A Clinical Overview of SI-6603 (Condoliase) for Radicular Leg Pain Associated With Lumbar Disc Herniation

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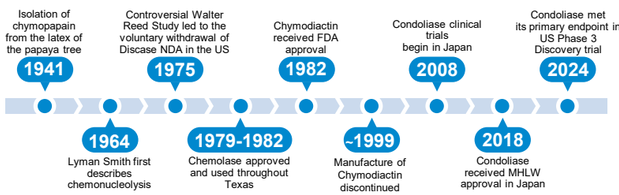
INTRODUCTION

- Patients with radicular leg pain associated with lumbar disc herniation (LDH) that does not adequately respond to conservative management have few treatment options aside from surgery[1,2]
- Chemonucleolysis is a nonsurgical method of injecting an enzyme or other substance into the disc to reduce nerve root compression through degradation of the nucleus pulposus
- In the 1980s and 1990s, chemonucleolysis with chymopapain was widely used as a less invasive alternative to surgery to treat LDH until becoming commercially unavailable in the United States (US) in ~1999[3]
- SI-6603 (condoliase; 1.25 unit [U]), a novel mucopolysaccharidase with high substrate specificity for chondroitin sulfate in the nucleus pulposus, is approved in Japan for LDH-associated radicular leg pain
- Efficacy and safety data from two pivotal phase 3 studies[4,5] and integrated safety data from four phase 2 and phase 3 randomized controlled trials (RCTs) of condoliase in the US and Japan[4-6] are summarized

Figure 1. History of Chemonucleolysis



FDA, Food and Drug Administration; MHLW, Ministry of Health, Labour, and Welfare; NDA, New Drug Application; US, United States.

METHODS

Table 1. US (1133) and JP (1031) Trial Study Design and Participants

	US trial (1133)	JP trial (1031)
Design	Randomization (1:1): SI-6603 (Condoliase) / Sham PRIMARY ENDPOINT: Week 13 FOLLOW-UP: Week 52	Randomization (1:1): SI-6603 (Condoliase) / Placebo PRIMARY ENDPOINT: Week 13 FOLLOW-UP: Week 52
Key inclusion criteria	• Adults aged **30-70 years** • Contained LDH; radicular leg pain despite ≥6 weeks of conservative treatment; positive SLR test (≤70° on the ipsilateral leg)	• Adults aged **20-70 years** • Contained LDH; radicular leg pain despite ≥6 weeks of conservative treatment; positive SLR test (≤70° on the ipsilateral leg)
Primary endpoint	• CFB to Week 13 in worst leg pain (VAS)[a]	• CFB to Week 13 in worst leg pain (VAS)[a]
Statistics	• Mixed model for repeated measures • Missing values were implicitly handled via a mixed-effect model without explicit imputation	• ANCOVA using the baseline value and duration of leg pain as covariates • Missing values imputed using LOCF method

[a]Worst leg pain was reported during the past 24 hours averaged over previous 7 days on the 100-mm VAS.
ANCOVA, analysis of covariance; CFB, change from baseline; JP, Japanese; LDH, lumbar disc herniation; LOCF, last observation carried forward; SLR, straight leg raise; US, United States; VAS, visual analogue scale.

KEY TAKEAWAYS

1 Chemonucleolysis has reemerged as a potential treatment for LDH that is less invasive than surgery

2 In two phase 3 RCTs, condoliase significantly improved worst leg pain at Week 13 (vs sham/placebo) in participants with LDH

3 Integrated safety data from four RCTs showed that condoliase was well tolerated in adults with LDH-associated radicular leg pain

4 Condoliase may offer a nonsurgical alternative treatment for LDH in the US

Table 2. Four RCTs Evaluating the Safety of Condoliase

Study #	Phase/ Location	N	Dose/ Comparator	Full Safety Monitoring[a]	Observation Period
1021	Phase 2/3 JP	195	1.25, 2.5, 5 U, placebo	13 weeks	52 weeks
1031	Phase 3 JP[b]	166	1.25 U, placebo	13 weeks	52 weeks
1131	Phase 3 US[b]	385	1.25 U, sham	104 weeks	104 weeks
1133 (Discovery)	Phase 3 US	352	1.25 U, sham	52 weeks	52 weeks

[a]After Week 13, Studies 1021 and 1031 only collected SAEs and AEs related to the disc/surrounding areas (leg pain, back pain, other AEs related to neurological tests or the stability of the intervertebral disc and its surrounding tissues).
[b]For 1031, sponsor unblinded after Week 13. For 1131, sponsor unblinded after Week 52.
AE, adverse event; JP, Japan; RCT, randomized controlled trial; SAE, serious adverse event; U, unit; US, United States.

