SI-6603 (Condoliase) in Patients With Radicular Leg Pain Associated With Lumbar Disc Herniation: A Phase 3, Randomized, Double-Blind, Sham-Controlled Trial

Kenneth Candido, MD[1]; Kee D. Kim, MD[2]; Farshad Ahadian, MD[3]; Hamid Hassanzadeh, MD[4]; Jose Rivera, MD[5]; Steven Gershon, MD[6]; Anand Patel, MD[7]; Pragya B. Gupta, MD[8]; Alan E. Miller, MD[9]; Ferdinand J. Formoso, DO[10]; Thomas Fuerst, PhD[11]; Takayuki Seo, PhD[12]; Jun Watanabe, RPh, EMBA, MSc[13]; Yukihiro Matsuyama, MD[14]; Kazuhiro Chiba, MD, PhD[15]; Kevin E. Macadaeg, MD[16]

[1]Chicago Anesthesia Pain Specialists, Chicago, IL, USA; [2]University of California, Davis, Department of Neurological Surgery, Sacramento, CA, USA; [3]University of California, San Diego, Department of Anesthesiology, La Jolla, CA, USA; [4]Johns Hopkins Medicine, Baltimore, MD, USA; [5]Tampa Pain Relief Centers, Tampa, FL, USA; [6]Gershon Pain Specialists, Virginia Beach, VA, USA; [7]Conquest Research, Winter Park, FL, USA; [8]Otrimed Clinical Research, Edgewood, KY, USA; [9]Coastal Spine & Pain Center, Fernandina Beach, FL, USA; [10]Coastal Spine & Pain Center, Jacksonville, FL, USA; [11]Clario, San Mateo, CA, USA; [12]Clinical Development Department, Research & Development Division, Seikagaku Corporation, Tokyo, Japan; [13]Seikagaku North America Corporation, Toronto, ON, Canada; [14]Department of Orthopedic Surgery, Hamamatsu University School of Medicine, Hamamatsu, Japan; [15]Department of Orthopedic Surgery, National Defense Medical College, Tokorozawa, Saitama, Japan; [16]Indiana Spine Group, Carmel, IN, USA

BACKGROUND

- Lumbar disc herniation (LDH), the displacement of disc material (nucleus pulposus) beyond the intervertebral disc space, is a leading cause of radicular leg pain[1]
- Prolonged duration of LDH symptoms (ie, >6 months) is associated with worse outcomes[2,3], highlighting the clinical importance of rapid symptom control
- SI-6603 (condoliase) is a novel chemonucleolytic enzyme with high substrate specificity for degrading glycosaminoglycans (primarily chondroitin sulfate) in the nucleus pulposus[4,5]
- Condoliase was approved in Japan in 2018 as a single intradiscal injection for the treatment of radicular leg pain associated with LDH[6,7]
- The Discovery 6603 study (NCT03607838) is a phase 3, randomized, double-blind, sham-controlled trial to evaluate the efficacy and safety of a single intradiscal injection of condoliase for radicular leg pain in individuals with LDH in the United States (US)
- We report efficacy and safety findings from the Discovery 6603 study, including efficacy outcomes preceding the primary endpoint timepoint of Week 13

Figure 1. Study Design

Visit 1	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Informed consent and screening procedures	Eligibility determination and randomization	Week 0 – Administration of condoliase or sham injection	Week 1	Week 2	Week 4	Week 6	Week 13 (Primary Efficacy Endpoint)	Week 26	Week 39	Week 52

