (1.9%)	6 (1.5%)
≥ 13 weeks	5 (0.9%)	1 (1.0%)

Source: ISS, Appendix 15-2-1, Table 3.17.1

*__SMQ__ = Standardized MedDRA Query

Hypersensitivity – By Severity

(Primary Safety Pool)

(All Time Points)

	SI-6603 1.25 U (n=578)	Pooled PBO/Sham (n=396)
Hypersensitivity (SMQ*)	31 (5.4%)	16 (4.0%)
Mild	16 (2.8%)	10 (2.5%)
Moderate	14 (2.4%)	6 (1.5%)
Severe	1 (0.2%)	0

Source: ISS, Appendix 15-2-1, Table 3.16.1

*__SMQ__ = Standardized MedDRA Query

Hypersensitivity Summary

- Condoliase is associated with hypersensitivity-related adverse events
- Most of the hypersensitivity AEs occurred early
- There were no cases of Grade 3 or 4 hypersensitivity
- There were no cases of anaphylaxis in the clinical trials
- Condoliase is also associated with SCAR

Severe Cutaneous Adverse Reactions (SCAR)

Severe Cutaneous Adverse Reaction

- Potentially life-threatening reactions
- SCARs are a risk with many approved drugs
- Five key diagnoses:
  - Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
  - Stevens-Johnson Syndrome (SJS)
  - Toxic Epidermal Necrolysis (TEN)
  - Erythema Multiforme (EM)
  - Acute Generalized Exanthematous Pustulosis (AGEP)

Japanese Postmarketing Data

Immune and Skin Disorder (SOC)

SOC	PT	Serious Number of patients	Not serious Number of patients	Total Number of patients
Immune system disorders	Anaphylactic reaction	2		2
	Anaphylactic shock		1	1
	Drug hypersensitivity		2	2
	Hypersensitivity		1	1
Skin and subcutaneous tissue disorders	Acute generalized exanthematous pustulosis	2		2
	Dermatitis allergic		6	6
	Dermatitis exfoliative generalized	1		1
	Drug eruption	6	22	28
	Eczema	1	4	5
	Erythema	1	7	8
	Erythema multiforme	1	1	2
	Pruritus	1	15	16
	Rash	3	64	67
	Rash pruritic		1	1
	Stevens-Johnson syndrome	1		1
	Toxic skin eruption		2	2
	Urticaria	5	53	58

Out of 29,000 Exposures*

Source: IR Response received February 2, 2024, for IND 100398

*Per Development Safety Update Report received on August 16, 2024 for IND 100398

Severe Cutaneous Adverse Reaction

- Symptoms started within the first 1-2 days post-injection
- Required hospitalization and prolonged steroid exposure
- Extended morbidity with cases of SCAR
- The intervertebral disc has poor vascularity

Other Clinical Considerations

Interventional Pain Practice

- IPM has a wide array of practice patterns
- No currently approved intradiscal drugs for LDH
- Intradiscal procedures have become less common
- Significant variation with choice of technique

Interventional Pain Practice

- Intradiscal needle trajectory has many potential pitfalls
- There may be a high rate of off-label usage:
  - Repeat Injection
  - Multiple Discs
  - Non-Lumbar Injections

Clinical Setting

- IPM procedures commonly performed in office clinic setting
- Support staff availability and training may vary between settings
- Resuscitation equipment can vary depending on setting

Summary

Efficacy Summary

- The Applicant has established substantial evidence of effectiveness
  - Study 1133 modified patient selection criteria from failed Study 1131 to explicitly exclude patients with conditions that may have contributed to diagnostic uncertainty
    - Study 1133 was positive
    - MRI-proven nerve root impingement is a clinically valid criterion for consideration of condoliase administration

Safety Summary:
Spine Related Adverse Events

- Condoliase Effects on the Spine:
  - Disc Volume
  - Back Pain
  - Modic Changes
- Long Term Follow-Up

Safety Summary:
Hypersensitivity

- Hypersensitivity
  - Association with hypersensitivity reactions
  - No cases of anaphylaxis in the clinical trial database
  - SCAR association

Safety Summary:
Proceduralist Qualifications and Setting

- Treatment with condoliase requires prescriber expertise with:
  - Patient selection
  - Meticulous procedural skills and advanced knowledge of anatomy
  - Ability to diagnose and manage hypersensitivity reactions
  - Ability to diagnose SCAR
- Facility should be appropriately staffed and have adequate resuscitation equipment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