Condoliase for the Treatment of Radicular Leg Pain Associated with Radiologically Confirmed Nerve Root Impingement Caused by Lumbar Disc Herniation (LDH) in Adults

January 10, 2025

Anesthetic and Analgesic Drug Products Advisory Committee

Seikagaku Corp.

Condoliase Introduction

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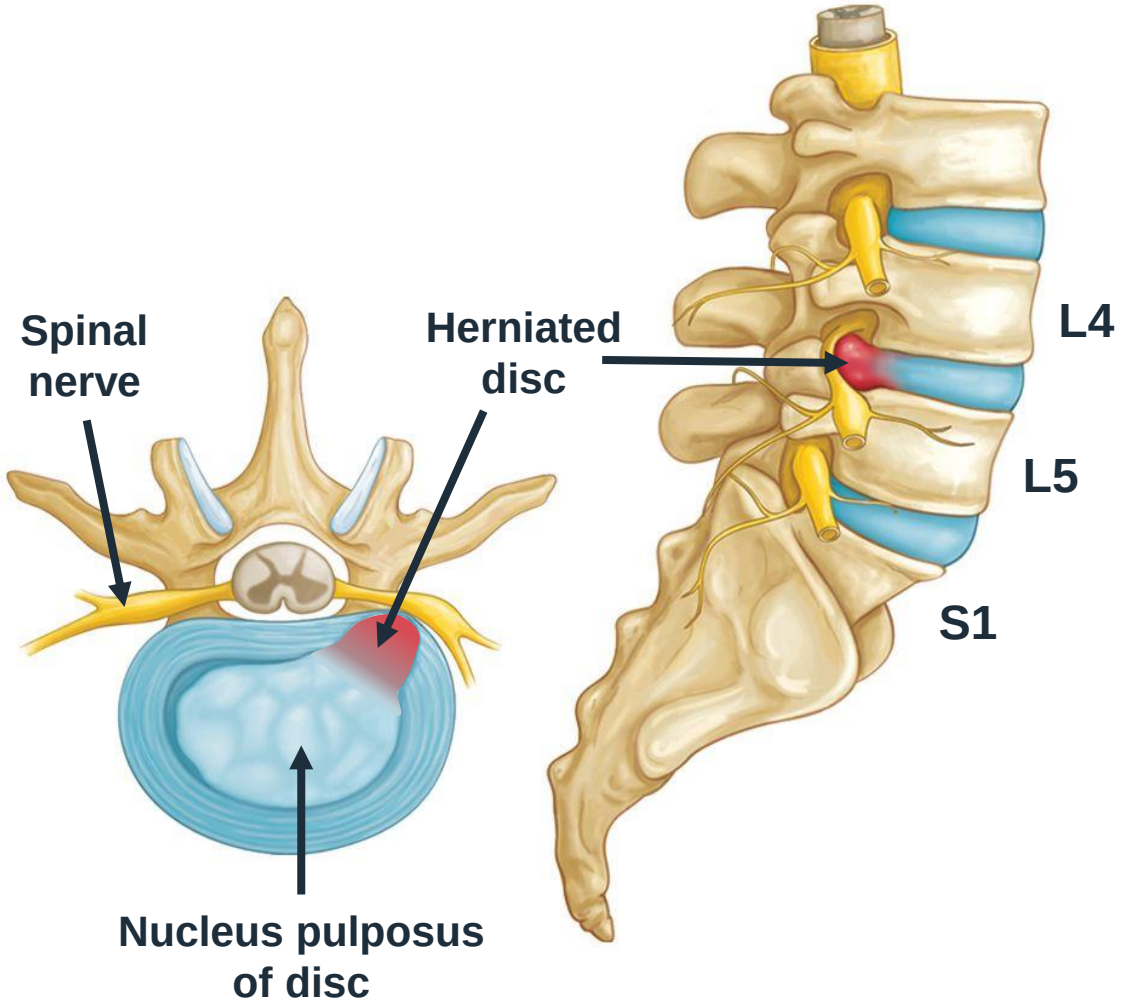
Lumbar Disc Herniation (LDH) Pathology

