FDA Briefing Document

BLA 761393

Drug name: Condoliase

Applicant: Seikagaku Corporation (SKK)

Anesthetic and Analgesic Drug Products Advisory Committee Meeting

January 10, 2025

Division of Anesthesiology, Addiction Medicine, and Pain Medicine

Office of Neuroscience

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Glossary

AC	Advisory Committee
AE	adverse event
AGEP	acute generalized exanthematous pustulosis
AWC	adequate and well-controlled
BLA	Biologics License Application
BMI	body mass index
BRF	Benefit-Risk Framework
DPACC	Division of Pulmonology, Allergy, and Critical Care
ED	emergency department
FDA	Food and Drug Administration
IPM	interventional pain management
LDH	lumbar disc herniation
MRI	magnetic resonance imaging
MSK	musculoskeletal
ODI	Oswestry Disability Index
RLP	radicular leg pain
SCAR	severe cutaneous adverse reactions
SD	standard deviation
SEE	substantial evidence of effectiveness
SKK	Seikagaku Corporation
SOC	system organ class
SPORT	Spine Patient Outcomes Research Trial
SRAE	spine-related adverse event
VAS	visual analog scale

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The Food and Drug Administration (FDA or *the Agency*) is convening this Advisory Committee (AC) meeting to discuss Biologics License Application (BLA) 761393, condoliase. The Applicant (Seikagaku [SKK]) seeks to market condoliase for a proposed indication of "the treatment of radicular leg pain associated with confirmed nerve root impingement caused by lumbar disc herniation in adults" (proposed indication revised on 11/08/24). The specific issues to be discussed to inform the benefit-risk assessment of condoliase are a clinical trial that failed to meet the primary endpoint and potential adverse events (AEs) related to the product mechanism of action, route of administration, and product composition.

This Application presents several challenges for the AC to consider:

1. Relevance of one negative adequate and well-controlled (AWC) trial, in the context of two positive AWC trials.
2. Identification of patients most appropriate for condoliase.
3. Significance of increased axial back pain and spine-related AEs due to the product mechanism of action.
4. Appropriate proceduralist and procedure setting requirements to ensure safe intradiscal administration and aftercare for condoliase injection.
5. Concern for immune-related AEs, including hypersensitivity reactions, anaphylaxis, and risk of severe cutaneous adverse reactions (SCARs), and corresponding mitigation and/or monitoring strategies.

1.2 Context for Issues to Be Discussed at the AC

Radicular leg pain (RLP) is a form of neuropathic pain consequent to pressure on a lumbar spinal nerve root. Lumbar disc herniation (LDH) is the most common cause of RLP in adults.[1] The intervertebral discs provide structural support for the spinal vertebrae, facilitate movement of the spine, and function as shock absorbers. Over time and/or with trauma, the gelatinous center of the disc (the nucleus pulposus) can breach the outer ring of the disc (the annulus fibrosus), or disc herniation. The majority of intervertebral disc herniations occur in the lumbar spine, with the most common being at the lowest lumbosacral (L4-L5 or L5-S1) levels due to biomechanical loading (Frymoyer 1988).

LDH can lead to direct compression of the lumbar/sacral nerve root, reduced blood flow, and activation of inflammatory pathways (Figure 1), which may result in burning, radiating pain in the concordant dermatome that is characteristic of RLP, as well as possible associated sensory changes and/or motor deficits. Collectively, the signs and symptoms resulting from spinal nerve root compression are known as radiculopathy. The diagnosis of RLP is guided primarily by clinical presentation, history, and physical examination (Soar et al. 2022). In the absence of clinical suspicion for urgent or emergent neurological pathology, such as cauda equina syndrome, spinal fracture, malignancy, or infection, routine imaging is not recommended. Otherwise, imaging such as magnetic resonance imaging (MRI) (sometimes computed tomography or X-ray imaging) is used to inform treatment options if pain does not resolve in the acute period, which is typically considered 4 to 6 weeks. Diagnostic nerve blocks, electrodiagnostic

studies, and myelography are not routinely indicated, although they may be of some utility if imaging is inconclusive or contraindicated.

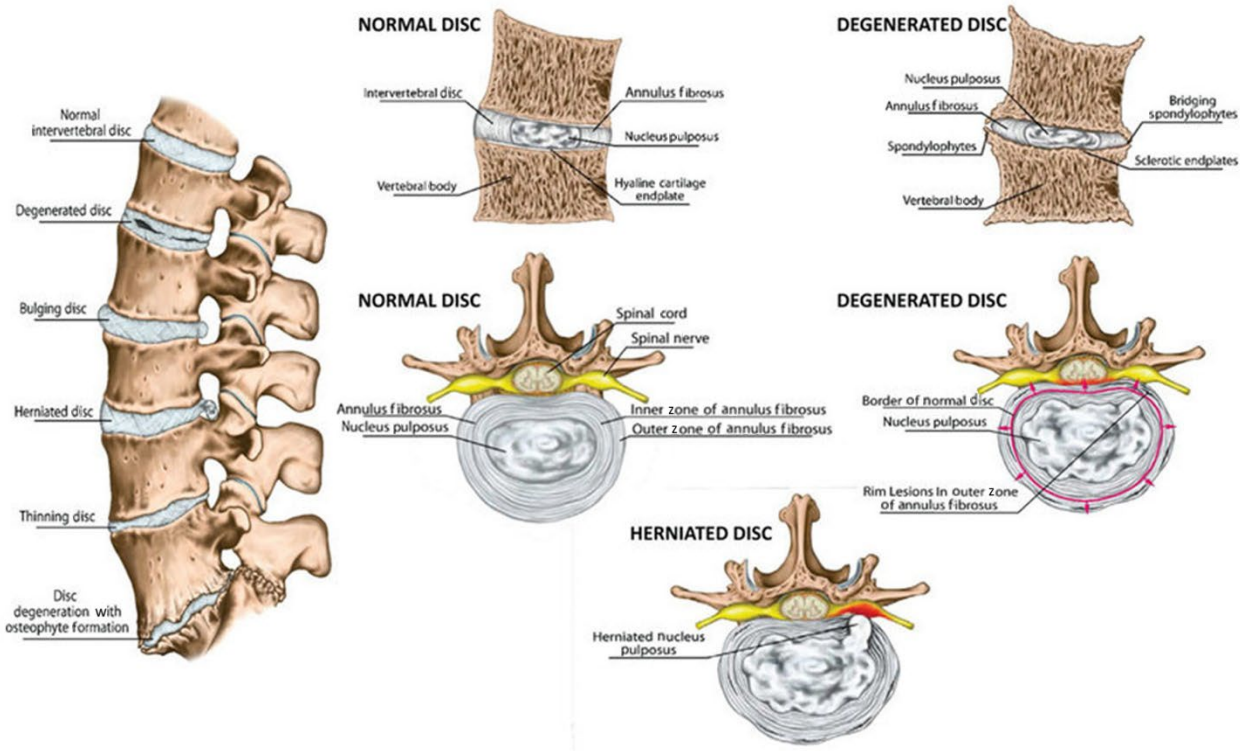
Acute radicular pain due to LDH usually resolves spontaneously or responds to conservative management, including physical activity, nonsteroidal anti-inflammatory drugs, acetaminophen, and/or systemic steroids. However, in patients with new-onset lumbar radiculopathy, 15 to 40% will experience chronic pain or a relapse of pain (Knezevic et al. 2021). Treatment options for continuing RLP can include physical therapy and use of drugs for neuropathic pain, including gabapentinoids, selective norepinephrine reuptake inhibitors and tricyclic antidepressants, although these drugs are not specifically indicated for the treatment of RLP. If RLP does not improve with initial management, lumbar epidural steroid injections may also be considered to reduce pain severity and improve patient functionality. In some patients, RLP may persist even after trials of many of these treatment options. Surgical treatments such as discectomy are an option for patients with progressive or persistent neurologic deficits and/or persistent radicular symptoms with functional limitations. Other nonsurgical interventional treatments, including spinal cord stimulation and percutaneous discectomy, may be considered as alternatives to surgery for patients with ongoing RLP.

Condoliase is an enzyme purified from a Gram-negative bacillus (*Proteus vulgaris)*. This enzyme degrades chondroitin sulfate, a glycosaminoglycan that, in its hydrated state, comprises most of the volume of the nucleus pulposus of the intervertebral disc. In BLA 761393, the Applicant proposes to market condoliase for injection into a herniated intervertebral disc to decrease disc volume, reduce herniation, and relieve impingement of the affected spinal nerve root, with the intent of decreasing RLP. If approved, this would be the first drug or biologic product approved for the treatment of RLP, and it would be the only product currently on the market for intradiscal injection for any indication.

Historically, the diagnostic and therapeutic utility of intradiscal procedures in discogenic pain has been balanced by concern for worsening disc degeneration and other potential adverse effects, depending on the specific intervention/injectate. Regardless of the intervention or injectate, intradiscal access requires careful benefit-risk assessment, as well as specific technical expertise, patient monitoring, and specialized equipment to ensure procedural safety (International Spine Intervention Society and Bogduk 2013).

In the particular case of condoliase, a key consideration is the product's purported mechanism of action to reduce RLP by reducing disc volume and alleviating pressure on the lumbar spinal nerve root. However, loss of intervertebral disc volume has potential mechanical and functional consequences for the spine, including loss of disc height, reduced spinal mobility, reduced shock absorption, and the development of bony growths (osteophytes) to stabilize the spine but which may also further exacerbate pain and nerve compression. Furthermore, condoliase is a bacterially derived enzyme. Biological products derived from foreign proteins are associated with the potential for rare immunologic adverse reactions, which are typically mild, but can include hypersensitivity, anaphylaxis, and SCARs. The intervertebral disc is a largely acellular, hypoxic environment with poor vascular supply, such that any product injected intradiscally can be presumed to have a long residence time within the disc. Immune-related AEs may be therefore more difficult to manage due to the potential longer latency and the irreversibility of product administration.

Figure 1. Anatomy of Lumbar Spine and Disc Pathology



Source: Soar et al. (2022)

1.3 Brief Description of Issues for Discussion at the AC

As noted in Section 1.2, there are no currently approved drugs or biologics for lumbosacral radicular pain, although there are a number of nonpharmacologic, off-label pharmacologic, and device-based therapies used. Treatment response is highly variable, and persistent or recurrent pain is common, leading some patients to undergo surgery for RLP due to LDH. However, spinal surgical procedures carry significant risks, and some patients may not be appropriate surgical candidates. Thus, there is a medical need for safe and effective therapies for this condition.

Efficacy

Three AWC studies were completed and submitted by the Applicant in support of this BLA. All the three studies used a randomized, double-blind, controlled, and parallel-group design to evaluate the primary endpoint of change in average leg pain from baseline to Week 13. Study 1031 used intradiscal injection of placebo (saline) as the control, while Studies 1131 and 1133 used a sham injection outside of the disc as the control to address concerns of potential adverse effects from intradiscal penetration. The first AWC study (Study 1031) was conducted in Japan from 2012 to 2014 and succeeded on the primary efficacy endpoint. The second AWC study (Study 1131) was conducted from 2013 to 2017 in the United States and failed to meet the primary efficacy endpoint. Based on analysis of this failed study, the Applicant refined the eligibility criteria to conduct a third study (Study 1133), which was also conducted in the United States, from 2018 to 2023. Study 1133 was positive.

Safety

There are two sources of safety data: the clinical trial database and postmarketing data. A total of eight clinical studies were completed; one Phase 1/2 study was terminated due to lack of site resources. Four

studies were controlled and blinded, the remainder were open label. A small number of patients were followed for up to 10 years, although most of the follow-up data are limited to 12 months.

The clinical trial safety data show an imbalance in hypersensitivity events favoring placebo; most of the hypersensitivity reactions were mild. There was also an imbalance of AEs related to the spine, which include anatomic abnormalities, increased axial back pain, and imaging findings suggesting reactive bone changes in the adjacent vertebral bodies. Collectively, these events will be referenced as spine-related adverse events (SRAE).

Postmarketing safety data are solely from Japan, as condoliase has been marketed there since August 2018 and has not been approved in any other countries. The Applicant estimates that 29,000 Japanese patients have received condoliase to date. The postmarketing data include cases of hypersensitivity, SRAE, and several of severe cutaneous adverse reactions (SCARs).

1.4 Draft Points for Consideration

Please consider the following points in preparation for the AC meeting:

- Comment on the significance of Study 1131 (negative study) in the context of the other two positive studies with respect to establishing the efficacy of condoliase.
- Discuss key elements to be included in the prescribing information that would help clinicians identify patients who would have a favorable benefit-risk profile if treated with condoliase. Applicant is proposing the indication of "[TRADENAME] is indicated for the treatment of radicular leg pain associated with confirmed nerve root impingement caused by lumbar disc herniation in adults." Should this indication be modified to reflect the most appropriate patient population for condoliase?
- Discuss whether the benefits of the drug mechanism to reduce RLP (disc volume reduction as a means to alleviate nerve impingement) outweigh the potential short- and long-term adverse effects of increased axial back pain and altered spine anatomy.
- Given the route of administration, the narrow population in which the drug has been established to be effective, and potential risks of both the product and the procedure, discuss appropriate proceduralist and setting requirements to support safe administration of the drug.
- Discuss the level of concern for immune-related adverse reactions, including hypersensitivity, anaphylaxis, and SCARs, as well as appropriate mitigation and monitoring strategies.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Etiology of Radicular Leg Pain (RLP)

The most common cause of RLP is LDH. The intervertebral discs located between each spinal vertebra provide ligamentous attachments for adjacent vertebrae, facilitate movement of the spine, and function as cushions to absorb impact to the spine. Each disc consists of a tough outer ring (annulus fibrosus) and a gelatinous center (nucleus pulposus) (Figure 1). A normal disc contains strong fibrocartilage in the annulus fibrosus and a well-hydrated nucleus pulposus. With age, the annulus fibrosus can weaken and the water content of the nucleus pulposus decreases. This degeneration, along with mechanical trauma that may occur even in healthy individuals, predisposes patients to disruption of the annular fibers and

herniation of the nucleus pulposus through the annulus fibrosus (Tarulli and Raynor 2007). Direct compression of lumbar or sacral nerve roots by the herniated disc, reduced blood flow, and activation of inflammatory pathways will often result in burning, radiating pain in the affected dermatome (i.e., RLP). This pain is often associated with sensory changes (e.g., numbness, paresthesias) and motor deficits (e.g., weakness, paralysis). Collectively, these symptoms arising from a compressed spinal nerve comprise the diagnosis of radiculopathy.