STUDY DESIGN AND PARTICIPANTS

- Participants were randomized 1:1 to a single intradiscal injection of condoliase (1.25 units) or sham injection (**Figure 1**)
- Inclusion criteria: Adults aged 30 to 70 years with contained posterolateral LDH, chief complaint of unilateral radiculopathy/radicular leg pain, and ≥6 weeks of conservative treatment
- Among 352 randomized participants, 341 constituted the modified intention-to-treat (mITT) population (assigned treatment: condoliase: 169; sham: 172; **Table 1**) and the safety population (treatment received: condoliase: 167; sham: 174)
- Primary endpoint: Change from baseline (CFB) to Week 13 in worst leg pain score during the past 24 hours averaged over the previous 7 days, as assessed by 100-mm visual analogue scale (VAS)
- Key secondary endpoints: CFB in average worst leg pain at Week 52, herniation volume at Week 13, and Oswestry Disability Index (ODI) score at Week 13
- Supportive endpoint: Percentage of participants with negative straight leg raise (SLR) test and 50% responder rates (participants with ≥50% improvement from baseline) for worst leg pain
- Primary and key secondary endpoint analyses used mixed model for repeated measures (MMRM)
  - A serial gatekeeping algorithm was used, wherein if the primary endpoint was significant at α=0.05, Week 52 worst leg pain would be evaluated, followed by Week 13 herniation volume, then Week 13 ODI score
  - If an endpoint failed to meet significance, then the algorithm was halted, and all remaining tests were declared nonsignificant

KEY TAKEAWAYS

1 Condoliase significantly improved radicular leg pain at Week 13 (vs sham) in participants with LDH

2 Condoliase was well tolerated, with no treatment-related serious adverse events

3 Condoliase was associated with rapid improvements (≤6 weeks) in leg pain and neurological findings

4 Condoliase may offer a nonsurgical treatment option for patients with LDH

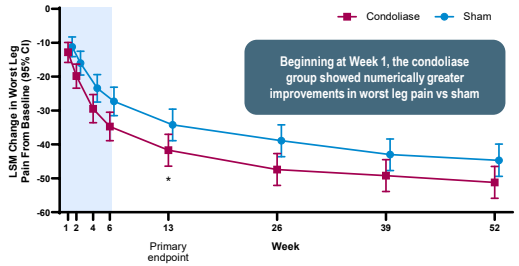
RESULTS

Table 1. Baseline Participant Characteristics

	Condoliase (n=169)	Sham (n=172)
Age, mean (SD), years	46.8 (9.4)	45.9 (9.8)
Sex, n (%)		
Male	95 (56.2)	89 (51.7)
Female	74 (43.8)	83 (48.3)
Race, n (%)		
White	137 (81.1)	142 (82.6)
Black/African American	18 (10.7)	14 (8.1)
Asian	6 (3.6)	9 (5.2)
Other[a]	8 (4.7)	7 (4.1)
Screening BMI, mean (SD), kg/m^2	29.0 (4.9)	28.4 (4.9)
Smoking status, 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)
Occupation, n (%)		
Light labor	130 (76.9)	123 (71.5)
Heavy labor	39 (23.1)	49 (28.5)
Worst leg pain, mean (SD), VAS	72.0 (9.6)	71.8 (9.8)
ODI score, mean (SD)	48.2 (11.8)	49.1 (11.9)
Modic classification, n (%)[b,c,d]	n=167	n=174
Type 0	106 (63.5)	115 (66.1)
Type 1	44 (26.3)	35 (20.1)
Type 2	23 (13.8)	27 (15.5)
Type 3	0	0

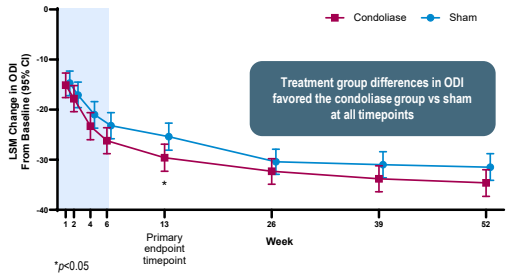
[a]"Other" includes American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, and Other.
[b]Safety population.
[c]Percentages are from participants with non-missing data.
[d]More than one type may be selected, therefore, percentages may add to more than 100%.
BMI, body mass index; ODI, Oswestry Disability Index; SD, standard deviation; VAS, visual analogue scale.