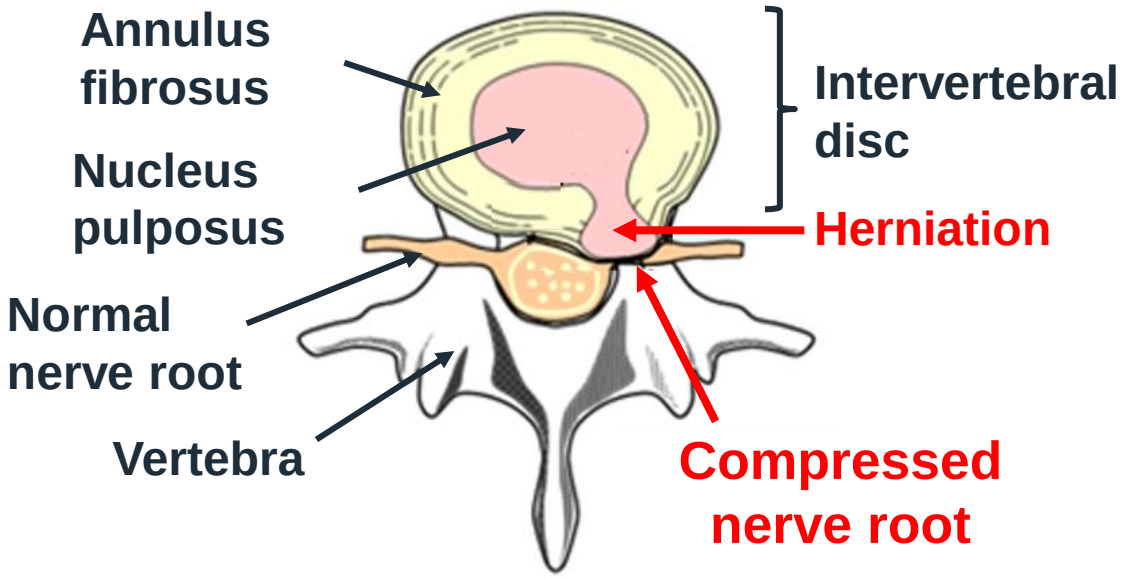
- Result of protrusion or prolapse of nucleus pulposus and annulus fibrosus of intervertebral disc posteriorly
- ~95% of herniations are LDH, occurring in L4-L5 or L5-S1 region



Adapted from American Academy of Orthopedic Surgeons

LDH Can Result in Direct Pressure on Spinal Nerve Root

Visible Compression of Nerve Root



- May cause leg pain, numbness, and/or weakness
- May cause lower back pain

First-Line Treatment for LDH is Conservative

- Rest, physical therapy, oral medications, steroid injections[1-4]
- Common standard of care for LDH in industrialized countries
- Most patients respond to conservative treatment
- Surgery is next option for 20 – 50% of patients non-responsive to conservative therapy[5-7]

1. Haro et al., 2022; 2. Lilly et al., 2021; 3. Wang et al., 2020; 4. Zou et al., 2023; 5. Peul et al., 2007; 6. Weinstein et al., 2006; 7. Shiga, 2022

No Option for Patients Ineligible for Surgery or Who Do Not Consent to Surgery

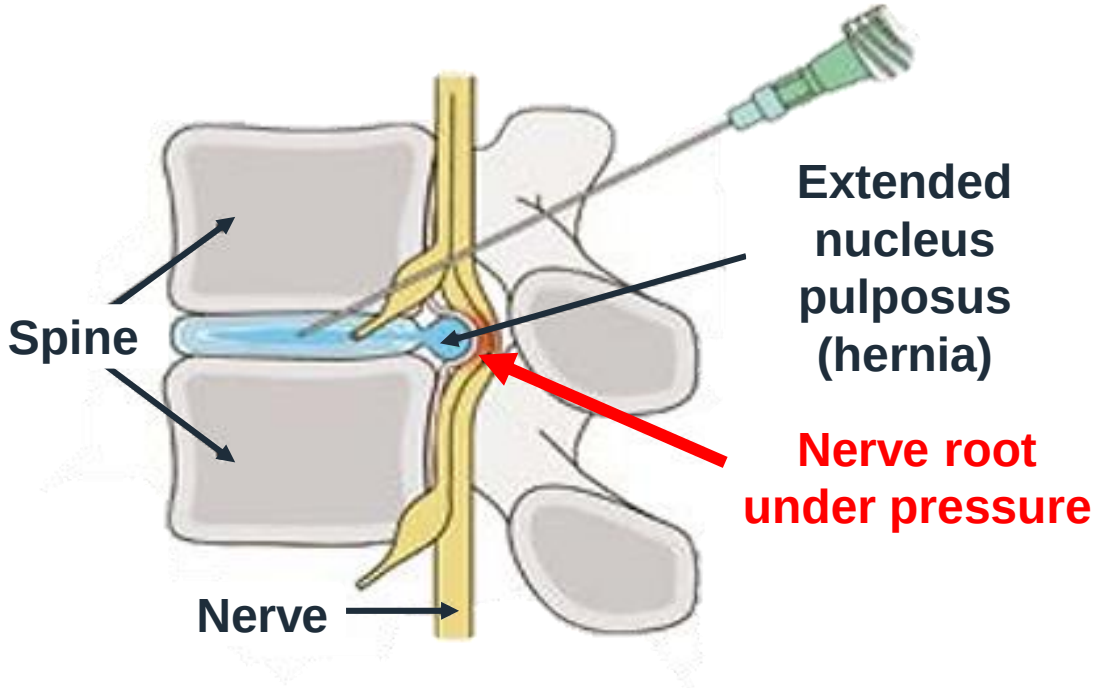
- Patients with leg pain due to nerve root impingement and inadequate response to conservative treatment need another treatment option

Condoliase Provides Targeted Enzyme to Degrade Glycosaminoglycan (GAG) and Shrink Disc Herniation

