Two Phase 3, Randomized, Double-Blind Controlled Trials of SI-6603 (Condoliase) for the Treatment of Radicular Leg Pain Associated With Lumbar Disc Herniation

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BACKGROUND

- 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]
- Prolonged duration of LDH symptoms (>6 months) is associated with worse functional outcomes[2,3]
- 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[4]
- SI-6603 (condoliase) is a novel mucopolysaccharidase with high substrate specificity for chondroitin sulfate in the nucleus pulposus[4]
- Condoliase has been approved in Japan (JP) for the treatment of LDH-associated radicular leg pain since 2018[5,6]
- We evaluated the early treatment response (≤6 weeks) to condoliase for radicular leg pain associated with LDH in two phase 3 randomized controlled trials (RCTs), one from Japan[6] and one from the US[7] (NCT03607838)

METHODS

Table 1. Study Design and Participants

	US trial	JP trial
Design	Randomization (1:1) → SI-6603 (Condoliase) / Sham; PRIMARY ENDPOINT: Week 13; FOLLOW-UP: Week	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]
Secondary endpoints	• CFB in worst leg pain at Week 52 • CFB in herniation volume at Week 13 • CFB in ODI score at Week 13	• CFB to Week 52 in worst leg pain, worst back pain, ODI, SF-36, neurologic examinations, imaging parameters, and herniation volume
Statistics	• Mixed model for repeated measures • Missing values were implicitly handled via a mixed-effect model without explicit imputation • Difference in proportions Z test was used to compare groups on the % of patients with negative SLR test and ≥50% improvement in worst leg pain from baseline (50% responders)	• ANCOVA • Missing values imputed using LOCF method • Endpoints with continuous values were analyzed by ANCOVA, and endpoints with discrete values were analyzed by logistic regression analysis. The baseline value and duration of leg pain were used as covariates

[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; ANOVA, analysis of variance; CFB, change from baseline; JP, Japanese; LDH, lumbar disc herniation; LOCF, last observation carried forward; ODI, Oswestry Disability Index; SF-36, 36-Item Short Form Health Survey; SLR, straight leg raise; US, United States; VAS, visual analogue scale.

KEY TAKEAWAYS

1. **Two phase 3 RCTs showed that condoliase significantly improved leg pain at Week 13 vs sham/placebo**
2. **Condoliase was associated with rapid improvements (≤6 weeks) in worst leg pain and neurological findings (SLR test) in both trials**
3. **Condoliase was well tolerated in both studies, with only 1 SAE considered possibly related to condoliase in the JP trial**
4. **Condoliase has demonstrated its therapeutic potential as a nonsurgical alternative treatment for LDH**

RESULTS

Table 2. Baseline Participant Characteristics

	US phase 3		JP phase 3	
	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; 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

- Both the US (N=341) and JP (N=163) 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% confidence interval [CI]: −14.1, −0.9; p=0.0263; JP: −15.2; 95% CI: −24.2, −6.2; p=0.0011)
- In the US trial, treatment group differences in ODI at Week 13 favored condoliase (LSM CFB: −29.6) vs sham (−25.4; LSM difference: −4.2; 95% CI: −8.0, −0.3; p=0.0336)
- In the JP trial, the condoliase group showed significantly greater improvements in the ODI (LSM CFB condoliase: −18.9, placebo −13.4; LSM difference: −5.6; 95% CI: −10.7, −0.4; p=0.0355) and significantly greater reductions in herniation volume (LSM CFB condoliase: −289.1, placebo −190.7; LSM difference: −98.3; 95% CI: −162.3, −34.4; p=0.0028) at Week 13

Figure 1. LSM CFB in Worst Leg Pain

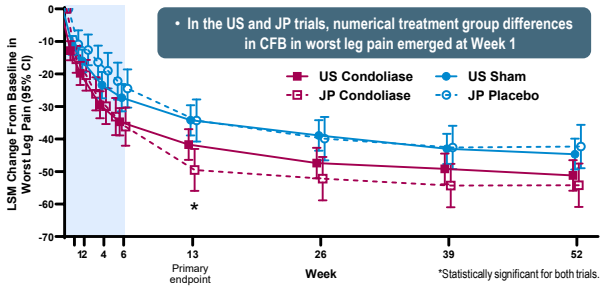


Figure 2. 50% Responder Rate for Worst Leg Pain

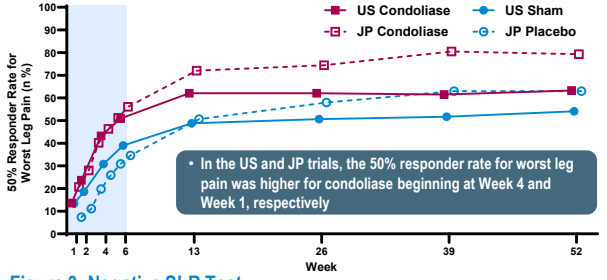
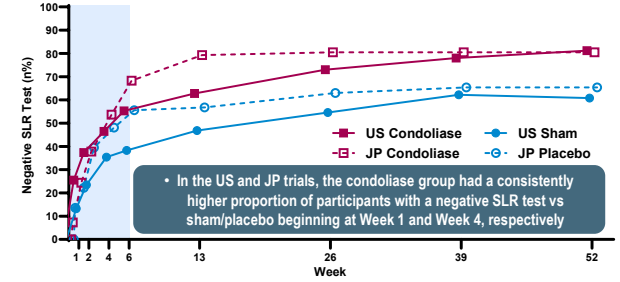


Figure 3. Negative SLR Test



RESULTS (CONTINUED)

Table 3. Adverse Events to Week 52

n (%)	US phase 3		JP phase 3[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

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