The prevalence of lumbar radiculopathy has been found to be up to 13.4%, with men between the ages of 45 to 64 years being the most commonly affected (Berry et al. 2019). It is a significant cause of disability and work absence worldwide. In particular, the RLP component of radiculopathy is often severe and functionally limiting, as patients may have difficulty standing, ambulating, and performing daily activities. As noted in Section 1.2, acute RLP due to LDH generally resolves in 4 to 6 weeks with conservative management. However, recurrence or persistence of pain beyond 6 weeks is common, leading many patients to seek treatment through interventional pain procedures or surgery.

There are two important subpopulations of patients with RLP due to LDH that are relevant to consideration of condoliase: the elderly and those with neurologic deficits. Elderly patients often have persistent, chronic radicular symptoms due to disc herniation, with comorbid spondylosis (i.e., spinal degeneration or spinal arthritis) and narrowing of the central spinal canal (i.e., spinal stenosis) or neural foramen where the spinal nerves exit (i.e., foraminal stenosis). Furthermore, these spinal degenerative changes promote the growth of bone spurs (i.e., osteophytes), which may encroach on the nerve root and contribute to RLP independent of LDH. The presence of multiple spinal pathologies can make it particularly challenging to alleviate RLP symptoms using only conservative treatments such as physical therapy and pharmacological therapies, which would lead these patients to be more likely to be considered for surgical treatment of LDH. However, elderly patients are also at increased risk for surgical complications and may take longer to recover postoperatively due to potential medical comorbidities and decreased physiologic reserve.

Another important subpopulation are patients with RLP due to LDH who exhibit severe neurologic deficits. Patients with LDH causing severe spinal stenosis may present with bowel or bladder incontinence and profound lower extremity weakness, a condition known as cauda equina syndrome. Although onset may be rapid or gradual, sudden onset is considered a medical emergency, and patients require immediate surgical decompression Patients with less severe neurologic dysfunction, including mild-to-moderate weakness and persistent numbness, may benefit from conservative measures prior to considering surgical treatment. Treatment recommendations are similar to patients with RLP only and no neurologic changes, although patients with neurologic symptoms may be more refractory to treatment.

Treatment Options

Conservative measures should be initiated in patients with RLP due to LDH who experience ongoing pain and functional limitations. Treatment can include medications, prescribed activity and interventional therapy. Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line treatments for acute RLP due to LDH. NSAIDs inhibit the cyclooxygenase enzymes that produce inflammatory mediators, such as prostaglandins, which can be highly efficacious for reducing the inflammatory component of RLP. However, NSAIDs are associated with significant dose-dependent morbidity, including gastrointestinal,

cardiovascular, and renal toxicity. The use of NSAIDs in the treatment of chronic painful conditions is often limited due to these dose-dependent toxicities.

Patients should be counseled that the symptoms of LDH typically self-resolve in about 4 to 6 weeks with conservative care. As there is an absence of high-level evidence for bed rest after LDH (Khorami et al. 2021), patients should be encouraged to maintain physical activity and continue with exercises as tolerated. If pain continues, a course of guided physical therapy can be effective in alleviating symptoms and improving function, even beyond the acute period after herniation. A randomized, controlled trial by Bakhtiary et al. demonstrated that a lumbar stabilizing exercise protocol could significantly increase lumbar stability and improve functional performance in patients with LDH for more than 2 months (Bakhtiary et al. 2005). There is an absence of consistent, high-level evidence for lumbar spine orthoses, traction therapy, electric nerve stimulation, or acupuncture for RLP due to LDH (Bakhtiary et al. 2005), although many patients consider these treatments prior to pursuing more invasive options.

If the above measures fail to improve their symptoms, patients may also consider interventional therapy including epidural steroid injections. There are currently no corticosteroids approved for epidural administration, yet they are commonly used off-label for RLP due to LDH. A meta-analysis demonstrated that epidural steroid injections for acute lumbar radiculopathy were significantly associated with early improvement in pain and functionality when compared to placebo, but there was no association with longer-term benefit (Chou et al. 2015). By contrast, a contemporaneous systematic review from a different group concluded that there was strong evidence for short-term efficacy and moderate evidence for long-term efficacy of epidural injections for managing lumbar disc herniation (Manchikanti et al. 2015). Another systematic review and meta-analysis by Bhatia et al. found evidence of modest benefit for transforaminal epidural steroid injections at 3 months, but no impact on physical disability or incidence of subsequent surgery (Bhatia et al. 2016). There remains substantial disagreement among experts regarding various aspects of epidural injections for LDH symptoms, including the degree and duration of benefit, the most appropriate injectate to be used, and the most appropriate procedural approach to the epidural space. Regardless, epidural injections have been considered as part of routine clinical care in the management of LDH symptoms for decades. The procedure is generally considered to be very safe when performed by trained proceduralists, but rare, serious AEs have been associated with epidural injections, including bleeding, infection, and nerve injury. The Prescribing Information of injectable steroids commonly used off-label for epidural injection contains a Boxed Warning regarding reports of serious neurologic events, including spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke following epidural injection.

If conservative measures fail, patients may consider surgery. The Spine Patient Outcomes Research Trial (SPORT) was an NIH-funded, randomized controlled trial enrolling 501 patients with LDH and signs and symptoms of lumbar radiculopathy for at least 6 weeks. Patients were randomized to undergo standard open discectomy versus nonoperative treatment. In the intention-to-treat analysis, both groups demonstrated significant improvement for all primary and secondary outcomes. The trial suffered from a high rate of crossover as patients were allowed to switch from the control arm to the active arm and vice versa. The as-treated analysis demonstrated favorability of surgery over conservative measures with a preserved duration of effect of pain reduction and functional improvements at the 2-year time point (Weinstein et al. 2006). However, the study lacked assay sensitivity as there was no placebo, sham, or no-treatment arm. SPORT also reported complications associated with open lumbar discectomy, including recurrent disc herniation (7%), wound infection (3%), dural tear (3%), and hematoma (1%).

Based on the available literature, the North American Spine Society guidelines for LDH and radiculopathy suggest that discectomy may provide more effective symptom relief than medical/interventional treatment for patients with significant functional limitations and severe pain. Notably, surgical intervention before 6 months have lapsed since the onset of symptoms is associated with faster recovery and improved long-term outcomes (Kreiner et al. 2014). The guidelines also suggest that, for patients with less severe symptoms, surgery or medical/interventional care appear to be effective for both short- and long-term relief.

2.2 Pertinent Drug Development and Regulatory History

Condoliase is an enzyme purified from the bacterium *Proteus vulgaris*. There is one relevant, previously approved product, chymopapain (BLA 18663), which was withdrawn from sale by the manufacturer in 2001. Chymopapain is discussed later in this section.

The indication for condoliase proposed in the initial BLA submission is:

> "[TRADENAME] is indicated for the treatment of radicular leg pain associated with lumbar disc herniation in adults.
>
> Limitations of Use
>
> [TRADENAME] has not been studied beyond a one-time single-dose injection in clinical trials."

On 11/08/24, pursuant to the Midcycle Communication, the Applicant submitted the following revised (underlined) indication:

> "[TRADENAME] is indicated for the treatment of radicular leg pain associated with confirmed nerve root impingement caused by lumbar disc herniation in adults.
>
> Limitations of Use
>
> [TRADENAME] has not been studied beyond a one-time single-dose injection in clinical trials."

Condoliase digestschondroitin sulfate, whichis a prominent component of the nucleus pulposus of an intervertebral disc. If a disc has herniated, causing compression of the adjacent nerve root, then a decrease in volume of the disc would decrease the volume of the herniation and relieve pressure on the nerve root. This putative mechanism of action has been proposed as the basis for symptomatic relief after condoliase administration in painful radiculopathy secondary to spinal nerve impingement.

The Applicant submitted the original IND for condoliase in 2007. The IND was initially placed on Clinical Hold. The key deficiencies leading to the clinical hold were the doses proposed (exceeded 1.25 U), issues with the Informed Consent Document, and duration of follow up. The Applicant addressed the deficiencies, and the clinical hold was removed later in 2007. Throughout development, the Applicant and Agency have interacted to gain agreements in key elements of development (chemistry/manufacturing/controls, nonclinical, clinical, and biostatistical), culminating in this BLA submission. This Application was received on 03/11/24 and filed 60 days hence.

The regulatory history of condoliase would be remiss not to include a discussion of a very similar product, chymopapain. Chymodiactin® (chymopapain injection) [BLA 18-663] was approved in November 1983 with the indication of "treatment of patients with documented herniated lumbar intervertebral discs whose symptoms and signs, particularly sciatica, have not responded to an adequate

period or periods of conservative therapy." The product is a cysteine protease purified from the latex of unripe papayas that was to be injected into a herniated intervertebral disc under fluoroscopic guidance.

The product was withdrawn from the market in 2001; in 2003, the FDA announced a determination that it was not withdrawn from sale for reasons of safety or effectiveness (Food and Drug Administration 2003). Publicly available sources indicate that use of chymopapain had become controversial due to notable cases of fatal anaphylaxis and permanent neurological deficits (Agre et al. 1984; Moss et al. 1985; Cusick et al. 1987). Chymopapain is potentially toxic in the subarachnoid space, especially when mixed with iodinated contrast, causing subarachnoid hemorrhage (Larkin et al. 2012); thus, incorrect injection of chymopapain into spinal structures other than the disc could have serious adverse consequences. The lessons of chymopapain emphasize the necessity of appropriately trained and qualified proceduralists should condoliase be approved. The Applicant notes that in contrast to chymopapain, condoliase has greater substrate specificity and fewer potential off-target effects, which confers a theoretical safety advantage.

3 Summary of Issues for the AC

3.1 Efficacy Issues

Two positive adequate and AWC studies and one negative study.

3.1.1 Sources of Data for Efficacy

Table 1 lists the controlled clinical studies that were conducted.

Table 1. Controlled Clinical Studies

Study Information	Study Design/ Duration	Dosage & Administration, Dosing Period, Subjects Per Treatment	Primary Endpoint
6603/1133 (Phase 3; Completed) US (N = 60)	Multicenter, randomized, sham- controlled comparative, double-blind 52 weeks	Single intervertebral administration in dosages of 1.25 U/mL in a volume of 1 mL or sham injection SI-6603: N = 176 Sham: N = 176	Primary: Change from baseline to Week 13 in average worst leg pain score during the past 24 hours over the previous 7 days, as assessed by 100 mm VAS.
6603/1031 (Phase 3; Completed) Japan (N = 35)	Multicenter, randomized, placebo- controlled, comparative double-blind[1] 52 weeks	Single intervertebral administration in dosages of 1.25 U/mL or placebo in a volume of 1 mL SI-6603: N = 84 Placebo: N = 82	Primary: Change from baseline to Week 13 in worst leg pain score during the past 24 hours, as assessed by VAS.
6603/1131 (Phase 3; Completed) US (N = 37)	Multicenter, randomized, sham-controlled, comparative double-blind[2] 104 weeks	Single intervertebral administration in dosages of 1.25 U/mL in a volume of 1 mL or sham injection SI-6603: N = 290 Sham: N = 95	Primary: Change from baseline to Week 13 in worst leg pain score during the past 24 hours, as assessed by VAS.
6603/1021 (Phase 2/3; Completed) Japan (N = 38)	Multicenter randomized, placebo- controlled, comparative, double-blind 52 weeks	Single intervertebral administration in dosages of 1.25, 2.5, 5 U/mL or placebo in a volume of 1 mL SI-6603: N = 148 Placebo: N = 47	Primary: Change from baseline to Week 13 in worst leg pain score during the past 24 hours, as assessed by VAS.

U = unit; VAS = Visual Analogue Scale.
[1] After Week 13, Study 1031 was single-blinded (subject and doctor).
[2] After Week 52, Study 1131 was single-blinded (subject and doctor).
Source: Integrated Summary of Efficacy, Table 1, pages 11-12

3.1.2 Efficacy Summary

Substantial evidence of effectiveness (SEE) for the condoliase application is predicated on two AWC studies. Three AWC studies were conducted. Two of the studies (Study 1031 from Japan and Study 1133 from the United States) are positive, i.e., the primary analysis supports rejection of the null hypothesis, favoring the active (condoliase) over the control. One study (Study 1131 from the United States) is negative, i.e., analysis of the primary endpoint failed to reject the null hypothesis. Note that the FDA requires substantial evidence of effectiveness for approval of human drug or biological products. Generally, the statutory requirement for such substantial evidence is two or more AWC clinical investigations to support efficacy. We believe the Applicant has met this requirement with Studies 1031 and 1133.

In the following section, Study 1133 (positive U.S. study) is described in detail. We assessed its similarities and differences with Studies 1031 (positive Japanese study) and 1131 (negative U.S. study) to investigate why Study 1131 failed. Study 1133 was the last AWC study conducted chronologically and used experience from Study 1131 to refine the patients enrolled to achieve a positive result.

The AC is asked to comment on the significance of Study 1131 (negative study) in the context of the other two positive trials with respect to establishing efficacy of condoliase. The differences in Study 1131 compared to Studies 1031 and 1133 suggest that the efficacy of condoliase may be limited to specific patient populations, particularly those with imaging-confirmed nerve root impingement. The

Agency is also asking the AC to consider elements that should be included in the prescribing information to guide clinicians in identifying patients most likely to have a favorable benefit-risk profile if treated with condoliase. The Applicant is proposing the indication of "treatment of radicular leg pain associated with confirmed nerve root impingement caused by lumbar disc herniation in adults." The AC is asked to consider whether this indication should be modified to reflect the most appropriate patient population for condoliase.

3.1.3 Efficacy Issues in Detail

Following a detailed description of the design of Study 1133, we will discuss the efficacy results from the three studies (1031, 1131, and 1133). Given that Study 1131 was negative, we will describe how we interrogated the studies to arrive at a conclusion regarding overall SEE for condoliase.

Study 1133 Design

Title

A Multicenter, Randomized, Double-Blind, Sham-Controlled, Comparative Study of SI-6603 in Subjects With LDH (Phase 3)

Primary Objective

To evaluate the effectiveness of a single-dose intervertebral disc injection of condoliase at a dose of 1.25 U compared to sham control in subjects with LDH by comparing the change in worst leg pain during the past 24 hours as assessed by visual analog scale (VAS) from baseline to Week 13 after injection of the investigational product.

Secondary Objective

To evaluate the efficacy of condoliase 1.25 U for key secondary endpoints at Week 13 and Week 52 and to demonstrate whether condoliase 1.25 U is safe and well tolerated.