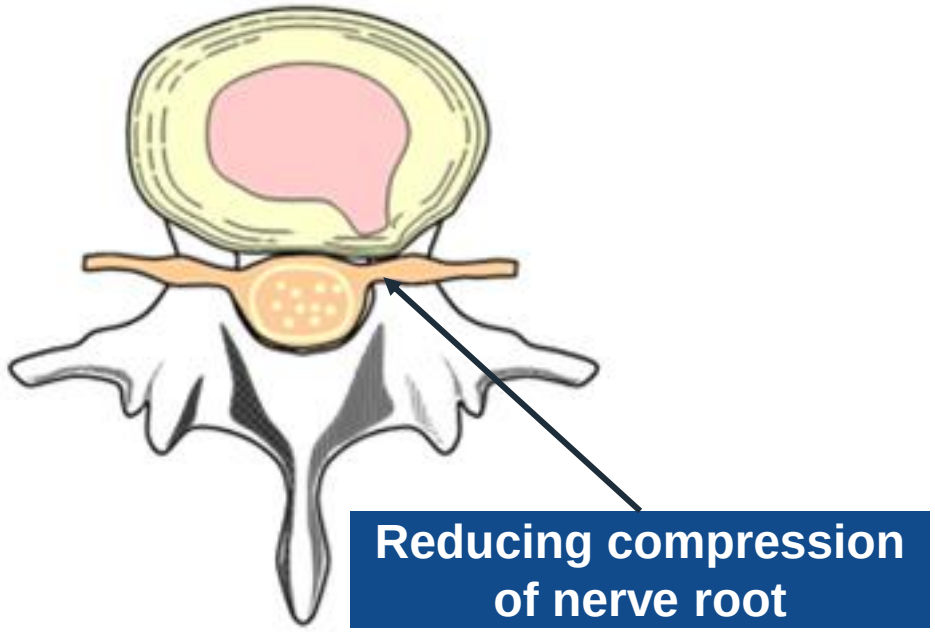
- Selectively degrades chondroitin sulfate and hyaluronic acid GAG chains
- Loss of GAG chains decreases water-retention capacity of nucleus pulposus
  - Decreases disc pressure on spinal nerve root

Condoliase is Less Invasive Treatment Option that Does Not Require General Anesthesia

Administration of condoliase



Reducing compression of nerve root



Condoliase Provides Patients with Non-Surgical Treatment Option

Proposed Indication[1]

…for the treatment of radicular leg pain associated with radiologically confirmed nerve root impingement caused by lumbar disc herniation (LDH) in adults

Proposed Dosing

Single-dose injection of 1.25 U into nucleus pulposus of herniated intervertebral disc

1. Revised indication proposed to FDA at the Late-Cycle Meeting on December 17, 2024 added “radiologically” as means for confirmation

Positive Condoliase Benefit-Risk Profile Supported by 4 Phase 2/3 Randomized Controlled Trials (RCTs)

Study 1021

Phase 2 RCT
52 Week Study
(Japan)

Safety

Condoliase vs Placebo

1.25 U (N = 49)	Saline (N = 47)
2.5 U (N = 50)	
5.0 U (N = 49)	

Study 1031

Phase 3 RCT
52 Week Study
(Japan)

Efficacy & Safety

Condoliase vs Placebo

1.25 U (N = 84)	Saline (N = 82)

Study 1131

Phase 3 RCT
104 Week Study
(US)

Safety

Condoliase vs Sham

1.25 U (N = 290)	**-** (N = 95)

Study 1133

Phase 3 RCT
52 Week Study
(US)

Efficacy & Safety

Condoliase vs Sham

1.25 U (N = 176)	**-** (N = 176)

Approved in Japan in 2018
Estimated 29,000 patients treated in post-market

Substantial Evidence of Effectiveness Demonstrated in Studies 1031 and 1133

Study 1031

Phase 3 RCT
52 Week Study
(Japan)

Supports Efficacy
Supports Safety

Condoliase vs Placebo

1.25 U	Saline
(N = 84)	(N = 82)

Study 1131

Phase 3 RCT
104 Week Study
(US)

Informs Patient Selection

Condoliase vs Sham

1.25 U	-
(N = 290)	(N = 95)

Study 1133

Phase 3 RCT
52 Week Study
(US)

Supports Efficacy
Supports Safety

Condoliase vs Sham

1.25 U	-
(N = 176)	(N = 176)

Approved in Japan in 2018
Estimated 29,000 patients treated in post-market

Appropriate Patient Population Identified by Clinical Trial Learnings

Appropriate patients treated with condoliase have

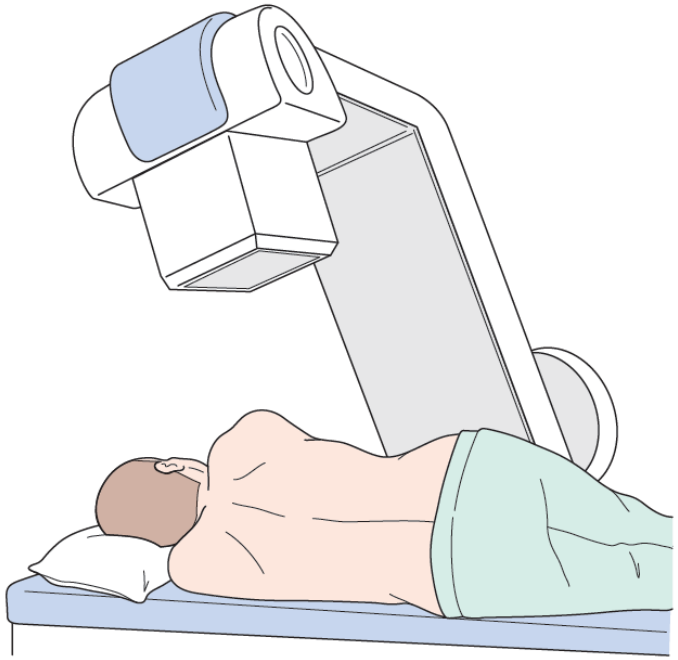
- ✓ Inadequate response to conservative therapy
- ✓ Radiologically confirmed, visible nerve root impingement, with awareness that patients without impingement are unlikely to benefit