RESULTS

Table 3. Baseline Characteristics for US (1133) and JP (1031) RCTs

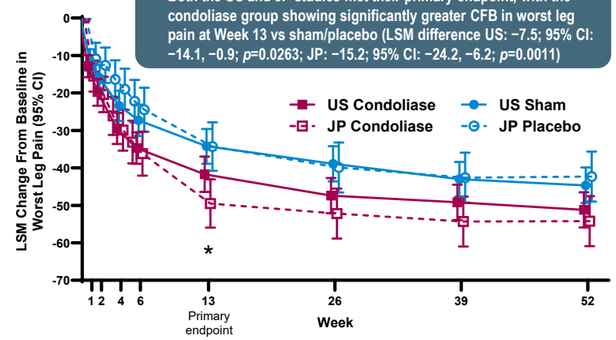
	US phase 3 (1133)		JP phase 3 (1031)	
	Condoliase (n=169)	Sham (n=172)	Condoliase (n=82)	Placebo (n=81)
Age, mean (SD), years	46.8 (9.4)	45.9 (9.8)	39.5 (11.1)	39.2 (12.4)
Female sex, n (%)	74 (43.8)	83 (48.3)	31 (37.8)	33 (40.7)
Race, n (%)				
White	137 (81.1)	142 (82.6)	0	0
Black/African American	18 (10.7)	14 (8.1)	0	0
Asian	6 (3.6)	9 (5.2)	82 (100.0)	81 (100.0)
Other[a]	8 (4.7)	7 (4.1)	0	0
Screening BMI, mean (SD), kg/m²	29.0 (4.9)	28.4 (4.9)	23.8 (3.8)	23.7 (4.1)
Current/past smoker, n (%)	63 (37.3)	69 (40.1)	43 (52.4)	46 (56.8)
Heavy labor, n (%)	39 (23.1)	49 (28.5)	50 (61.0)	53 (65.4)
Worst leg pain, mean (SD), mm	72.0 (9.6)	71.8 (9.8)	72.4 (12.3)	74.6 (12.5)
ODI score, mean (SD)	48.2 (11.8)	49.1 (11.9)	38.0 (12.9)	40.5 (13.6)
Herniation site, n (%)				
L4-L5	70 (41.4)	71 (41.3)	45 (54.9)	37 (45.7)
L5-S1	99 (58.6)	101 (58.7)	36 (43.9)	40 (49.4)
L5-L6	0	0	1 (1.2)	4 (4.9)

[a]"Other" includes American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, and Other.
BMI, body mass index; JP, Japanese; ODI, Oswestry Disability Index; RCT, randomized controlled trial; SD, standard deviation; US, United States.

- US trial participants were older, more frequently female, had a higher mean BMI, and were less likely to have an occupation requiring heavy labor vs JP trial participants

Figure 2. LSM CFB in Worst Leg Pain from US (1133) and JP (1031) Phase 3 Trials

- Both the US and JP studies met their primary endpoint, with the condoliase group showing significantly greater CFB in worst leg pain at Week 13 vs sham/placebo (LSM difference US: −7.5; 95% CI: −14.1, −0.9; p=0.0263; JP: −15.2; 95% CI: −24.2, −6.2; p=0.0011)



CFB, change from baseline; CI, confidence interval; JP, Japan; LSM, least squares mean; US, United States.