Study Design

A Phase 3, multicenter, randomized, double-blind, sham-controlled study in patients with LDH. Patients randomized to the condoliase treatment group were to have received a single dose of 1.25 U into the nucleus pulposus of the affected intervertebral disc. Patients randomized to the control group received a sham injection were to have received a needle to the lumbar musculature outside of the annulus without injection. Patients were to have been followed for 52 weeks.

Primary Efficacy Endpoint

The change from baseline to Week 13 in average worst leg pain score (100-mm VAS) during the past 24 hours over the previous 7 days.

Key Secondary Efficacy Endpoints

- The change from baseline to Week 13 in herniation volume
- The change from baseline to Week 13 in Oswestry Disability Index (ODI) score
- The change from baseline to Week 52 in average worst leg pain score (100-mm VAS) during the past 24 hours over the previous 7 days

Study 1133 Key Selection Criteria

Inclusion Criteria

- Patients aged 30 to 70 years.
- Body mass index (BMI) <40.
- Patients with contained posterolateral LDH at either L4-5 or L5-S1 (or L5-6) with root impingement on MRI (judged first by investigator, then confirmed by central reader).
- Patient must have a chief complaint of unilateral radiculopathy or radicular leg pain in the concordant dermatome of the affected nerve root.
- Patient must have positive straight leg raise on the symptomatic side (≤70º).
- Radicular pain must be in one leg only and present for ≥6 weeks but ≥12 months.
- Patients must have failed 6 weeks or more of conservative treatment including medications, physical therapy, chiropractic treatment, acupuncture, spinal injection, epidural injection, or nerve block.
- Patients whose worst leg pain during the 7 days prior to randomization had: been recorded for at least 5 of 7 days, been between 50 to 90 (100 mm VAS), with a range of fluctuation <25 mm.
- Patients with ≥30% on the ODI at time of randomization.

Exclusion Criteria

- Two or more levels of LDH with nerve root impingement on MRI with symptoms in the affected dermatomes.
- LDH with rupture into the posterior longitudinal ligament (extrusion or sequestration), isolated central herniation, anterolateral herniation and/or extraforaminal herniation on MRI.
- Clinical symptoms of radiculopathy on the contralateral leg.
- Received any of the following within 28 days of randomization: epidural injection, spinal injection, or nerve block for LDH and/or systemic steroids.
- Received any of the following within 7 days of randomization: opioids, cannabis, or local anesthesia by injection to lumbar region. Opioids may be allowed if patient agrees to wash out dose. (See the Rescue Medication section).
- Low back pain due to disorders other than LDH.
- Mean of worst low back pain for 7 consecutive days up to the day before randomization was >90 or >10 mm higher than the mean of worst leg pain (must have ≥5/7 days entered)
- X-ray with vertebral body angle body ≥5 degrees (in flexion), and/or spondylolisthesis (translation ≥3 mm) in the disc to be treated.
- Presence of osteophytes (third degree or more Nathan's classification) spondylosis deformans, degenerative spondylolisthesis, spinal tumor, discitis, vertebral fracture of vertebral body above or below disc, bony stenosis with nerve root impingement from L3-S1 or severe lumbar degenerative disc disease in the disc to be treated.

- Presence of any of the following disorders associated with low back pain that may interfere with safety or efficacy evaluations: non-LDH spinal stenosis, 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 spinal deformity: scoliosis (Cobb >20 degrees) or lordosis (L1-S1 Cobb <20 degrees).
- History of lumbar surgery, nucleotomy or intradiscal treatment at the affected level or surgery at any other lumbar spine level with persistent symptoms or failed back surgery syndrome.
- Patients with comorbid chronic pain disorders (e.g., fibromyalgia, restless legs syndrome), peripheral neuropathy caused by certain disorders (e.g., diabetes), Parkinson disease, complex regional pain syndrome, osteoarthritis (unless symptoms are only in the upper extremities), osteoporosis, spondyloarthritis, ankylosing spondylitis, rheumatoid arthritis, gout, or any other disorder that is likely to interfere with pain assessments.
- Any history of psychosis/psychotic disorder or any other psychiatric disorder that has been sufficiently severe to cause functional impairment within 6 months prior to screening. This does not include patients with adequately treated anxiety or depression on a stable medication regimen.
- History of substance abuse or dependency of alcohol, opioids, cannabis, stimulants and/or depressants within the last 5 years.
- Patients who test positive at screening or randomization for drugs of abuse.
- Patients with alcohol consumption >2 drinks per day or patients who test positive for blood alcohol at screening.
- Patients who are unable to wash-out opioids or cannabis for relief of pain or patients with opioid withdrawal symptoms.
- History of malignancy within the past 5 years (except basal cell or squamous cell carcinoma of the skin).
- Cauda equina syndrome or neurologic disorders that demonstrate rapid progression.
- Motor weakness graded less than 4/5.
- Patients on anticoagulants or patients with a history of a bleeding diathesis.
- Systemic infection requiring antimicrobial treatment or current HIV infection.
- History of clinically significant disorders such as uncontrolled pulmonary disease, uncontrolled hypertension, DMI, uncontrolled DMII, or other serious heart, liver, kidney or blood disease or immunodeficiency.
- History of CVA, pulmonary infarction, CHF or arrythmia.
- History or signs of CAD or MI within 6 months.
- History of seizure within the past 5 years or currently taking anticonvulsants for any other reason than neuropathic pain.
- Patients with any of the following lab values: AST or ALT ≥2.5-fold the upper limit of normal, total bilirubin ≥1.5-fold the upper limit of normal, serum creatinine ≥1.5-fold the upper limit of normal, and HCV Ab or HBV Ag positive.
- Patients who are receiving compensation according to the Workers Compensation Act or are involved in personal injury litigation due to a lumbar-related injury.

Study 1133 Procedures

Test Drug, Dose, and Mode of Administration

Condoliase 1.25 U was to have been administered intradiscally once by an unblinded investigator. Saline (1.2 mL) was to have been added to a vial of condoliase and the contents were to have been dissolved to prepare 1.25 U/mL. Patients randomized to the active treatment arm were to have been placed in a lateral or prone position. Under fluoroscopic guidance, the tip of the needle was to have penetrated the annulus fibrosus and entered the center of the nucleus pulposus. The prepared drug (1.0 mL) was to have been drawn up and administered via the intradiscal route using a 3 mL syringe. Concomitant use of an intravenous antibiotic was to have been permitted to prevent infection at the injection site.

Control Treatment, Dose, and Mode of Administration

Patients assigned to the control group were to have received a sham injection. Boxes with empty vials and identical labeling to condoliase were to have been used. Patients randomized to the control treatment arm were to have been placed in a lateral or prone position with a fluoroscopy machine in place. A needle was to have been inserted to the space outside of the annulus by an unblinded investigator and be comparable to the active treatment procedure. No substance was to have been administered. Concomitant use of an intravenous antibiotic was to have been permitted to prevent infection at the injection site.

Duration of Treatment

Patients were to have received a single injection.

Prohibited Concomitant Treatments

Patients were to have been discontinued from the study if they received any of the following:

- Lumbar surgery.
- Lumbar percutaneous nucleotomy or intradiscal therapies for symptoms caused by LDH.
- Epidural steroid injection, nerve or facet block for symptoms caused by LDH (before Week 13).

Restricted Concomitant Treatments

Patients who had been receiving physical therapy to treat LDH beginning 7 days or more prior to randomization could continue with that therapy at the same or lower frequency/intensity.

Prohibited Concomitant Medications

Use of the following medications (including over-the-counter products) was prohibited after wash-out:

- Opioids (except for the prescribed hydrocodone/acetaminophen for rescue).
- Cannabis and cannabis-derived products.
- Systemic steroids (inhaled, nasal, or topical steroids permitted in small areas).
- Local anesthesia to the low back, buttock, or affected leg.

Restricted Concomitant Medications

Patient on stable doses for at least 7 days prior to randomization could continue at the same or lower dose (any medications taken only as needed were prohibited):

- NSAIDs
- Acetaminophen
- Muscle relaxants
- Neuropathic agents (e.g., pregabalin, gabapentin, antidepressants)

Rescue Medication

Rescue Medication #1: Acetaminophen

- All patients were to be provided with acetaminophen at each clinic visit to use as a rescue for breakthrough pain resulting from LDH or for treatment of AEs.
- Patients were to be limited to <3,000 mg per day and reminded to not use other acetaminophen containing OTC medications.

Rescue Medication #2: Hydrocodone/acetaminophen 5/300 mg

- Patients who were taking opioids at the time of informed consent or in the prior 2 months were eligible.
- Patients must have washed out prior regimen to be eligible.
- Patients were to be given 60 tablets to last the entire study and encouraged to use this rescue medication only when rescue medication #1 failed. They were to be encouraged to not take the opioid rescue until 4 hours after rescue medication #1.
- Patients were not to exceed four tablets in a 24-hour period.
- Rescue medication #2 was prohibited 7 days prior to Visit 6 (Week 6), Visit 7 (Week 13), Visit 8 (Week 26), Visit 9 (Week 39), and Visit 10 (Week 52)
- For Visit 7 (Week 13) and Visit 10 (Week 52), patients were to stop using rescue medication #2 at least 10 days prior to the visit.

Study 1133 Data Collection

Primary Endpoint

The primary endpoint was the change from baseline to Week 13 in average worst leg pain score during the past 24 hours over the previous 7 days, as assessed by 100-mm VAS.

Key Secondary Endpoints

- Change from baseline to Week 13 in herniation volume.
- Change from baseline to Week 13 in ODI score.
- Change from baseline to Week 52 in average worst leg pain score during the past 24 hours over the previous 7 days, as assessed by 100-mm VAS.

Other Secondary Endpoints

- Change from baseline in worst leg pain score at each time point.
- Change from baseline in worst low back pain score at each time point.
- Change from baseline in ODI score at each time point.
- Percentage of subjects with negative straight leg raise test.
- Percentage of subjects without hypoesthesia, muscle weakness or hyporeflexia.
- Patient Global Impression of Change score at each time point.
- Clinical Global Impression of Change score at each time point.
- Change from baseline in 36-item Short-Form Health Survey scores at each time point.
- EuroQol Group 5-Dimension Quality of Life instrument, five-level version quality of life score and VAS score at Week 13 and Week 52.
- Work Productivity and Activity Impairment Questionnaire score at Week 13 and Week 52.
- Incidence and amount of rescue medication use over 13 weeks.
- Change from baseline in amount of rescue medication use at each time point.
- Cumulative distribution of percentage change from baseline in worst leg pain score at Week 13 and Week 52.
- Cumulative distribution of percentage change from baseline in ODI score at Week 13 and Week 52.
- Responder rate by composite definition at Week 13.
- Change from baseline in intervertebral disc volume at Week 13 and Week 52.
- Change from baseline in herniation volume at Week 13 and Week 52.
- Incidence of post-treatment surgery for LDH at the same level of investigational product injection.
- Number of patients with recurrence of LDH at Week 52.

Safety Assessments

- Adverse events
- Laboratory tests
- Vital signs/physical examination
- Imaging assessments by X-ray and MRI
    - — Disc height (disc index)
    - — Vertebral body translation
    - — Vertebral body angle formed by flexion
    - — Modic classification
- Occurrence of post-treatment lumbar surgery
    - — Surgery for treatment of LDH at a different level than administration of the investigational product
    - — Lumbar surgery not for the treatment of LDH

Study 1133 Statistical Analysis

Statistical Methods

The primary endpoint was to have been the change from baseline to Week 13 in average worst leg pain score during the past 24 hours over the previous 7 days, as assessed by 100-mm VAS. The primary endpoint was to have been analyzed by a mixed model for repeated measures for the modified intention-to-treat population.

Sample Size

The study was to have enrolled 320 patients with a 1:1 randomization. The sample size estimation was based on using the mean difference in the worst leg pain score change from the baseline in the primary efficacy analysis with the following assumptions.

- The two-sample *t*-test comparing the group means of the change from baseline was used. (The two-sample *t*-test approximates the test of the null hypothesis based on the repeated measures model that was used in the primary efficacy analysis.)
- Treatment difference between SI-6603 and sham injection control groups of 12 mm.
- Common standard deviation (SD) of 30 mm.
- Dropout rate of 15%.
- Power of 90%.
- Two-sided significance level of 5%.

Stratification at Randomization

Patients were to have been randomized 1:1 to either condoliase or sham injection. Each patient was to have received a unique randomization number. An Interactive Web Response System was to have assigned patients to treatment groups based on the predefined randomization list. The randomization was to have been balanced by randomly permuted blocks and stratified by site.

Interim Analyses

No interim analyses were planned.

Handling of Missing and Indeterminate Data

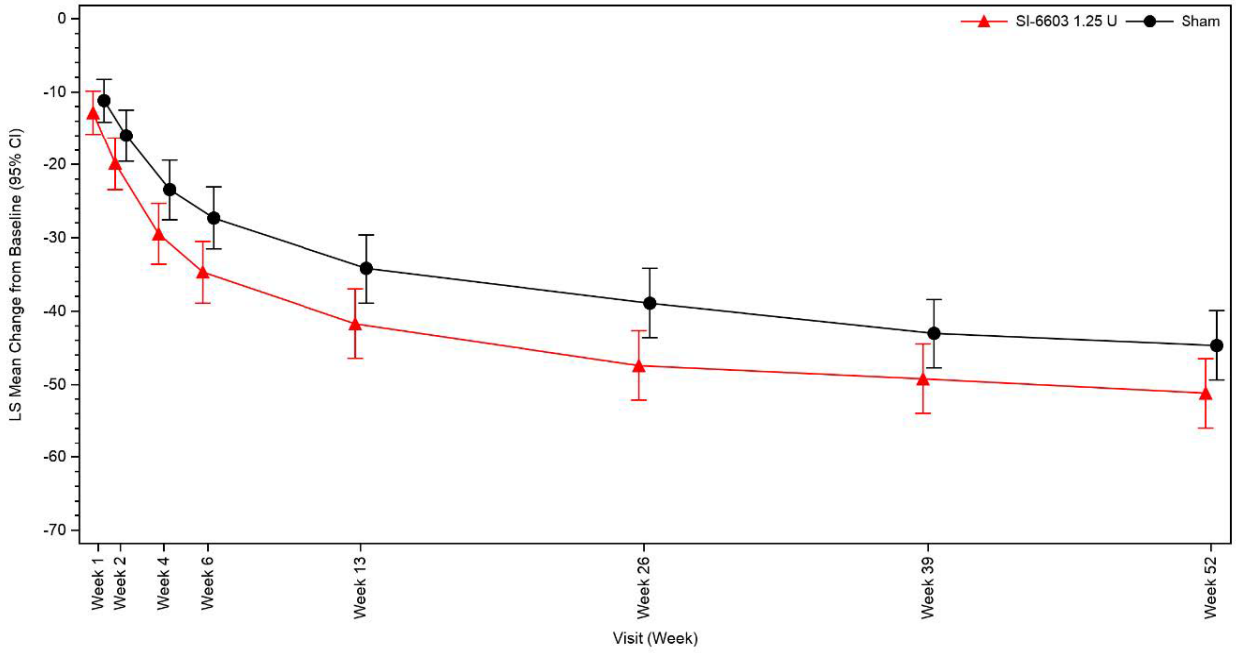
The primary efficacy endpoint was to have been analyzed by a mixed model for repeated measures assuming the data were missing at random, based on the prespecified analysis method.