Condoliase will be Administered by Interventional Pain Specialists

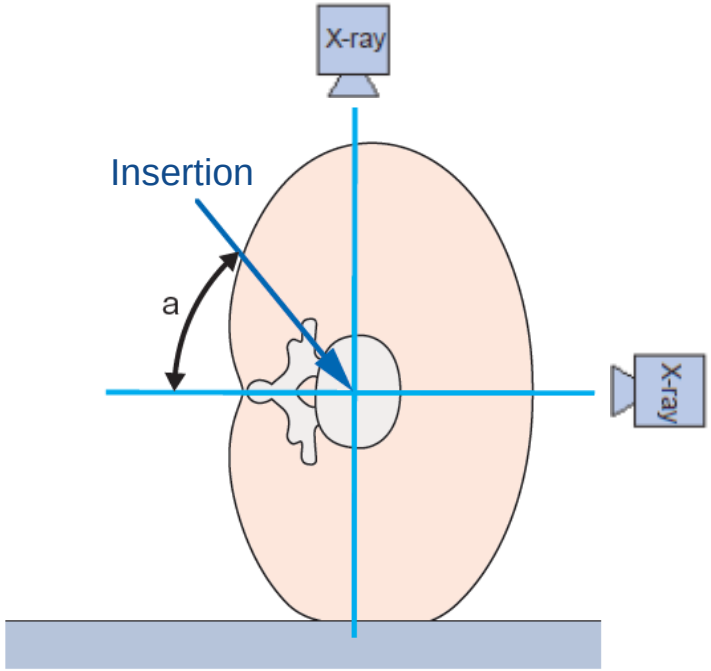
- By the time conservative therapy fails, patients will be managed by a trained specialist
  - Fellowship trained in interventional pain medicine
- Spinal injections are well established procedures
  - Specialists use fluoroscopic guidance during injection procedure to increase precision

Fluoroscopic Guidance (C-Arm) Used During Injection Procedure for Safe Administration

Injection procedure performed under C-Arm fluoroscopy

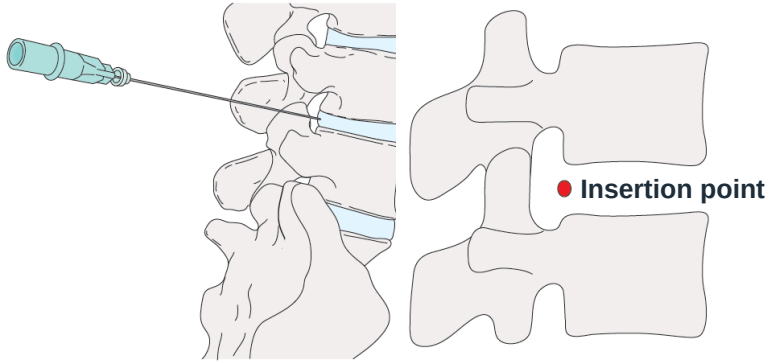


Patient positioned so that disc space injected is parallel to x-ray direction

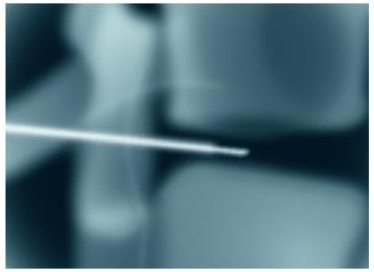


Lateral Position

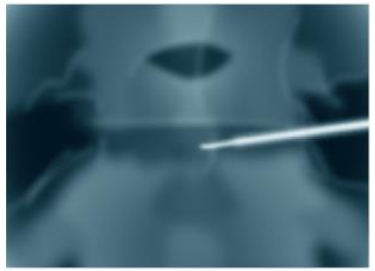
Needle placement confirmed throughout procedure



Lateral Position



Lateral view



Frontal view

Positive Condoliase Benefit-Risk for Treatment of Radicular Leg Pain Associated with Nerve Impingement from Herniation

Benefits

- Met primary endpoint in 2 pivotal studies
- Significant, clinically meaningful improvement in relief of worst leg pain compared with control
  - Durable up to 12 months
- Reduction in herniation volume and improvement in function at Week 13 that persisted over time

Risks

- Well-tolerated with acceptable safety profile for patients with LDH associated radicular leg pain
  - Hypersensitivity warning, including anaphylaxis
- Safety profile supported by clinical use and post-marketing surveillance in ~ 29,000 patients