Table 4. AEs to Week 52 in the US (1133) and JP (1031) Phase 3 Trials

n (%)	US phase 3 (1133)		JP phase 3 (1031)[a]	
	Condoliase (n=167)	Sham (n=174)	Condoliase (n=82)	Placebo (n=81)
Any TEAE	120 (71.9)	105 (60.3)	74 (90.2)	64 (79.0)
Any treatment-related TEAE[b]	47 (28.1)	18 (10.3)	47 (57.3)	27 (33.3)
Any SAE	7 (4.2)	6 (3.4)	4 (4.9)	6 (7.4)
Any treatment-related SAE	0	0	1 (1.2)	0
AEs leading to study discontinuation	2 (1.2)	4 (2.3)	0	5 (6.2)
AEs in ≥10% of participants				
Abnormal spinal MRI	47 (28.1)	16 (9.2)	24 (29.3)	14 (17.3)
Back pain	32 (19.2)	22 (12.6)	30 (36.6)	24 (29.6)
Pain in extremity	18 (10.8)	13 (7.5)	18 (22.0)	23 (28.4)
Abnormal spinal X-ray	13 (7.8)	3 (1.7)	20 (24.4)	7 (8.6)
Nasopharyngitis	4 (2.4)	4 (2.3)	18 (22.0)	10 (12.3)
Injection site pain	6 (3.6)	5 (2.9)	11 (13.4)	10 (12.3)

[a]JP study collected full safety monitoring data up to Week 13, after which only SAEs and AEs related to the disc/surrounding tissues were collected. [b]Referred to as "adverse drug reaction" in the JP trial and defined as having a "related" causal relationship with study drug.
AE, adverse event; JP, Japanese; MRI, magnetic resonance imaging; SAE, serious adverse event; TEAE, treatment-emergent adverse event; US, United States.

- No treatment-related SAEs occurred in the US trial, while 1 SAE (exacerbation of low back pain) was considered possibly related to condoliase in the JP trial

Table 5. Summary of AEs Up to Week 13 in Four RCTs

n (%)	Condoliase 1.25 U (n=578)	Condoliase >1.25 U (n=98)	Placebo/ Sham (n=396)
Any TEAE	381 (65.9)	75 (76.5)	215 (54.3)
Any treatment-related TEAE	149 (25.8)	43 (43.9)	52 (13.1)
Any SAE	15 (2.6)	2 (2.0)	13 (3.3)
Any treatment-related SAE	1 (0.2)	0	0
TEAE leading to study discontinuation	3 (0.5)	0	9 (2.3)
TEAEs in ≥5% of participants			
Back pain	133 (23.0)	22 (22.4)	59 (14.9)
Abnormal spinal MRI	107 (18.5)	17 (17.3)	12 (3.0)
Pain in extremity	65 (11.2)	14 (14.3)	48 (12.1)
Nasopharyngitis	34 (5.9)	8 (8.2)	16 (4.0)
Abnormal spinal X-ray	29 (5.0)	13 (13.3)	7 (1.8)
Injection site pain	27 (4.7)	5 (5.1)	16 (4.0)

Percentages are from participants with non-missing data at that visit. AEs were classified by PT according to MedDRA version 24.0.
AE, adverse event; AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; MRI, magnetic resonance imaging; PT, preferred term; RCT, randomized controlled trial; SAE, serious adverse event; TEAE, treatment-emergent adverse event; U, unit.

- The incidence of SAEs was similar for condoliase 1.25 U and placebo/sham groups
- TEAEs leading to study discontinuation were less frequent in the condoliase groups vs placebo/sham

- No deaths were considered treatment-related; 3 participants died from unrelated causes
- The incidence of post-treatment lumbar surgery at the target level was 5.5% for condoliase 1.25 U, 0% for condoliase >1.25 U, and 7.2% for placebo/sham

Table 6. AESIs by PT in ≥1% of Participants in Four RCTs Across All Time Intervals

	Condoliase 1.25 U (n=578)	Condoliase >1.25 U (n=98)	Placebo/ Sham (n=396)
Any AESI, n (%)	43 (7.4)	7 (7.1)	25 (6.3)
Rash	11 (1.9)	1 (1.0)	3 (0.8)

Adverse events were classified by PT according to MedDRA version 24.0.
AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; RCT, randomized controlled trial; U, unit.

- There was a low incidence of AESIs in both treatment groups

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