Study 1133 Results

A total of 807 patients were screened, and 352 were randomized. Condoliase was dosed to 169 patients, and 172 received a sham injection. The baseline characteristics will be described in greater detail in Section 3.2 Safety Issues, for the purposes of comparison with previous Studies 1031 and 1131. Briefly, the patients enrolled in Study 1133 tended to be in their mid-40s with a slight male predominance (54% versus 46% female). More than 80% of the patients enrolled were White, followed by ~10% being Black. The most common level of LDH was L5-S1 (59%), followed by L4-L5 (41%). The mean baseline worst leg pain was 72/100 on the VAS.

For the primary efficacy endpoint, Study 1133 was positive, with a treatment effect size of 7.5/100 mm favoring condoliase over placebo at Week 13 (p=0.026). The pain curves for Study 1133 are shown in Figure 2.

Figure 2. Change From Baseline in Weekly Averages of Worst Leg Pain (Primary Endpoint, Modified Intention-to-Treat Population)

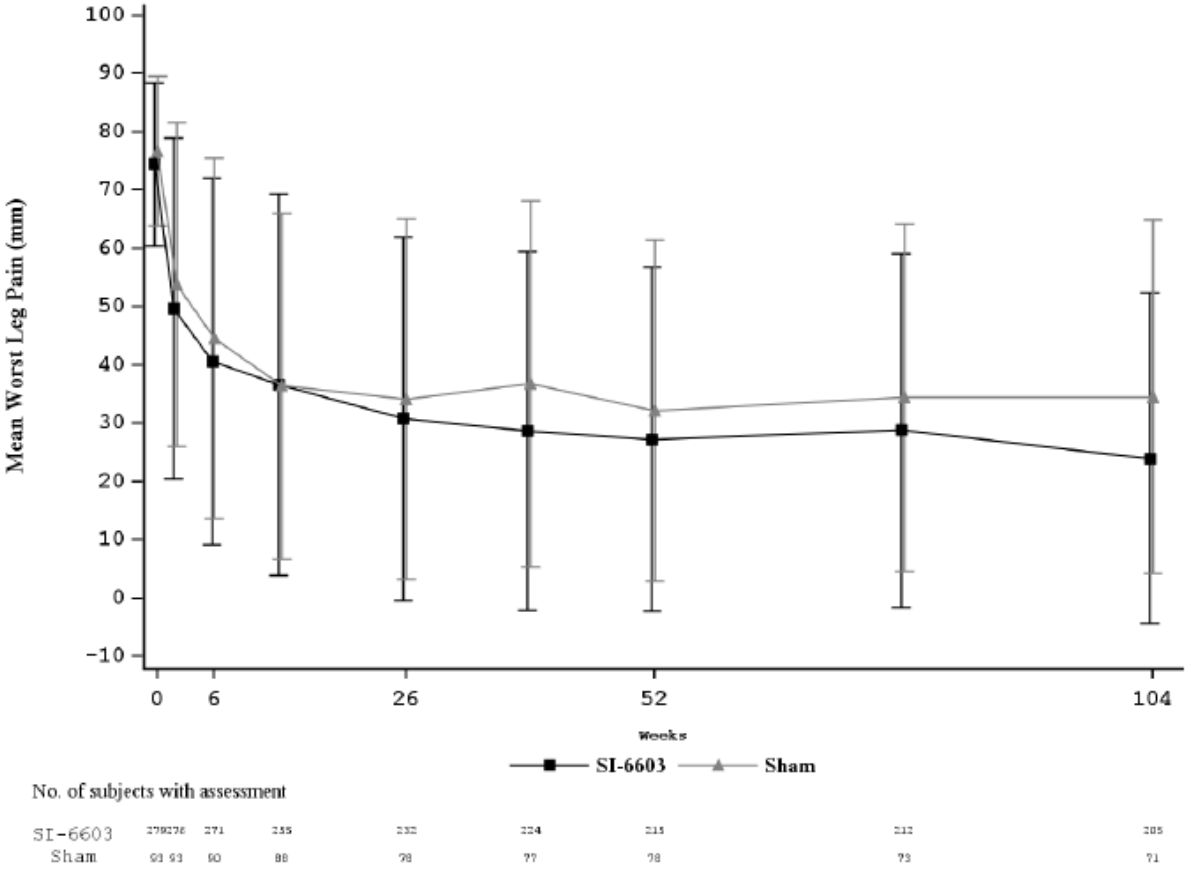


Source: Integrated Summary of Safety, page 78
Abbreviations: CI, confidence interval; LS, least squares

Study 1131 Synopsis and Results

Study 1131 was a Phase 3 study conducted in the United States immediately prior to Study 1133. It was intended to be one of the two AWC trials to support SEE (after Study 1031). It was the first U.S study and was the largest Phase 3 study by enrollment (385 total, 280 dosed with active treatment and 94 with a sham injection). It was also the longest study, with safety monitoring for 104 weeks, in contrast to the 52-week monitoring in Studies 1031 and 1133. Study 1133 failed to demonstrate efficacy on the primary endpoint of change in worst leg pain from baseline at Week 13. While of very low magnitude (1.9/100 mm), the point estimate on the primary endpoint favored placebo (p=0.62). The pain curve is shown in Figure 3.

Figure 3. Mean Worst Leg Pain by Visit (Primary Endpoint, Intention-to-Treat Population)

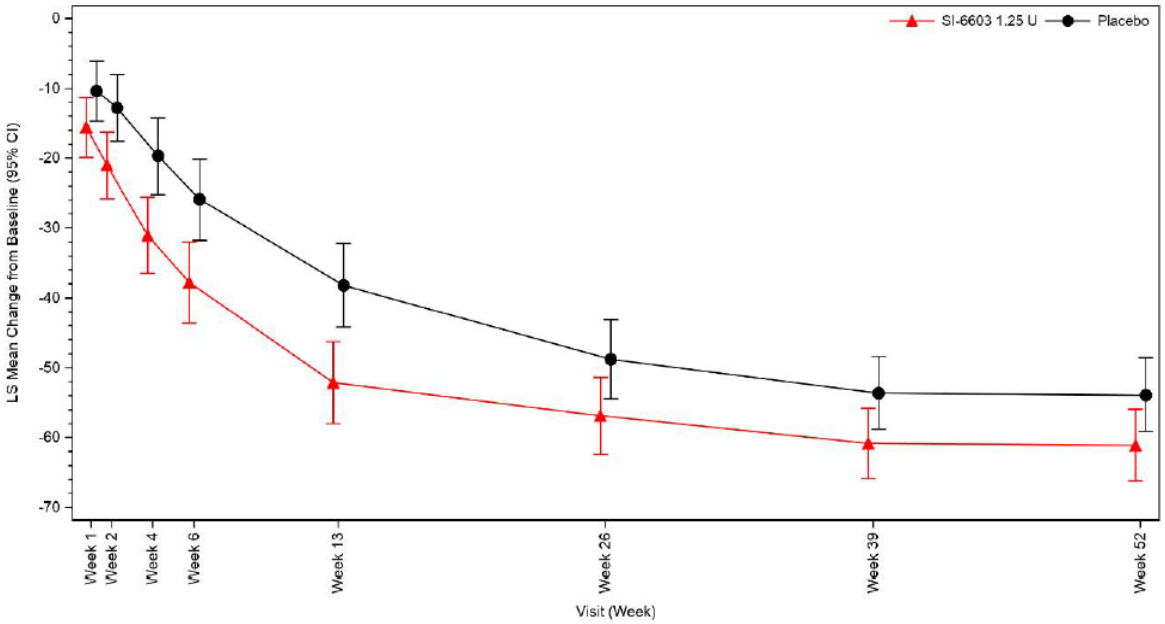


Source: Clinical Study Report, Figure 2

Study 1031 Synopsis and Results

Study 1031, conducted exclusively in Japan, was chronologically the first Phase 3 AWC study conducted for condoliase. Unlike the two later U.S. studies, this study used a true control where the disc was pierced and injected with saline. Study 1031 enrolled 163 patients, with 82 receiving condoliase and 81 receiving the placebo. The study was positive on the primary efficacy variable with a treatment effect size of 15.2/100 mm at Week 13 (p=0.001). The pain curve for Study 1031 is shown in Figure 4.

Figure 4. Change From Baseline in Weekly Average Worst Leg Pain (Primary Endpoint, mITT Population)



Source: Integrated Summary of Efficacy, page 78
Abbreviations: CI, confidence interval; LS, least squares; mITT, modified intention-to-treat

Discussion of Inconsistent Study Results

Applicant's Assessment

As noted above, Study 1131 did not meet its primary efficacy endpoint (change in worst leg pain from baseline to Week 13), nor did it meet either of its two key secondary endpoints, including a responder analysis at Week 13 and a pain outcome assessment at Week 52. Responders were defined as experiencing a 30% reduction in worst leg pain, 30% improvement in ODI, maintenance or improvement of neurologic status, and no defined treatment failure. The proportion of responders at Week 13 was not significantly different between the two arms, 35% in the active group and 39% in the control group. The change from worst leg pain from baseline to Week 52 slightly favored the control, but the difference was not statistically significant.

After reviewing the results of Study 1131, the Applicant performed a detailed analysis to explain the negative U.S. findings despite the positive findings in Study 1031 in Japan. They proposed two key issues as contributors to the negative outcome of Study 1131. First, the Applicant noted that a majority of patients did not have definitive impingement of the nerve root by the disc herniation on MRI. Second, the Applicant found that baseline back pain was significantly higher in Study 1131 (74.8 mm) compared to Study 1031 (51.3 mm). To address these inconsistencies, the Applicant updated the eligibility criteria for Study 1131 in the design of the new study, Study 1133. Key modifications to the patient-selection criteria included MRI-proven nerve impingement, absence of comorbid chronic pain diagnoses, and back pain worse than leg pain. As discussed above, Study 1133 was positive on its primary efficacy endpoint.

FDA's Assessment

Our approach to assessing the totality of the efficacy data was as follows:

- Compare study results.
- Compare design differences (e.g., selection criteria, comparator).
- Compare baseline characteristics of the patients enrolled.
- Assess protocol compliance/study conduct.
- Assess the quantity of missing data/imputation.
- Hypothesis generation.
- Obtain targeted subgroup analyses.
- Determine whether the failure of Study 1131 is explicable.
- Determine whether SEE was met.

For brevity, the data presented are limited to informative or critical elements of our assessment. The study results are summarized in Table 2.

Table 2. Primary Efficacy Endpoint Results for the Phase 3 Studies

Study Characteristic	Study 1031 (Positive)	Study 1131 (Negative)	Study 1133 (Positive)
Location	Japan	United States	United States
Dates conducted	3/2012 to 2/2014	9/2013 to 8/2017	11/2018 to 3/2023
Active LS mean	−49.5	−37.7	−41.7
Control LS mean	−34.3 (placebo)	−39.6 (sham)	−34.2 (sham)
Treatment effect size	−15.2	+1.9	−7.5
p-value	p=0.0011	p=0.6212	p=0.0263

Source: Study 1031, 1131, and 1133 Clinical Study Reports
Abbreviation: LS, least squares

We have summarized the study design key differences in Table 3.

Table 3. Key Selection Criteria Differences for the Phase 3 Studies

Selection Criterion	Study 1031 (Positive)	Study 1131 (Negative)	Study 1133 (Positive)
Worst leg pain for enrollment and primary endpoint (VAS)	VAS ≥50 Fluctuation ≤25 on ≥3/7 days	VAS ≥50 over 24 hours	VAS 50-90 Fluctuation ≤25 on ≥5/7 days
Duration of radicular leg pain	≥6 weeks	≥6 weeks and ≤1 year	≥6 weeks and ≤1 year
Low back pain	None	None	Exclude low back pain if ≥10 mm worse than leg pain (VAS) Exclude LBP caused by disorders other than LDH Exclude baseline LBP VAS ≥90 the week prior to randomization
Comparator	Placebo	Sham	Sham

Selection Criterion	Study 1031 (Positive)	Study 1131 (Negative)	Study 1133 (Positive)
Age	20-70	30-70	30-70
BMI	Exclude BMI ≥35	Exclude BMI ≥35	Exclude BMI ≥40
ODI Requirements	None	≥30%	≥30%
Imaging requirements for nerve impingement	None required	None required	Enroll MRI-proven nerve impingement confirmed by a central reader
Disc herniation type	Exclude extrusion or sequestration with rupture into PLL	Exclude LDH with rupture into PLL (extrusion or sequestration) Include protrusion or extrusion type in the posterior lateral or central location	Exclude extrusion or sequestration LDH with rupture into PLL Exclude central, anterolateral or extraforaminal herniation
Chronic pain comorbidities	None	None	Exclude chronic pain comorbidities (RLS, PN, CRPS, OA of LE, gout)
Spinal comorbidities	Exclude spinal OA, stenosis, severe osteophytes, AS, discitis	Exclude non-LDH stenosis, discitis, AS, severe osteophytes Exclude scoliosis, kyphosis, or lordosis	Exclude non-LDH stenosis, AS, SA, VCF, severe facet OA, or severe osteophytes Exclude scoliosis, kyphosis, or lordosis
Chronic opioids	Baseline opioid regimen was allowed to continue if at current or lower dose (excluding long-acting opioids)	Baseline opioid regimen was allowed to continue if at current or lower dose	Patients must wean chronic opioids and agree to hydrocodone acetaminophen 5/300 mg rescue up to 60 tabs for the entire study

Source: Study 1031, Study 1131, and Study 1133 Clinical Study Reports
Abbreviations: AS, ankylosing spondylitis; BMI, body mass index; CRPS, complex regional pain syndrome; LBP, low back pain; LDH, lumbar disc herniation; LE, lower extremity; MRI, magnetic resonance imaging; OA, osteoarthritis; PLL, posterior longitudinal ligament; PN, peripheral neuropathy; RLS, restless leg syndrome; SA, spondyloarthritis; VAS, visual analogue scale; VCF, vertebral compression fracture

There were no substantial differences in study conduct, protocol compliance, or missing data to explain the inconsistent results among the three studies. Based on our review of the data, there were three differences in the study populations that potentially explain the failure of Study 1131 compared to Studies 1031 and 1133.