Agenda

Unmet Need	**Ajay D. Wasan, MD, MSc** Professor; Vice Chair for Pain Medicine; Director, Chronic Pain Research Program; Director, Center for Innovation in Pain Care University of Pittsburgh School of Medicine
Condoliase Efficacy	**Joe Stauffer, DO, MBA, FAPCR** Chief Medical Advisor
Condoliase Safety	**Diane Martire, MD, MPH** Safety Advisor
Disc-related Imaging Findings	**Thomas Fuerst, PhD** Radiology Advisor
Clinical Perspective	**Kee D Kim, MD** Chief, Spinal Neurosurgery; Co-Director, Professor of Neurological Surgery University of California, Davis Spine Center

Additional Experts

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Seikagaku Corporation

Unmet Need

Ajay D. Wasan, MD, MSc

Professor of Anesthesiology, Perioperative Medicine, and Psychiatry

Vice Chair for Pain Medicine

Director, Center for Innovation in Pain Care

University of Pittsburgh School of Medicine

Radicular Leg Pain Due to Lumbar Disc Herniation

- Radicular pain is severe and associated with distress and suffering
- Many therapies have failed to provide adequate relief

- Persistent leg pain, unresponsive to conservative treatment often leads to worsening health and quality of life
- Potential for longer-term disability, increased care-giver burden, and lost days from work

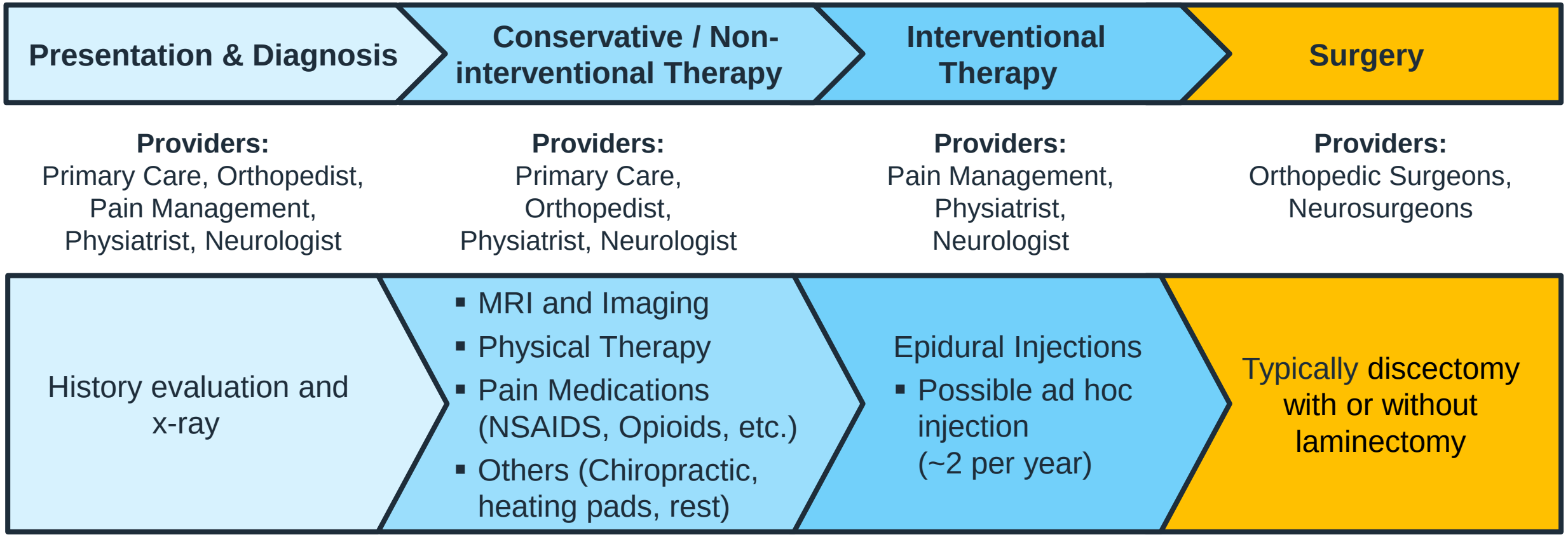
- Currently, no approved therapies deliver long-term pain reduction, improve functionality, and allow patients to avoid risks associated with surgery and long-term pharmacotherapy

Symptomatic LDH Affects ~ 1 – 3% of US Population[1]

- Males affected more often[2]
- Mean age 30 – 50 years old[3]
  - Rare in < 20 or ≥ 65[3]
- Obesity can lead to increased herniation risk[4]

1. Haro et al, 2022; Shiga, 2022; Anderson et al, 2021; Lilly et al., 2021; 2. Davis, 1994; Kirita, 1975; Schroeder et al., 2016; 3. Dydyk et al., 2023; Haro et al, 2022; Matsuyama et al, 2023; 4. Schroeder et al., 2016

LDH Treatment Similar in Industrialized Countries (e.g., US, Japan, Europe)



Multimodal Therapy for LDH

Conservative / Non-Interventional Therapies

- Traction therapy
- Spinal manipulation
- Chiropractic therapy
- Exercise and physical therapy
- Steroids, analgesics, NSAIDs
- Neuropathic medications