Figure 2. LSM CFB in Average Worst Leg Pain



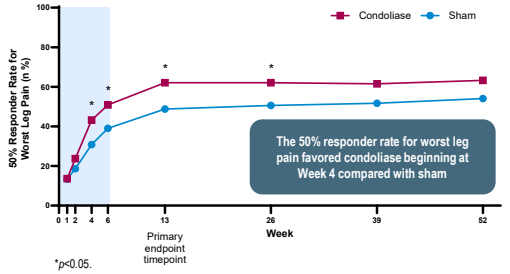
*Denotes statistical significance, $p<0.05$.
CFB, change from baseline; CI, confidence interval; LSM, least squares mean.

Figure 3. LSM CFB in ODI Score



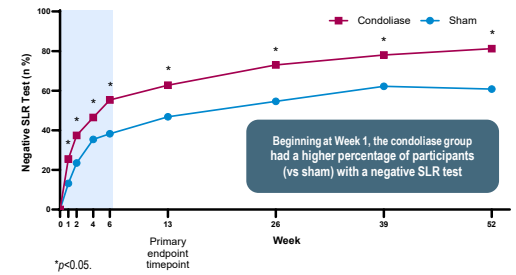
*$p<0.05$
CFB, change from baseline; CI, confidence interval; LSM, least squares mean; ODI, Oswestry Disability Index.

Figure 4. 50% Responders – Worst Leg Pain



*$p<0.05$.

Figure 5. Negative SLR Test



*$p<0.05$.
SLR, straight leg raise.

RESULTS (CONTINUED)

Table 2. Summary of Adverse Events

n (%)	Condoliase (n=167)	Sham (n=174)
Any TEAE	120 (71.9)	105 (60.3)
Any treatment-related TEAE	47 (28.1)	18 (10.3)
Any SAE	7 (4.2)	6 (3.4)
Treatment-related SAE	0	0
AEs leading to study discontinuation	2 (1.2)	4 (2.3)
TEAEs in ≥5% of participants[a]		
Abnormal spinal MRI	47 (28.1)	16 (9.2)
Back pain	32 (19.2)	22 (12.6)
Pain in extremity	18 (10.8)	13 (7.5)
Abnormal spinal X-ray	13 (7.8)	3 (1.7)
COVID-19	11 (6.6)	17 (9.8)
C-reactive protein increased	10 (6.0)	6 (3.4)
Headache	8 (4.8)	4 (2.3)
Any AESI	87 (52.1)	55 (31.6)

[a]By preferred term, classified according to MedDRA version 24.0.
AE, adverse event; AESI, adverse event of special interest; COVID-19, Coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; MRI, magnetic resonance imaging; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

No adverse events (AEs) leading to study discontinuation or serious adverse events (SAEs) were considered treatment-related

- Condoliase showed significantly greater improvement in worst leg pain at Week 13 (LSM CFB: –41.7) vs sham (–34.2; LSM difference: –7.5; 95% CI: –14.1, – 0.9; p=0.0263; **Figure 2**)
- The treatment group difference in CFB in worst leg pain at Week 52 favored condoliase but did not achieve significance
- CFB in herniation volume (LSM CFB condoliase: –103.8; sham: –78.1; LSM difference: –25.8) and ODI score (**Figure 3**) at Week 13 were considered not significant regardless of their p values
- Notable differences in 50% responders for worst leg pain favored condoliase at Week 4, Week 6, Week 13, and Week 26 (**Figure 4**)
- A higher percentage of participants in the condoliase group (vs sham) had a negative SLR test beginning at Week 1, which was sustained to Week 52 (**Figure 5**)
- Post-treatment surgery for LDH at the same level of injection was numerically more frequent in the sham group (6.4%; n=11) vs the condoliase group (3.0%; n=5)

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Acknowledgments & Disclosures

This study was sponsored by Seikagaku Corporation. Medical writing support was provided by Scient Healthcare Communications and funded by Ferring Pharmaceuticals.

Contact Information

For comments or questions, contact Kenneth Candido at kdcandido1@gmail.com.

Presented at the American Society of Regional Anesthesia and Pain Medicine (ASRA Pain) 23rd Annual Meeting | November 21-23, 2024 | Las Vegas, Nevada