1. Confirmation of nerve root impingement: Study 1133 required MRI-confirmed nerve root impingement. In Study 1031, which was silent on an eligibility requirement for imaging-proved nerve impingement, 86% (placebo) and 90% (active) of patients had documented nerve impingement. Study 1133 required nerve impingement verified by a central reader for eligibility. In contrast, only 27% of patients enrolled in Study 1131 had imaging-proven nerve impingement.
2. Exclusion of comorbid chronic pain conditions and other spinal pathology: Study 1133 explicitly excluded patients with back pain greater than leg pain, as well as those with chronic pain comorbidities including: fibromyalgia, restless legs syndrome, diabetic peripheral neuropathy, complex regional pain syndrome, lower extremity osteoarthritis and gout. More spinal comorbidities were excluded from 1133 than from 1131 (Table 3). At least one of the above comorbidities was

present in 7.2% of the patients enrolled in Study 1131. Subgroup analyses based on the presence or absence of these comorbidities are shown in Table 4.

Table 4. Change in Worst Leg Pain VAS at Week 13 for the 1.25 U Dose of Condoliase (Study 1131)

Subgroup	Factor Present	Factor Absent
MRI-confirmed nerve root impingement	−40.1 (n=69)	−36.2 (n=186)
Back pain greater than leg pain	−27.3 (n=55)	−44.6 (n=34)
Chronic pain comorbidities	−12.3 (n=18)	−39.2 (n=237)
Spinal comorbidities	−23.2 (n=9)	−37.7 (n=246)

Source: July 16, 2024 IR Response, Table IR17.3.1a.1, IR17.3.1d, IR17.3.2 and 74-Day Letter Response, Table D74.18c
Abbreviations: MRI, magnetic resonance imaging; VAS, visual analogue scale

3. Lower prevalence of prior musculoskeletal (MSK) disease: Study 1131 had a higher rate of prior MSK disease (38% of patients enrolled versus 24% in Study 1133). Subgroup analyses comparing treatment effects in patient with versus those without prior MSK disease in each of the three studies showed a smaller treatment effect size in patients with prior MSK disease. Subgroup analyses are shown in Table 5.

Table 5. Difference in Least Squares Mean at Week 13 for the 1.25 U Dose of Condoliase

Variable	Study 1031		Study 1131		Study 1133	
H/O MSK disease	Any	None	Any	None	Any	None
Effect size	−12.8*	−14.0	12.2	−6.3	−4.0	−8.4

Source: 74-Day Letter Response, Table D74.17b.1 and Table D74.17b.2
* Study 1031 had a very small number of patients with musculoskeletal comorbidities; therefore, the sample size is small for this data point.
Abbreviations: H/O, history of; MSK, musculoskeletal

FDA Conclusions

The data indicate that Study 1131 likely failed because a condition imperative for the mechanism of action of the product (herniation resulting in symptomatic nerve impingement) was not present in most of the patients enrolled. In the two studies where nerve impingement conducive to condoliase treatment was confirmed by imaging, the results were positive. Our analysis suggests that confounding painful and MSK conditions may compromise benefit for condoliase. Thus, the issues of diagnostic certainty and specificity appear to be crucial considerations in evaluating the potential benefit of condoliase for a given patient.

We note that one of the positive AWC studies (Study 1031) was conducted exclusively in Japanese patients. We investigated whether the findings of efficacy with condoliase in a Japanese population could be generalized to the U.S. population. While there were some differences in the baseline characteristics between the Japanese and U.S. populations (BMI, age, proportion of heavy laborers), the diagnostic criteria, LDH treatment paradigms, and putative mechanism of action were adequately similar between Study 1031 and Study 1133 to permit generalization of efficacy to a population outside of Japan.

Our review of condoliase finds that in appropriate patients with imaging-proven nerve impingement, the Applicant has demonstrated SEE with two AWC studies. However, the negative study may inform the benefit-risk assessment for specific populations who may be considered for treatment with condoliase if the product is approved.

3.2 Safety Issues

The clinical trial data and postmarketing safety data show signals of potential adverse reactions to condoliase in three major areas. These will be discussed below:

- Severe cutaneous adverse reactions (SCARs)
- Spine-related adverse events
- Other hypersensitivity reactions

3.2.1 Sources of Data for Safety

As noted in Section 1.3, there are two sources of safety data: the clinical trial database and postmarketing data. The Applicant has met the number and duration of exposures agreed by the Agency to constitute an adequate safety database. At the time of BLA submission, the clinical trial database contained data on 1679 patients dosed with at least 1.25 U, with 1101 patients followed for at least 26 weeks, 326 patients for at least 52 weeks, and 204 patients at least 104 weeks. The largest data source, Study 1132, was an open-label study conducted in the United States and Europe and was not considered a pivotal trial. All 530 subjects followed for at least 52 weeks were from the two U.S. Phase 3 studies (1131 and 1133). Numbers broken down by study and follow-up duration are shown in Table 6.

Table 6. Safety Database: Number of Patients Exposed to >1.25 U Condoliase by Study and Follow-up Time

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

NA = not applicable; U = unit

[1] Week 104 visit had a window of +/- 4 weeks. Three subjects in Study 6003/1131 exposed to 1.25 U dose had protocol deviations for completing the Week 104 visit out of window (prior to Week 100).

Note: For ≥26 weeks and ≥52 weeks follow-up categories, only Studies 6603/1131, 6603/1132, and 6603/1133 with full safety monitoring are included.

Source: Summary of Clinical Safety, Table 3

At the time of BLA submission, approximately 24,000 patients had been dosed with condoliase, all in Japan, where the product is approved. The submission indicates that 4,157 exposures had solicited AE data. In the most recent Development Safety Update Report submitted on 08/16/24, approximately 29,000 patients had been dosed in Japan.

3.2.2 Safety Summary

Across all available studies, condoliase was not associated with imbalances in death or serious AEs where condoliase was considered causal. We do note that while the Applicant's tables of AEs show discontinuations for AEs and there were no significant differences across the three studies, we question such coding because the drug is injected only once and there is no way to discontinue dosing.

Section 3.2.3 Safety Issues in Detail, is organized into three parts. The General Safety section summarizes general safety, including major safety findings (deaths, nonfatal serious adverse events, and AEs leading to discontinuation) and Common Adverse Events. The next section discusses Adverse Events of Special Interest. The final section, Safety Unknowns and Relevance to Conditions of Use, discusses the available data and will integrate those data to facilitate the AC's discussion of salient issues in this application, including the quantity of long-term data available and how risks might be mitigated.

The AC is asked to consider the level of concern for each of the identified safety issues (SCARs, SRAEs, and other hypersensitivity reactions), as well as potential risk mitigation and/or monitoring strategies.

3.2.3 Safety Issues in Detail

General Safety

Baseline Characteristics

As noted in the Efficacy Issues section, three AWC studies comprise the key randomized, controlled trial data. While there is one other randomized, controlled trial (Study 1021), that Phase 2 dose-ranging study enrolled a small number of patients (48) at a dose of 1.25 U and is excluded here for concision. Table 7 shows the key baseline characteristics across the three Phase 3 studies, with treatment groups aggregated. Past medical history is arranged by system organ class (SOC), truncated for incidence ≥5% in any study.

Table 7.Baseline Characteristics of the Phase 3 Studies

Parameter	Study 1031 (N=163)	Study 1133 (N=341)	Study 1131 (N=374)
Age (mean and range)	39.3 (20,69)	46.3 (30,69)	48.8 (30,70)
Sex (% female)	39.3%	46.0%	51.9%
Race – American Indian or Alaska Native	0%	0.3%	0%
Race – Asian	100%	4.4%	1.3%
Race – Black	0%	9.4%	12.8%
Race – Native Hawaiian or other Pacific Islander	0%	0%	0%
Race – White	0%	81.8%	84.2%
Race – Other	0%	4.1%	1.6%
BMI (mean and range)	23.7 (15.9,34.4)	27.8 (17,40)	28.3 (17,37)
Occupational history	63.2% heavy labor	25.8% heavy labor	20.6% heavy labor
Past medical history – endocrine	1.2%	8.2%	9.6%
Past medical history – eye	8.0%	3.5%	9.9%

Parameter	Study 1031 (N=163)	Study 1133 (N=341)	Study 1131 (N=374)
Past medical history – gastrointestinal	16.6%	24.0%	33.8%
Past medical history – general disorders	0.6%	3.2%	5.7%
Past medical history – immune	16.6%	27.3%	24.4%
Past medical history – infections and infestations	11.0%	13.5%	14.0%
Past medical history – injury, poisoning, procedural complications	3.7%	11.7%	10.1%
Past medical history – investigations	Not listed	11.7%	10.6%
Past medical history – metabolism and nutrition	17.2%	24.0%	28.1%
Past medical history – musculoskeletal	12.3%	23.5%	37.8%
Past medical history – neoplasms	6.7%	8.8%	6.5%
Past medical history – nervous system	8.0%	17.6%	32.2%
Past medical history – psychiatric	5.5%	25.8%	43.6%
Past medical history – renal	1.2%	7.0%	7.5%
Past medical history – reproductive and breast	6.7%	9.1%	8.1%
Past medical history – respiratory	6.7%	12.8%	14.8%
Past medical history – skin	8.0%	7.0%	6.5%
Past medical history – social circumstances	Not listed	15.8%	8.1%
Past medical history – surgical and medical procedures	Not listed	42.1%	35.3%
Past medical history – vascular	17.8%	24.3%	33.0%
Past medical history – hepatobiliary	8.6%	5.9%	1.0%
Past medical history – concomitant disease or at least one condition	69.6%	81.5%	90.6%

Source: Studies 1031, 1131, and 1133 Clinical Study Reports and 74-Day Letter Response, Table: D74.13
Abbreviations: BMI, body mass index; CSR, clinical study report; N, number of patients in the study; SOC, system organ class

From a demographic perspective, Study 1031 differs from Studies 1131 and 1133 in that the patients enrolled were all Japanese, younger, had a lower BMI, were more likely to perform heavy labor, and had fewer comorbidities at baseline. Comparison of the rates of pre-existing comorbid conditions for Studies 1131 and 1133 show that patients enrolled in Study 1133 had lower rates of comorbid conditions than Study 1131, most pronounced in the MSK and psychiatric SOCs. Given the potential for condoliase to cause hypersensitivity reactions, the history of immune disorders in the range of 25% is of interest. The most common preferred terms (PTs) in the pre-existing immune system disorders SOC were drug hypersensitivity (11.7% and 14.7%) and seasonal allergy (10.4% and 11.1%) (Studies 1131 and 1133, respectively).

Major Safety Findings

The Applicant divided AE data into four epochs, correlating with when the AE was reported in relation to the injection. Epoch 1 was injection to Week 13, Epoch 2 was Weeks 13 to 26, Epoch 3 was Weeks 26 to 52, and Epoch 4 was >Week 52. Study 1031 was limited to 13 weeks of follow-up, Study 1133 followed patients for 52 weeks, and Study 1131 for up to 104 weeks (Table 8).

As noted in the Efficacy Issues section of this document, the controlled studies used either a placebo control whereby the affected disc was pierced and injected with saline or a sham injection where the adjacent, non-disc tissue was instrumented. For the purposes of presentation, the treatment-emergent AEs are shown for both the separate sham and placebo arms, as well as the pooled controls from all three pivotal trials.

Table 8. Treatment-Emergent Adverse Events, up to Week 13 (Randomized, Controlled Studies)

			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	878	151	221	289	510
Subjects with events	381 (65.9)	75 (76.5)	88 (68.8)	127 (47.4)	215 (54.3)
Subjects who died	0	0	0	0	0
Subjects with events leading to study discontinuation	3 (0.5)	0	5 (3.9)	4 (1.5)	9 (2.3)
Subjects with events by severity [1]					
Mild	191 (33.0)	42 (42.9)	36 (28.1)	74 (27.6)	110 (27.8)
Moderate	157 (27.2)	26 (26.5)	45 (35.2)	41 (15.3)	86 (21.7)
Severe	33 (5.7)	7 (7.1)	7 (5.5)	12 (4.5)	19 (4.8)
Subjects with events by relationship [2]					
Related	149 (25.8)	43 (43.9)	28 (21.9)	24 (9.0)	52 (13.1)
Not Related	232 (40.1)	32 (32.7)	60 (46.9)	103 (38.4)	163 (41.2)
Subjects with events by onset [3]					
≤1 day	91 (15.7)	15 (15.3)	33 (25.8)	20 (7.5)	53 (13.4)
2-7 days	88 (15.2)	25 (25.5)	16 (12.5)	25 (9.3)	41 (10.4)
8 days-13 weeks	202 (34.9)	35 (35.7)	39 (30.5)	82 (30.6)	121 (30.6)
Related treatment-emergent AEs					
Total number of events	212	66	38	40	78
Subjects with events	149 (25.8)	43 (43.9)	28 (21.9)	24 (9.0)	52 (13.1)
Subjects who died	0	0	0	0	0
Subjects with events leading to study discontinuation	0	0	0	0	0
Subjects with events by severity [1]					
Mild	108 (18.7)	33 (33.7)	19 (14.8)	15 (5.6)	34 (8.6)
Moderate	38 (6.6)	8 (8.2)	9 (7.0)	9 (3.4)	18 (4.5)
Severe	3 (0.5)	2 (2.0)	0	0	0
Subjects with events by onset [3]					
≤1 day	37 (6.4)	8 (8.2)	11 (8.6)	4 (1.5)	15 (3.8)
2-7 days	42 (7.3)	14 (14.3)	10 (7.8)	9 (3.4)	19 (4.8)
8 days-13 weeks	70 (12.1)	21 (21.4)	7 (5.5)	11 (4.1)	18 (4.5)
Serious treatment-emergent AEs					
Total number of Serious events	16	2	7	7	14
Subjects with Serious events	15 (2.6)	2 (2.0)	7 (5.5)	6 (2.2)	13 (3.3)