Interventional Therapies

- Transforaminal or interlaminar epidural steroid injections

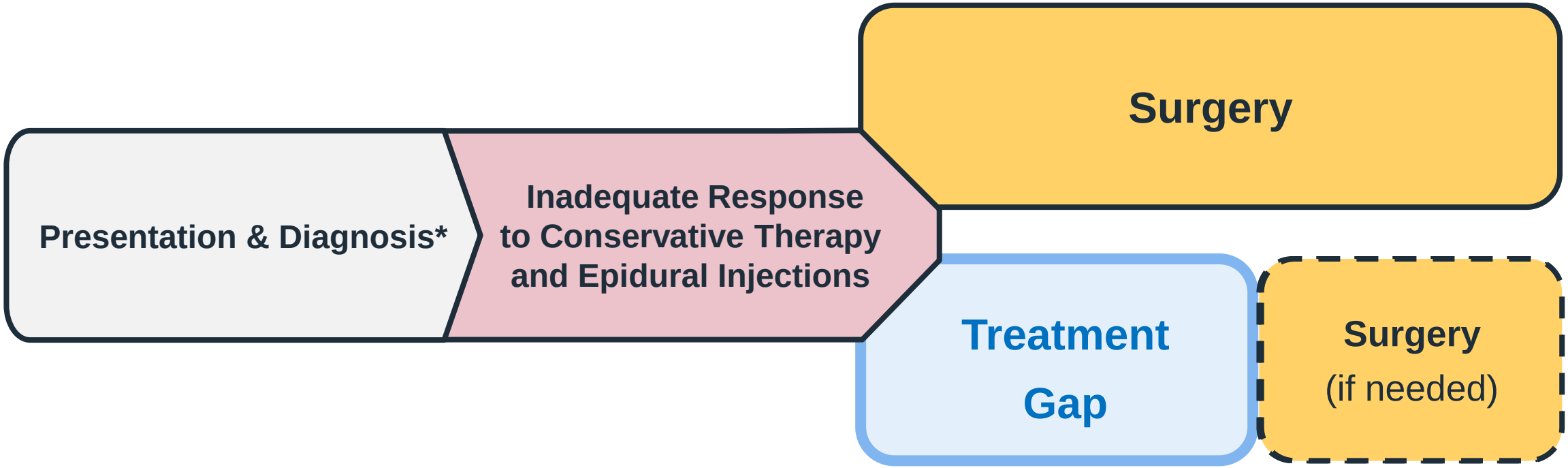
Haro et al., 2022; Lilly et al., 2021; Wang et al., 2020; Zou et al., 2023; Ackerman et al, 2007; Beall et al, 2024

Conservative Therapy May Provide Pain Relief

- “Most patients will improve independent of treatment. Disc herniation will often shrink/regress over time. Many, but not all, articles have demonstrated a clinical improvement with decreased size of disc herniations.”[1]
- 20% to 50% of patients with LDH with radicular pain do not respond to conservative treatment[2-4]

1. North American Spine Society (NASS) Guideline, 2012; 2. Peul et al., 2007; 3. Weinstein et al., 2006; 4. Shiga, 2022

Limited Options for Patients Who Do Not Gain Symptomatic Relief with Conservative Therapy



*Patients with significant motor deficit and/or cauda equina syndrome should be promptly evaluated for surgery

Surgical Risks and Postoperative Complications

Infections	Procedural Complications	Persistent Neurological
▪ Discitis ▪ Wound infection	▪ Recurrent disc herniation ▪ Dural sac injury / dural tear ▪ End-plate osteochondritis ▪ Epidural hematoma ▪ Facet injury ▪ Nerve root injury	▪ Motor dysfunction ▪ Neurologic deterioration ▪ Paresthesia ▪ Transient dysesthesia ▪ Urinary retention

- Norwegian longitudinal observation study from > 34,000 herniated lumbar disc surgeries found
  - 2.7% surgical complication
  - 2.1% repeat surgery within 90 days
  - 2.4% non-surgical readmission within 90 days
  - 6.7% ≥ 1 of these unfavorable events

Park et al., 2023; Shi et al., 2023; Song et al., 2021; Zeng et al., 2020; Jaiswal et al., 2019; Kong et al., 2019; Patil et al., 2018; Fjeld et al., 2019

Unmet Need Summary

- No approved pharmacological therapies for patients with LDH that provide early and long-term reduction in leg pain while improving functionality
- Alternative treatment options needed for patients with radicular leg pain who do not respond to conservative therapy and seek non-surgical solutions

Condoliase Efficacy in Appropriately Selected Patients

Joe Stauffer, DO, MBA, FAPCR

Chief Medical Advisor

Seikagaku

Clinical Studies Overview and Learnings

Significance of Study 1131

Selection of Appropriate Patients

Condoliase Efficacy Supported by 2 Positive Pivotal Phase 3 RCTs

Study 1031

Phase 3
52-Week Study
(Japan)

Supports Efficacy
Supports Safety

Condoliase vs Placebo

1.25 U	Saline
(N = 84)	(N = 82)

Study 1131

Phase 3
104-Week Study
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Informs Patient Selection

Condoliase vs Sham

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1.25 U	**-**
(N = 176)	(N = 176)

SKK Investigated Potential Differences from Study 1031 to Understand Study 1131 Failure

3 Key Identified Differences	Study 1031 (N = 163)	Study 1131 (N = 374)
Clear nerve root impingement	88%	27%
No chronic low back pain[1]	100%	52%
No opioid use	85%	42%

1. Back pain for > 1 year, use of concomitant medication for back pain > 1 year, or concomitant medications for CLBP

Why Study 1131 Failed to Demonstrate Benefit for Leg Pain

Key factors in Study 1131 inconsistent with Study 1031	Clinical study implications
Only 27% of patients had clear nerve root impingement	▪ Can't assume leg pain is due to LDH ▪ Need impingement in order for LDH shrinkage to relieve leg pain
Inclusion of patients with chronic low back pain	▪ Low back pain may confound evaluation of leg pain
Majority of patients used opioids or other concomitant pain meds	▪ Analgesia from opioid use may confound evaluation of leg pain

Study 1133 Enrollment Criteria Adapted to Recruit Patients Similar to Study 1031

Key factors in Study 1131 inconsistent with Study 1031	Implications for Study 1133
Only 27% of patients had clear nerve root impingement	▪ Require MRI confirmed nerve root impingement confirmed by both study investigators and central reader
Inclusion of patients with chronic low back pain	▪ Exclude patients with chronic low back pain ≥ 1 year ▪ Exclude low back pain not from LDH
Majority of patients used opioids or other concomitant pain meds	▪ Exclude patients on chronic opioid therapy

Interpretation of Study 1131 Limited by Low Overlap with Key Identified Factors

	Condoliase N = 280	Sham N = 94
Clear nerve root impingement	79 **(28%)**	21 **(22%)**
No opioid use	123 **(44%)**	35 **(37%)**
No chronic low back pain[1]	144 **(51%)**	49 **(52%)**
Target patients	20 **(7%)**	5 **(5%)**
	25 patients limits ability to assess results	

1. Back pain for > 1 year, use of concomitant medication for back pain > 1 year, or concomitant medications for CLBP

Clinical Efficacy Results

Studies 1031 and 1133

Study 1031 and Study 1133 Demonstrated Substantial Evidence of Condoliase Efficacy

Study 1031

Phase 3
52-Week Study
(Japan)

Supports Efficacy
Supports Safety

Condoliase vs Placebo

1.25 U	Saline
(N = 84)	(N = 82)

Study 1133

Phase 3
52-Week Study
(US)

Supports Efficacy
Supports Safety

Condoliase vs Sham

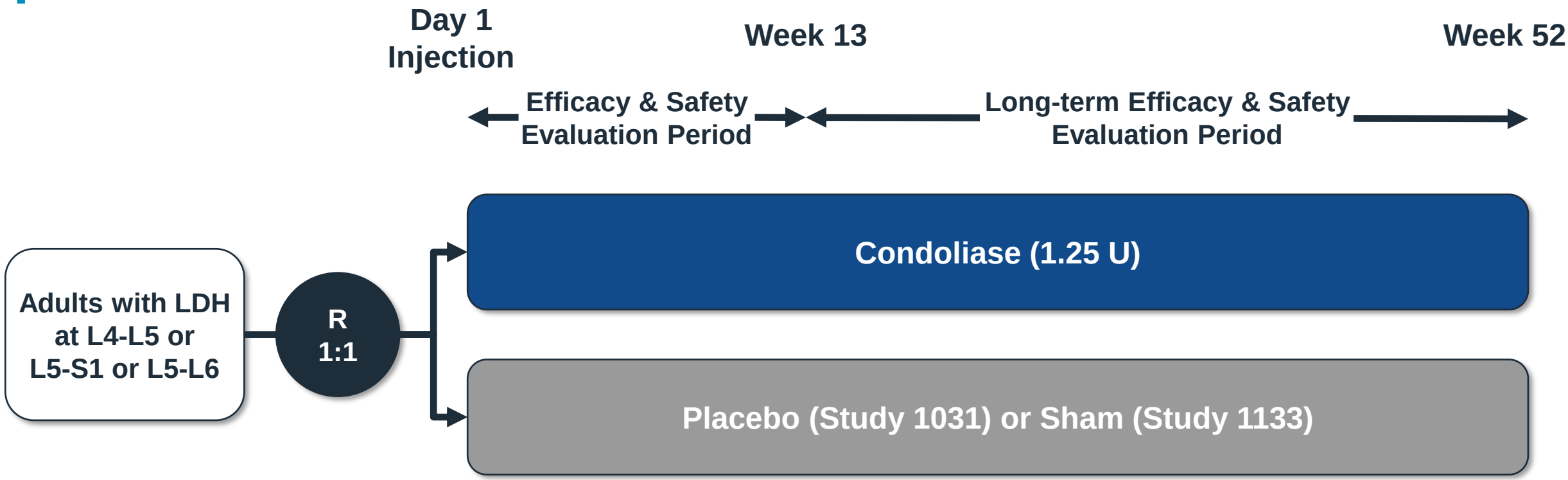
1.25 U	-
(N = 176)	(N = 176)