AE = adverse event; TEAE = treatment-emergent adverse event; U = unit
[1] Subjects are reported once at the highest severity. Missing severity is imputed as Severe.
[2] Subjects are reported once at the closest relationship.
[3] Subjects are reported once at the earliest onset.
Note: Up to Week 13 includes any TEAEs that start up until study day 98, inclusive. Percentages based on Safety Population.
Source: Summary of Clinical Safety, Table 7 (truncated to delete related serious adverse events)

Table 9. Treatment-Emergent Adverse Events, After Week 13 to Week 26 (Randomized, Controlled Studies)

	Pooled				
	SI-6603 1.25 U n (%)	SI-6603 >1.25 U n (%)	Placebo n (%)	Sham Control n (%)	Placebo/ Sham Pooled n (%)
Treatment-emergent AEs [1]					
Subjects at risk for Any event	421	NA	NA	252	252
Total number of events	131			63	63
Subjects with events	94 (22.3)			41 (16.3)	41 (16.3)
Subjects who died	1 (0.2)			1 (0.4)	1 (0.4)
Subjects with events leading to study discontinuation	3 (0.7)			2 (0.8)	2 (0.8)
Subjects with events by severity [2]					
Mild	57 (13.5)			22 (8.7)	22 (8.7)
Moderate	28 (6.7)			12 (4.8)	12 (4.8)
Severe	9 (2.1)			7 (2.8)	7 (2.8)
Subjects with events by relationship [3]					
Related	6 (1.4)			2 (0.8)	2 (0.8)
Not Related	88 (20.9)			39 (15.5)	39 (15.5)
Related treatment-emergent AEs [1]					
Subjects at risk for Any event	421	NA	NA	252	252
Total number of events	6			2	2
Subjects with events	6 (1.4)			2 (0.8)	2 (0.8)
Subjects who died	0			0	0
Subjects with events leading to study discontinuation	0			0	0
Subjects with events by severity [2]					
Mild	5 (1.2)			1 (0.4)	1 (0.4)
Moderate	1 (0.2)			1 (0.4)	1 (0.4)
Severe	0			0	0
Serious treatment-emergent AEs [4]					
Subjects at risk for any Serious event	538	88	107	252	359
Total number of Serious events	9	0	1	7	8
Subjects with Serious events	9 (1.7)	0	1 (0.9)	5 (2.0)	6 (1.7)

AE = adverse event; NA = not applicable; TEAE = treatment-emergent adverse event; U = unit

[1] For Any rows (serious or non-serious events), after Week 13 to Week 26 includes only studies 6603/1131 and 6603/1133 in both numerator and denominator of subjects at risk.

[2] Subjects are reported once at the highest severity. Missing severity is imputed as Severe.

[3] Subjects are reported once at the closest relationship.

[4] For Serious event rows, after Week 13 to Week 26 includes all studies in the Pool (6603/1021, 6603/1031, 6603/1131, and 6603/1133) in both numerator and denominator of subjects at risk.

Note: After Week 13 to Week 26 includes any TEAEs that start between study day 99 and study day 189, inclusive. Percentages are based on subjects who were still in the study up until the start of the interval.

Source: Summary of Clinical Safety, Table 8 (truncated to delete related serious adverse events)

Table 10. Treatment-Emergent Adverse Events, After Week 26 to Week 52 (Randomized, Controlled Studies)

	Pooled				
	SI-6603 1.25 U n (%)	SI-6603 >1.25 U n (%)	Placebo n (%)	Sham Control n (%)	Placebo/ Sham Pooled n (%)
Treatment-emergent AEs [1]					
Subjects at risk for Any event	388	NA	NA	233	233
Total number of events	199			105	105
Subjects with events	113 (29.1)			67 (28.8)	67 (28.8)
Subjects who died	1 (0.3)			0	0
Subjects with events leading to study discontinuation	0			1 (0.4)	1 (0.4)
Subjects with events by severity [2]					
Mild	70 (18.0)			42 (18.0)	42 (18.0)
Moderate	35 (9.0)			21 (9.0)	21 (9.0)
Severe	8 (2.1)			4 (1.7)	4 (1.7)
Subjects with events by relationship [3]					
Related	11 (2.8)			3 (1.3)	3 (1.3)
Not Related	102 (26.3)			64 (27.5)	64 (27.5)
Related treatment-emergent AEs [1]					
Subjects at risk for Any event	388	NA	NA	233	233
Total number of events	11			3	3
Subjects with events	11 (2.8)			3 (1.3)	3 (1.3)
Subjects who died	0			0	0
Subjects with events leading to study discontinuation	0			0	0
Subjects with events by severity [2]					
Mild	10 (2.6)			3 (1.3)	3 (1.3)
Moderate	1 (0.3)			0	0
Severe	0			0	0
Serious treatment-emergent AEs [4]					
Subjects at risk for any Serious event	493	80	100	233	333
Total number of Serious events	19	0	1	6	7
Subjects with Serious events	14 (2.8)	0	1 (1.0)	5 (2.1)	6 (1.8)

AE = adverse event; NA = not applicable; TEAE = treatment-emergent adverse event; U = unit

[1] For Any rows (serious or non-serious events), after Week 26 to Week 52 includes only studies 6603/1131 and 6603/1133 in both numerator and denominator of subjects at risk.

[2] Subjects are reported once at the highest severity. Missing severity is imputed as Severe.

[3] Subjects are reported once at the closest relationship.

[4] For Serious event rows, after Week 26 to Week 52 includes all studies in the Pool (6003/1021, 6003/1031, 6003/1131, and 6003/1133) in both numerator and denominator of subjects at risk.

Note: After Week 26 to Week 52 includes any TEAEs that start between study day 190 and study day 379, inclusive. Percentages are based on subjects who were still in the study up until the start of the interval.

Source: Summary of Clinical Safety, Table 9 (truncated to delete related serious adverse events)

Table 11. Treatment-Emergent Adverse Events, After Week 52 (Randomized, Controlled Studies)

			Pooled		
	SI-6603 1.25 U (N = 229)	SI-6603 >1.25 U (N = 0)	Placebo (N = 0)	Sham Control (N = 78)	Placebo/ Sham Pooled (N = 78)
Treatment-emergent AEs					
Total number of events	115	NA	NA	32	32
Subjects with events	75 (32.8)			20 (25.6)	20 (25.6)
Subjects who died	1 (0.4)			0	0
Subjects with events leading to study discontinuation	1 (0.4)			0	0
Subjects with events by severity [1]					
Mild	43 (18.8)			10 (12.8)	10 (12.8)
Moderate	26 (11.4)			6 (7.7)	6 (7.7)
Severe	6 (2.6)			4 (5.1)	4 (5.1)
Subjects with events by relationship [2]					
Related	0			0	0
Not Related	75 (32.8)			20 (25.6)	20 (25.6)
Related treatment-emergent AEs					
Total number of events	0	NA	NA	0	0
Subjects with events	0			0	0
Subjects who died	0			0	0
Subjects with events leading to study discontinuation	0			0	0
Subjects with events by severity [1]					
Mild	0			0	0
Moderate	0			0	0
Severe	0			0	0
Serious treatment-emergent AEs					
Total number of Serious events	10			2	2
Subjects with Serious events	7 (3.1)			2 (2.6)	2 (2.6)

AE = adverse event; NA = not applicable; TEAE = treatment-emergent adverse event; U = unit
[1] Subjects are reported once at the highest severity. Missing severity is imputed as Severe.
[2] Subjects are reported once at the closest relationship.
Note: After Week 52 includes any TEAEs that start from study day 380 onwards. Percentages are based on subjects who were still in the study up until the start of the interval.
Note: After Week 52 only applies to Study 6603/1131.

Source: Summary of Clinical Safety, Table 10 (truncated to delete related serious adverse events)

Comparison of the overall AE rates by treatment group and epoch show that, in Epoch 1, the AE rate was lower in the patients who received a sham injection compared to a placebo intradiscal injection. Epoch 1 (first 13 weeks postinjection) had the highest rates of AEs for all groups. For the subsequent epochs, there were no clear patterns with regard to the emergence of AEs in relation to the time of the injection. Overall, patients injected with condoliase tended to have slightly higher AE rates than the comparator groups.

With regard to major safety findings, there were seven deaths in patients treated with condoliase. All deaths and serious adverse events were reviewed individually, and condoliase was not likely causal in the deaths.

The majority of serious adverse events that could be related to condoliase was due to failure of treatment or exacerbation of degenerative disc disease requiring hospitalization and lumbar discectomy and/or fusion. While there were some cases coded as discontinuation for AE, it is difficult to know how to interpret those since the product is only injected once. Regardless, there were no clear patterns with regard to early discontinuations.

Common Adverse Events

Given that the incidence of AEs was considerably higher in Epoch 1, we consider that to be the most sensitive epoch to assess common AEs. The Applicant's table of common AEs during Epoch 1 is reproduced as Table 12.

Table 12. Common TEAEs up to Week 13, All Randomized Studies

			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)
Gamma-glutamyltransferase increased	7 (1.2)	5 (5.1)	1 (0.8)	1 (0.4)	2 (0.5)
Upper respiratory tract infection	6 (1.0)	0	0	6 (2.2)	6 (1.5)
Blood lactate dehydrogenase increased	5 (0.9)	0	0	6 (2.2)	6 (1.5)
Blood triglycerides increased	5 (0.9)	3 (3.1)	5 (3.9)	3 (1.1)	8 (2.0)
Neutrophil count decreased	5 (0.9)	5 (5.1)	8 (6.3)	0	8 (2.0)
Influenza	4 (0.7)	2 (2.0)	2 (1.6)	0	2 (0.5)
Musculoskeletal pain	4 (0.7)	2 (2.0)	1 (0.8)	5 (1.9)	6 (1.5)
Pyrexia	4 (0.7)	2 (2.0)	7 (5.5)	2 (0.7)	9 (2.3)
Alanine aminotransferase increased	3 (0.5)	6 (6.1)	0	2 (0.7)	2 (0.5)
Dermatitis contact	3 (0.5)	4 (4.1)	1 (0.8)	0	1 (0.3)
White blood cell count decreased	3 (0.5)	3 (3.1)	3 (2.3)	0	3 (0.8)
Aspartate aminotransferase increased	2 (0.3)	4 (4.1)	0	0	0
Intervertebral disc protrusion	2 (0.3)	0	5 (3.9)	1 (0.4)	6 (1.5)
Pharyngitis	1 (0.2)	2 (2.0)	1 (0.8)	0	1 (0.3)
Anal fissure	0	2 (2.0)	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event; U = unit

Note: TEAEs were defined as adverse events that begin or that worsen in severity after the investigational drug has been administered. In preferred term summarization, a subject was counted once if he/she reported one or more events. Adverse events were classified according to MedDRA version 24.0.

Note: Preferred terms are sorted by descending frequency in the SI-6603 1.25 U column.

Note: Up to Week 13 includes any TEAEs that start up until study day 98, inclusive. Percentages based on Safety Population.

Source: Summary of Clinical Safety, Table 11

As noted above, in Epoch 1, the AE rate was lowest in the patients who received a sham injection (47% versus 66% and 69% for active treatment and intradiscal placebo, respectively). This may be due to irritation from disc puncture and saline injection for patients randomized to the placebo group.

Therefore, the most sensitive comparator group to detect adverse reactions specifically related to condoliase is the intradiscal placebo injection performed in the Japanese studies. However, the number of patients treated with a sham injection is more than double those with placebo (268 to 128), and the pooled placebo data should be interpreted in this context. For example, the complaint of back pain was higher in patients treated with condoliase and placebo than sham (23% to 26% versus 10%). This finding may be an acute consequence of instrumenting the disc, because later epochs showed much lower rates of back pain in the same groups (1% to 5%).

The other notable finding in Table 12 relates to imaging findings (MRI abnormal and spine X-ray abnormal). In Epoch 1, there was an imbalance in the rates of imaging abnormalities in the range of 3% versus 19% (MRI) and 2% versus 5% (X-ray) for the comparators and condoliase, respectively. While the to-be-marketed dose is 1.25 U, the table clearly shows that higher doses of condoliase resulted in higher rates of X-ray abnormalities. This constellation of findings is discussed further below.

Adverse Events of Special Interest

Severe Cutaneous Adverse Reactions (SCARs)

SCARs are rare, potentially life-threatening skin reactions occurring as a consequence of hypersensitivity to one or more culprit drugs. The drug classes most commonly associated with SCARs are anticonvulsants, antibiotics, and nonsteroidal anti-inflammatory drugs. The literature suggests that lamotrigine, acetaminophen, and allopurinol are most commonly related to SCARs in analyses of pharmacovigilance databases (Li et al. 2023). Five diagnoses are generally considered SCARs: Drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and acute generalized exanthematous pustulosis (AGEP). SCARs tend to have higher incidence in patients of East Asian descent.

There was one potential case of SCAR in the controlled trials. It was from an early phase study (SKK6603J01) in 2000. The case narrative follows:

Potential SCAR
48-year-old male who underwent condoliase injection on (b) (6) *at L4-5. On Day 2, he developed rash with pruritus which progressed to cover a large percentage of his skin including his limbs, abdominal/dorsal region, thigh, and buttocks. He then developed bullae on his left arm and left buttock on Day 4. He was kept in the hospital to manage his skin reaction. He was started on antihistamines. He had been on cefdinir which was discontinued. CRP was elevated. The exanthem spread to both hands and palms. He was started on PO and topical steroids. The bullae sloughed off over the next week. The rash began to improve, and the patient was discharged on Day 15. The rash was noted to be improved by Day 27. Patch testing (Day 20) was negative for concomitant medications including antibiotics. An intracutaneous test performed on Day 34 was found to be positive for the study drug and negative for cefdinir.*

Additionally, the Japanese postmarketing database for condoliase contains five cases of confirmed or suspected SCAR. Brief narratives of the cases follow:

Erythema Multiforme ((b) (6))
41-year-old female who underwent condoliase injection on (b) (6) *at L5-S1. She developed diffuse pruritis and erythema over her trunk and extremities the next day. She went to the Emergency Department (ED) the next morning and received IV steroids and antihistamines. She returned to the ED*

2 days later after erythema continued to worsen. She was prescribed a taper of PO steroids over 3-4 weeks followed by 3 weeks of olopatadine. She was diagnosed with erythema multiforme. Symptoms were improving 6 weeks after reaction onset.

Stevens-Johnson Syndrome/Anaphylaxis ((b) (6))
45-year-old female underwent condoliase injection on (b) (6) *at L4-5. The next morning, she developed wheals and pruritis. Two days after injection, she developed fever, dyspnea, pharyngeal tightening with multiple episodes of emesis and was admitted to the hospital. The rash continued to spread, and she developed oral mucosal lesions and swelling around the eyes over the next few days. She was treated with IV steroids and then discharged on PO steroids. Her symptoms resolved around one month after symptoms began. While there was some question whether this was a true case of Stevens-Johnson syndrome, we are unable to rule out this diagnosis given the patient's full constellation of symptoms.*

Acute Generalized Exanthematous Pustulosis ((b) (6))
34-year-old female underwent condoliase injection on (b) (6) *for LDH at L5-S1. She developed diffuse erythema over her trunk with pustules within 24 hours of injection. Erythema spread to cover 70% of her body surface area and spread all the way up to her jaw when she went to the ED the next day. She was treated with IV then oral and topical steroids and recovered over 3-4 weeks.*

Acute Generalized Exanthematous Pustulosis ((b) (6))
64-year-old female underwent condoliase injection on (b) (6) *at L4-5. She developed diffuse redness from the buttocks to the upper extremities the day after the injection. The next day the rash spread to both lower extremities. She went to the ED and was treated with IV then PO steroids. She developed pustules over her body over the next few days. She followed up with a dermatologist who continued outpatient PO steroids and initiated minocycline. Skin biopsy demonstrated necrosis and she was diagnosed with AGEP. She was maintained on oral steroids for 5 weeks and her symptoms were fully resolved by 8 weeks post-injection. All patch testing was negative. Drug induced lymphocyte stimulation test was positive for limaprost 5 months after injection. Limaprost was initiated over 2 months prior to the onset of her reaction.*

Acute Generalized Exanthematous Pustulosis ((b) (6))
77-year-old male underwent condoliase injection on (b) (6) *. He developed extensive rash and was admitted to dermatology. Systemic steroids were initiated, and patient required a 3-week hospitalization. Skin biopsy confirmed AGEP, and he was discharged on oral steroids with most symptoms resolved.*

Steroids were tapered from (b) (6) *to early* (b) (6) *. AGEP symptoms recurred (on* (b) (6) *), 21 days after discontinuing steroids. This case is ongoing as the patient resumed treatment after recurrence of symptoms.*

The cases of SCAR from postmarketing required hospitalization and the use of IV, oral, and topical steroids. Most cases declared in the first day or two after injection with condoliase. While there were no deaths, some cases required months for recovery and protracted corticosteroid therapy. One case of AGEP flared following steroid taper. AGEP reactions longer than 2 weeks are rare, so its recurrence in the most recent case may be indicative of slow elution of condoliase or immunogenic chondroitin sulfate degradants from the disc, although it is also possible that the patient was exposed to another inciting medication.

The Annual Report dated 08/16/24, indicates that ~29,000 patients had been dosed with condoliase in Japan. If all six cases described above are considered SCAR, this represents a rate of 6:29,000 or ~1:5,000. We conducted a literature search to estimate the incidence of drug-related SCAR. The literature indicates that SCAR is more common in patients of East Asian ancestry and much of the data are from Asian countries. It is difficult to obtain the incidence of SCAR with certainty. Most of the literature reports case numbers and relative risks in comparisons of different drug moieties (lamotrigine, allopurinol, co-trimoxazole) and drug classes (anti-epileptics, antibiotics).

- Owen and Jones (2021) reported a population risk for drug reaction with eosinophilia and systemic symptoms at 1 in 1,000 to 1 in 10,000 for high-risk drugs and a population risk of 1 to 5 cases per million per year for AGEP.
- Tempark et al. (2022) reported a global frequency rate of 0.4 to 1.2 cases per million per year.
- Mockenhaupt (2012) summarized epidemiological studies. He reported a range in prevalence from 3.6 to 7 per 1,000 hospitalized patients/year.
- Ng et al. (2022) reported an incidence of 2.5 cases per 1,000 new years for allopurinol in Malaysian patients.

We could not find an estimated incidence of SCAR for lamotrigine (high-risk anti-epileptic drug) or other specific drugs recognized as high-risk in a population relevant to the U.S. population. The contextual data available to us suggest that the incidence of SCAR for condoliase falls within the range of approved drugs, although it might be toward the high end of the range. We also note that all of the cases were in Japanese patients, an East Asian population known to be more susceptible to SCARs. However, there have been many fewer exposures to condoliase outside of Japan, so safety data for condoliase in non-Japanese populations is limited.

Spine-Related Adverse Events

As noted in the General Safety section, treatment with condoliase or placebo appears to be associated with 1) higher rates of axial back pain within 13 weeks of injection, and 2) the development of MRI and X-ray abnormalities. Given the function of a healthy intervertebral disc and the mechanism of action of this product, it is predictable that injection of condoliase may have unintended consequences on spine anatomy. The Applicant monitored spine anatomy by conducting physical examinations and spine imaging. The prespecified imaging endpoints were disc height loss, Modic changes, vertebral posterior angle ≥5 degrees, and vertebral body translation of ≥3 mm. Modic changes are pathological lesions of the vertebral body endplates that are believed to indicate an inflammatory reaction in the bone marrow. Modic changes can be visualized on MRI and are commonly seen in degeneration of the spine. There are three types of Modic changes:

- Type 1 changes are due to inflammation and edema.
- Type 2 changes are due to fatty infiltration.
- Type 3 changes are due to sclerotic change and endplate thickening.

A systematic review of 82 journal articles by Jensen et al. concluded that there is an association between Modic changes and chronic nonspecific low back pain. However, these studies vary widely in quality, patient population, presence of other spinal pathology, and clinical outcomes, and the exact relationships between the type or size of Modic changes and the severity of pain or activity limitations

are inconsistent across studies (Herlin et al. 2018). Thus, the clinical relevance of Modic changes is not well-established.

The prespecified imaging findings are summarized in Table 13.

Table 13. Prespecified Imaging Findings by Visit (Population: Primary Safety Pool: Phase 2/3 Controlled Studies)

			Pooled		
Visit Category	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 (%)
Baseline					
Vertebral posterior angle flexion >=5 degrees	12/574 (2.1)	9/98 (9.2)	6/128 (4.7)	0/268	6/396 (1.5)
Vertebral body translation of >=3 mm	5/574 (0.9)	1/98 (1.0)	0/128	0/268	0/396
Modic Type 1	137/577 (23.7)	15/98 (15.3)	12/128 (9.4)	61/268 (22.8)	73/396 (18.4)
Modic Type 2	98/577 (17.0)	3/98 (3.1)	24/128 (18.8)	51/268 (19.0)	75/396 (18.9)
Modic Type 3	4/577 (0.7)	0/98	0/128	3/268 (1.1)	3/396 (0.8)
Week 6					
Decrease from baseline in disc height >=30%	5/395 (1.3)	8/97 (8.2)	0/124	0/89	0/213
Vertebral posterior angle flexion >=5 degrees	8/395 (2.0)	9/97 (9.3)	4/124 (3.2)	0/89	4/213 (1.9)
Vertebral body translation of >=3 mm	1/392 (0.3)	1/97 (1.0)	1/124 (0.8)	0/89	1/213 (0.5)
Modic Type 1	152/397 (38.3)	37/97 (38.1)	14/124 (11.3)	25/89 (28.1)	39/213 (18.3)
Modic Type 2	62/397 (15.6)	3/97 (3.1)	22/124 (17.7)	24/89 (27.0)	46/213 (21.6)
Modic Type 3	4/397 (1.0)	0/97	0/124	3/89 (3.4)	3/213 (1.4)
Modic Change from 'No' to 'Yes' [1]					
Modic Type 1	62/305 (20.3)	22/82 (26.8)	2/112 (1.8)	2/65 (3.1)	4/177 (2.3)
Modic Type 2	1/326 (0.3)	0/94	0/101	0/65	0/166
Modic Type 3	0/393	0/97	0/124	0/86	0/210
Week 13					
Decrease from baseline in disc height >=30%	20/512 (3.9)	10/91 (11.0)	0/112	0/238	0/350
Vertebral posterior angle flexion >=5 degrees	7/514 (1.4)	10/91 (11.0)	2/112 (1.8)	0/237	2/349 (0.6)
Vertebral body translation of >=3 mm	1/512 (0.2)	1/91 (1.1)	3/112 (2.7)	2/235 (0.9)	5/347 (1.4)
Modic Type 1	231/521 (44.3)	39/91 (42.9)	14/112 (12.5)	62/238 (26.1)	76/350 (21.7)
Modic Type 2	81/521 (15.5)	3/91 (3.3)	20/112 (17.9)	44/238 (18.5)	64/350 (18.3)
Modic Type 3	3/521 (0.6)	0/91	0/112	2/238 (0.8)	2/350 (0.6)
Modic Change from 'No' to 'Yes' [1]					
Modic Type 1	104/391 (26.6)	25/77 (32.5)	4/102 (3.9)	9/184 (4.9)	13/286 (4.5)
Modic Type 2	2/432 (0.5)	0/88	0/92	0/194	0/286
Modic Type 3	2/194 (1.0)	NA	NA	1/68 (1.5)	1/68 (1.5)
Modic Change from 'No' to 'Yes' [1]					
Modic Type 1	41/146 (28.1)	NA	NA	6/50 (12.0)	6/50 (12.0)
Modic Type 2	18/147 (12.2)	NA	NA	5/48 (10.4)	5/48 (10.4)
Modic Type 3	0/192	NA	NA	0/67	0/67
Last Post-Baseline Visit					
Decrease from baseline in disc height >=30%	35/554 (6.3)	14/98 (14.3)	0/127	1/249 (0.4)	1/376 (0.3)
Vertebral posterior angle flexion >=5 degrees	10/555 (1.8)	6/98 (6.1)	6/127 (4.7)	1/248 (0.4)	7/375 (1.9)
Vertebral body translation of >=3 mm	4/553 (0.7)	1/98 (1.0)	1/127 (0.8)	1/246 (0.4)	2/373 (0.5)
Modic Type 1	249/555 (44.9)	45/98 (45.9)	28/127 (22.0)	75/249 (30.1)	103/376 (27.4)
Modic Type 2	107/555 (19.3)	3/98 (3.1)	23/127 (18.1)	52/249 (20.9)	75/376 (19.9)
Modic Type 3	5/555 (0.9)	0/98	0/127	3/249 (1.2)	3/376 (0.8)
Modic Change from 'No' to 'Yes' [1]					
Modic Type 1	128/422 (30.3)	30/83 (36.1)	16/115 (13.9)	22/192 (11.5)	38/307 (12.4)
Modic Type 2	25/461 (5.4)	0/95	0/103	6/202 (3.0)	6/305 (2.0)
Modic Type 3	1/551 (0.2)	0/98	0/127	0/246	0/373

NA = not applicable; U = unit

[1] Percent of subjects with modic change from No to Yes from baseline are out of subjects that do not have 'Yes' at baseline for that Modic type and have non-missing data at that visit.

Note: All other percentages are based on the number of subjects with image results at each visit.

Note: Baseline is the last non-missing measurement observed prior to the study injection.

Note: Study 6603/1133 did not evaluate imaging findings at Weeks 6 and 26. Week 104 was evaluated for Study 6603/1131 only.

Modic Type 3	0/518	0/91	0/112	0/236	0/348
Week 26					
Decrease from baseline in disc height >=30%	21/329 (6.4)	9/82 (11.0)	0/101	0/75	0/176
Vertebral posterior angle flexion >=5 degrees	8/331 (2.4)	8/82 (9.8)	4/101 (4.0)	0/74	4/175 (2.3)
Vertebral body translation of >=3 mm	3/329 (0.9)	0/82	2/101 (2.0)	0/74	2/175 (1.1)
Modic Type 1	154/336 (45.8)	38/82 (46.3)	20/101 (19.8)	24/77 (31.2)	44/178 (24.7)
Modic Type 2	57/336 (17.0)	3/82 (3.7)	19/101 (18.8)	20/77 (26.0)	39/178 (21.9)
Modic Type 3	3/336 (0.9)	0/82	0/101	1/77 (1.3)	1/178 (0.6)
Modic Change from 'No' to 'Yes' [1]					
Modic Type 1	75/253 (29.6)	24/68 (35.3)	10/91 (11.0)	4/56 (7.1)	14/147 (9.5)
Modic Type 2	6/270 (2.2)	0/79	0/82	0/57	0/139
Modic Type 3	0/333	0/82	0/101	0/76	0/177
Week 52					
Decrease from baseline in disc height >=30%	27/438 (6.2)	14/76 (18.4)	0/89	1/202 (0.5)	1/291 (0.3)
Vertebral posterior angle flexion >=5 degrees	11/437 (2.5)	5/76 (6.6)	6/89 (6.7)	1/199 (0.5)	7/288 (2.4)
Vertebral body translation of >=3 mm	4/434 (0.9)	0/76	0/89	1/199 (0.5)	1/288 (0.3)
Modic Type 1	201/439 (45.8)	37/76 (48.7)	24/89 (27.0)	63/200 (31.5)	87/289 (30.1)
Modic Type 2	79/439 (18.0)	3/76 (3.9)	18/89 (20.2)	39/200 (19.5)	57/289 (19.7)
Modic Type 3	3/439 (0.7)	0/76	0/89	1/200 (0.5)	1/289 (0.3)
Modic Change from 'No' to 'Yes' [1]					
Modic Type 1	106/334 (31.7)	25/64 (39.1)	15/80 (18.8)	19/152 (12.5)	34/232 (14.7)
Modic Type 2	15/358 (4.2)	0/73	0/71	2/161 (1.2)	2/232 (0.9)
Modic Type 3	0/436	0/76	0/89	0/199	0/288
Week 104					
Decrease from baseline in disc height >=30%	14/192 (7.3)	NA	NA	0/71	0/71
Vertebral posterior angle flexion >=5 degrees	1/192 (0.5)	NA	NA	0/71	0/71
Vertebral body translation of >=3 mm	1/190 (0.5)	NA	NA	0/71	0/71
Modic Type 1	79/194 (40.7)	NA	NA	23/68 (33.8)	23/68 (33.8)
Modic Type 2	59/194 (30.4)	NA	NA	24/68 (35.3)	24/68 (35.3)

Source: Integrated Summary of Safety, Table 35

Abbreviation: N, number of patients in study arm; NA, not applicable; U, unit

Inspection of Table 13 shows that:

- Most of the disc height loss occurred in the first 26 weeks.
- Average disc height loss was 15.54% in the 1.25 U treatment group.
- Early studies using doses higher than 1.25 U showed dose-dependent loss of disc height.
- The Primary Safety Pool shows an association between treatment with condoliase and subsequent progression of Modic changes.
- For the 1.25 U dose group, the proportion of patients with progression from no Modic changes to Type 1 was 20.3% at Week 6, increasing to 26.6% at Week 13, 29.6% at Week 26, and 31.7% at Week 52. In the placebo/sham pooled group, the proportion of patients with progression from no Modic changes to Type 1 was 2.3% at Week 6, 4.5% at Week 13, 9.5% at Week 26, and 14.7% at Week 52.
- For the 1.25 U dose group, the proportion of patients with progression from Modic Type 1 to Type 2 changes was 0.3% at Week 6, 0.5% at Week 13, 2.2% at Week 26, and 4.2% at Week 52. In the placebo/sham pooled group, the proportion of patients with progression from Modic Type 1 to Type 2 changes was 0% at Week 6, 0% at Week 13, 0% at Week 26, and 0.9% at Week 52.
- There is a clear association of progression of Modic changes with condoliase treatment. A plausible mechanism would be that condoliase reduces disc volume, causing progressive disc height loss, which leads to biomechanical and biochemical changes that result in imaging findings of endplate degeneration and progression of Modic changes.
- There were no consistent patterns with regard to vertebral posterior angle and translation.

Other Hypersensitivity Reactions

We consulted the Division of Pulmonology, Allergy, and Critical Care (DPACC) to assess the risk of hypersensitivity reactions with condoliase injection. DPACC's summary table for hypersensitivity reactions is reproduced as Table 14 from their consult response. In pharmacovigilance, terms from the Medical Dictionary for Regulatory Activities (MedDRA) are used for the analysis of pharmaceutical safety information, and Standardized MedDRA Queries are groups of MedDRA terms that are used to identify AEs related to various disease processes (e.g., hypersensitivity).

Table 14. Summary of Safety Topics of Interest (Hypersensitivity): All Time Intervals, Phase 2/3 Studies

			Pooled		
Category 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	43 (7.4)	7 (7.1)	8 (6.3)	17 (6.3)	25 (6.3)
Hypersensitivity (SMQ)	31 (5.4)	7 (7.1)	6 (4.7)	10 (3.7)	16 (4.0)
Rash	11 (1.9)	1 (1.0)	1 (0.8)	2 (0.7)	3 (0.8)
Asthma	3 (0.5)	0	0	1 (0.4)	1 (0.3)
Conjunctivitis	3 (0.5)	0	0	0	0
Dermatitis contact	3 (0.5)	4 (4.1)	1 (0.8)	0	1 (0.3)
Pruritus	3 (0.5)	0	0	0	0
Urticaria	3 (0.5)	0	0	1 (0.4)	1 (0.3)
Toxic skin eruption	2 (0.3)	0	0	0	0
Conjunctivitis allergic	1 (0.2)	0	0	0	0
Contrast media allergy	1 (0.2)	0	0	0	0
Cough variant asthma	1 (0.2)	0	0	0	0
Drug hypersensitivity	1 (0.2)	0	0	0	0
Eczema nummular	1 (0.2)	0	0	0	0
Eosinophilia	1 (0.2)	0	0	0	0
Erythema	1 (0.2)	0	0	0	0
Flushing	1 (0.2)	0	0	0	0
Hand dermatitis	1 (0.2)	0	0	0	0
Allergic cough	0	0	1 (0.8)	0	1 (0.3)
Angioedema	0	0	0	1 (0.4)	1 (0.3)
Drug eruption	0	1 (1.0)	0	0	0
Eczema	0	1 (1.0)	2 (1.6)	0	2 (0.5)
Eosinophil count increased	0	0	1 (0.8)	0	1 (0.3)
Injection site dermatitis	0	0	0	1 (0.4)	1 (0.3)
Injection site rash	0	0	0	1 (0.4)	1 (0.3)
Rash maculo-papular	0	0	0	1 (0.4)	1 (0.3)
Rhinitis allergic	0	0	0	1 (0.4)	1 (0.3)
Seasonal allergy	0	0	0	1 (0.4)	1 (0.3)

Source: Integrated Summary of Safety, Table 31, page 82

Briefly, DPACC concluded the following:

- Based on the hypersensitivity standardized MedDRA queries (broad), the incidence of hypersensitivity reactions was greater in the condoliase (1.25 U) group compared with the placebo/sham control group (5.4% [31 subjects] and 4% [16 subjects], respectively).
- The most common hypersensitivity AE reported in the condoliase (1.25 U) group was: rash (11 subjects in the condoliase [1.25 U] [1.9%] and 3 in the placebo/sham control [0.8%] group).
- As adjudicated by the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criterion 1 (Sampson et al. 2006), there was no case of anaphylaxis in the clinical trial database.

- Most of the hypersensitivity AEs were mild in severity and were not concerning for Type 1, immediate-type hypersensitivity reactions as they did not occur on the day of study drug administration.
- Two cases of toxic skin eruption were reported, with one categorized as severe.
- There was one case meeting the criteria for anaphylaxis in the postmarketing database.

While the overall rate of hypersensitivity reactions was greater in the condoliase group compared to placebo, most reactions were mild, and severe reactions were rare in the clinical trial database. In the postmarketing data, there was only one case that met the criteria for anaphylaxis among ~29,000 exposures.

Safety Unknowns and Relevance to Conditions of Use

The clinical trial database and postmarketing data are insufficient to make conclusions regarding two concerns regarding the use of condoliase: Impact on future treatment options for RLP due to LDH and requirements for proceduralists/settings to ensure safe administration.

Long-Term Outcomes, Including Progression to Surgery

There are insufficient data to reliably predict long-term structural outcomes from condoliase administration. In theory, the association between condoliase and SRAEs (e.g., Modic changes) raises concern that patients who require surgery after condoliase treatment may have less favorable outcomes. Although some studies suggest that there may be a negative correlation between Modic changes and surgical outcomes following discectomy for LDH (Laustsen and Bech-Azeddine 2016), other studies have found no significant association between Modic changes and health-related quality of life, disability, back or leg pain, or patient satisfaction for up to 2 years after discectomy (Udby et al. 2020). It is also unclear whether the SRAEs associated with condoliase administration may make patients more likely to require spinal surgery in the future.

There are some long-term follow-up data available. The Applicant submitted two studies.

Study 10r2 followed patients enrolled in Study 1021 and Study 1031 (Japanese studies) after unblinding of the parent study. This study involved the data of 258 patients (128 intradiscal placebo; 130 condoliase) from Studies 1021 and 1031 who were on the to-be-marketed dose of 1.25 U. The study had two forms of assessment: interview and in-hospital assessment. When limited to patients who also complied with the in-hospital evaluations, the sample size decreased to 70 placebo and 69 at 1.25 U. The mean follow-up durations for patients who underwent in-hospital evaluations were 71.0 and 25.4 months for Studies 1021 and 1031, respectively. Key metrics around surgery after treatment with study drug (active or placebo) are summarized in Table 15.

Table 15. Presence/Absence of Surgery for LDH (Two Studies Combined)

Population: Participants in the clinical study

		Two studies combined (6603/1021, 6603/1031)		
		Placebo group N=128	Condoliase group a) N=228	1.25 U group in condoliase group N=130
Surgery for lumbar disc herniation	Yes	17(13.3)	18(7.9)	11(8.5)
	No	72(56.3)	129(56.6)	80(61.5)
	Unknown b)	39(30.5)	81(35.5)	39(30.0)
Frequency of surgery for lumbar disc herniation c)	Once	16/89(18.0)	17/147(11.6)	11/91(12.1)
	Twice	1/89(1.1)	1/147(0.7)	0/91(0.0)
	3 times	0/89(0.0)	0/147(0.0)	0/91(0.0)
	4 times	0/89(0.0)	0/147(0.0)	0/91(0.0)
	5 times	0/89(0.0)	0/147(0.0)	0/91(0.0)
Timing of initial surgery c)	Within 6 months	12/89(13.5)	12/147(8.2)	8/91(8.8)
	7-12 months	2/89(2.2)	3/147(2.0)	3/91(3.3)
	13-24 months	3/89(3.4)	0/147(0.0)	0/91(0.0)
	After 25 months	0/89(0.0)	3/147(2.0)	0/91(0.0)
Timing of initial surgery (months) d)	Mean±SD	7.5±7.7	10.8±16.1	4.7±3.4
	Median	3.7	4.0	3.6
	(Q1,Q3)	(2.4,10.8)	(2.3,9.2)	(2.3,7.2)
	(Min, max)	(1,24)	(1,59)	(1,12)
Surgery in the same disc as the injected disc	Yes	17(13.3)	18(7.9)	11(8.5)
	No	72(56.3)	129(56.6)	80(61.5)
	Unknown b)	39(30.5)	81(35.5)	39(30.0)
Timing of initial surgery in the same disc as the injected disc c)	Within 6 months	12/89(13.5)	12/147(8.2)	8/91(8.8)
	7-12 months	2/89(2.2)	3/147(2.0)	3/91(3.3)
	13-24 months	3/89(3.4)	0/147(0.0)	0/91(0.0)
	After 25 months	0/89(0.0)	3/147(2.0)	0/91(0.0)
Timing of initial surgery in the same disc as the injected disc (months) d)	Mean±SD	7.5±7.7	10.8±16.1	4.7±3.4
	Median	3.7	4.0	3.6
	(Q1,Q3)	(2.4,10.8)	(2.3,9.2)	(2.3,7.2)
	(Min, max)	(1,24)	(1,59)	(1,12)
Surgery in a different disc from the injected disc	Yes	0 (0.0)	1(0.4)	1(0.8)
	No	89(69.5)	146(64.0)	90(69.2)
	Unknown b)	39(30.5)	81(35.5)	39(30.0)
Timing of initial surgery in a different disc from the injected disc c)	Within 6 months	0/89(0.0)	1/147(0.7)	1/91(1.1)
	7-12 months	0/89(0.0)	0/147(0.0)	0/91(0.0)
	13-24 months	0/89(0.0)	0/147(0.0)	0/91(0.0)
	After 25 months	0/89(0.0)	0/147(0.0)	0/91(0.0)
Timing of initial surgery in a different disc from the injected disc (months) d)	Mean±SD	-	4.1±-	4.1±-
	Median	-	4.1	4.1
	(Q1,Q3)	-	(4.1,4.1)	(4.1,4.1)
	(Min, max)	-	(4,4)	(4,4)

Number of subjects (%)

a) 1.25 U + 2.5 U + 5 U

b) Including subjects who did not consent to the present study

c) The denominator was subjects with "yes" or "no" for surgery for lumbar disc herniation, except for those with "unknown."

d) In population of subjects with "yes" for surgery for lumbar disc herniation

Source: Clinical Study Report for Study 10r2: Table 11.4.1.1.1.1-1

Abbreviations: N, number of patients in study arm; LDH, lumbar disc herniation; max, maximum; min, minimum; Q, quartile; SD, standard deviation; U, unit

Study 10r2 showed that the rate of progression to spine surgery was lower in the active group compared to the placebo group. Most of the spine surgeries were performed within 6 months of injection. Regarding surgery for recurrent herniation, the comparison again favored condoliase (2.3% versus 3.9%). There was a small number of cases meeting the prespecified criteria for radiographic lumbar

spine instability: 5 (7.4%) versus 4 (5.9%), again favoring active treatment over placebo. At the in-hospital evaluation for Study 10r2, patients randomized to placebo had a 10.0% reduction in mean disc height (as measured by x-ray and compared to preinjection) while those randomized to the 1.25 U dose of condoliase had a 16.8% reduction in mean disc height. The percentage of patients with clinical lumbar spinal instability also favored the active arm (0% versus 2.9%). Given the low event rate for some outcomes and small sample size overall, there is a high rate of uncertainty around conclusions.

Study 10r3 followed up patients from Study 1031 with the intent to collect 10-year data following Study 1031. This study was based on the data of 37 patients from Study 1031 and followed patients for at least 10 years. Five of thirty-seven patients had subsequent spine surgery. The patients were followed clinically and with X-ray and MRI. No patients underwent spine surgery for spinal instability. One patient met the criteria of posterior angle dilation of ≥5° in the flexed position and vertebral body translation of ≥3 mm, although the clinical study report indicates that the findings were present at baseline. The results of Study 10r3 should be reviewed in context given the small sample size and lack of follow-up with a control group.

Collectively, the long-term follow-up data are in a small number of patients although the evaluations were thorough, and the follow-up was lengthy. Based on these data, condoliase does not appear to result in higher rates of radiographic instability or progression of disc height loss compared to placebo. There are no corresponding data on no treatment or sham injection. We note that any instrumentation of the disc may further compromise the integrity of the annulus fibrosis; thus, having long-term data in only the intradiscal condoliase and placebo groups limits the scope of long-term benefit-risk assessment for condoliase.

Importance of Proceduralist Training, Procedure Setting, and Follow-Up

In the United States, condoliase would likely be administered by interventional pain management (IPM) physicians, although credentialing for intradiscal injection would not likely require specific post-graduate training. However, similar to other IPM procedures involving the neuraxis, instrumenting the intervertebral disc requires detailed anatomic and fluoroscopic knowledge, as well as meticulous aseptic sterile technique. Disc access is associated with serious risks including discitis, durotomy, nerve injury, vascular injury, and disc degeneration. While these are rare, they can lead to prolonged morbidity.

Physicians who are well-trained in the anatomic and technical aspects of the procedure are more likely to be able to identify and mitigate those risks. IPM has a wide array of practice patterns with many specialties and backgrounds represented. There is likely to be significant variability in training, technique, imaging, and periprocedural protocols. It is unknown which (or whether) specific proceduralist requirements would mitigate the potential risks of intradiscal access required for condoliase administration.

Furthermore, beyond the inherent risks of the procedure itself, the product presents potential risks that could be mitigated by appropriate proceduralist qualifications and procedure setting. Due to the risk of hypersensitivity and SCAR, it would be important that this product be administered in a facility with appropriate equipment and personnel to manage adverse reactions, to provide adequate counseling and postprocedural guidance to patients, and to identify and manage severe cutaneous events should they occur. It is important to consider the history of chymopapain when considering the capabilities and training of proceduralists and facilities.

3.3 Risk Mitigation

The Applicant's risk assessment for SCAR did not identify risk factors for development of that AE. The other identified risks (hypersensitivity and spine-related adverse events) do not have any particular risk mitigations. If condoliase is approved, labeling should carefully address limiting use to patients with a positive benefit-risk profile, with drug administration by appropriate HCPs in an appropriate facility, and the risks of hypersensitivity and SCAR adequately addressed and mitigated to the extent possible.

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