Pivotal Studies: Baseline Demographics and Characteristics

		Study 1031 (Japan)		Study 1133 (US)	
		Condoliase (N = 82)	Placebo (N = 81)	Condoliase (N = 169)	Sham (N = 172)
Age (years) [1]		**37.5**	**38.0**	**46.0**	**45.0**
Sex, n (%)	Male	51 **(62%)**	48 **(59%)**	95 **(56%)**	89 **(52%)**
	Female	31 **(38%)**	33 **(41%)**	74 **(44%)**	83 **(48%)**
Race	American Indian or Alaska Native	0	0	1 **(0.6%)**	0
	Asian	82 **(100%)**	81 **(100%)**	6 **(4%)**	9 **(5%)**
	Black or African American	0	0	18 **(11%)**	14 **(8%)**
	White	0	0	137 **(81%)**	142 **(83%)**
	Other	0	0	7 **(4%)**	7 **(4%)**
BMI (kg/m^2) [1]		**23.1**	**22.9**	**28.4**	**28.1**
Herniation site	L4 – L5	45 **(55%)**	37 **(46%)**	70 **(41%)**	71 **(41%)**
	L5 – S1	37 **(45%)**	44 **(54%)**	99 **(59%)**	101 **(59%)**
Worst leg pain [1]		**73.3**	**74.6**	**73.1**	**71.9**
Worst back pain [1]		**55.1**	**61.6**	**62.3**	**60.8**
ODI score [1]		**37.0**	**40.0**	**48.0**	**49.0**

1. Median

Similar Phase 3 RCT Design with Study 1031 (Japan) and 1133 (US)



Primary Endpoint

- Change from Baseline to Week 13 in worst leg pain 100mm Visual Analog Scale (VAS) score

LDH = Lumbar Disc Herniation; R = Randomized

Statistical Hierarchy of Common Efficacy Endpoints

- Primary Endpoint
  - Change from baseline in average worst leg pain score[1] at Week 13
  - Primary analysis: mixed model for repeated measures (MMRM) without imputation assuming data were missing at random (MAR)

- Key Secondary Endpoints[2]
  - Change from baseline in average worst leg pain score[1] at Week 52
  - Change from baseline in herniation volume at Week 13
  - Change from baseline in Oswestry Disability Index (ODI) score at Week 13

1. Assessed by 100 mm VAS, with value over past 24 hours taken an average of at least 1 day for Study 1031 and at least 3 days for Study 1133 in the week prior to baseline and prespecified evaluation time points
2. Prespecified as key secondary endpoints in Study 1133 and secondary endpoints in Study 1031

Worst Leg Pain Methodology Using 100-mm Visual Analog Scale (VAS)

- Patients indicate pain intensity based on descriptors placed along horizonal line

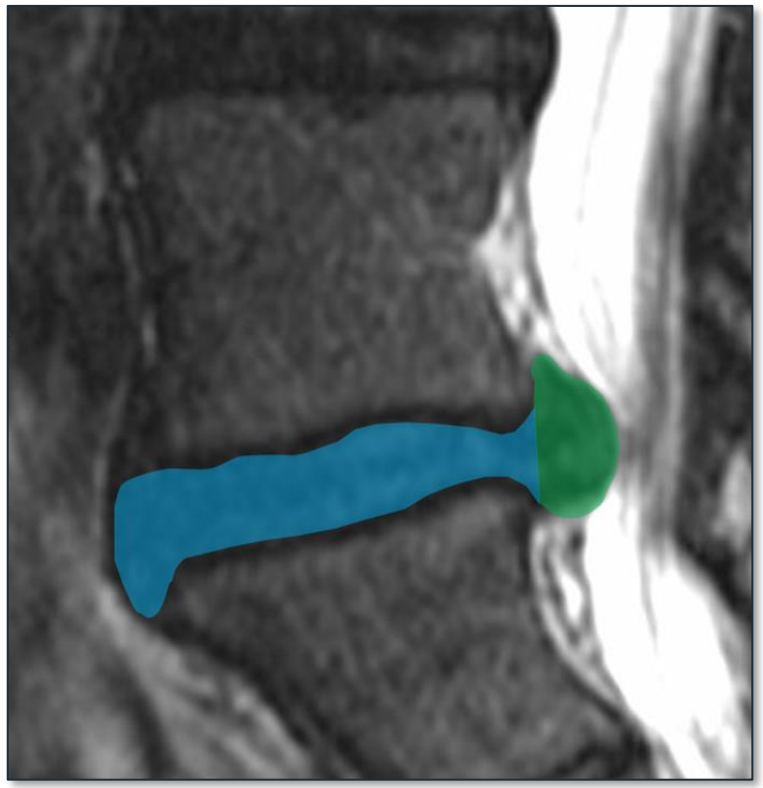
No Pain

Pain as bad as you can imagine

- Patients VAS recording is mm distance from no pain

Measuring Herniation Volume

- MRI scans were transmitted to central imaging facility for analysis
  - Tissue margins outlined on each slice
  - Herniation volume calculated as cross-sectional area multiplied by slice separation
  - Total herniation volume equaled sum of volume from each slice

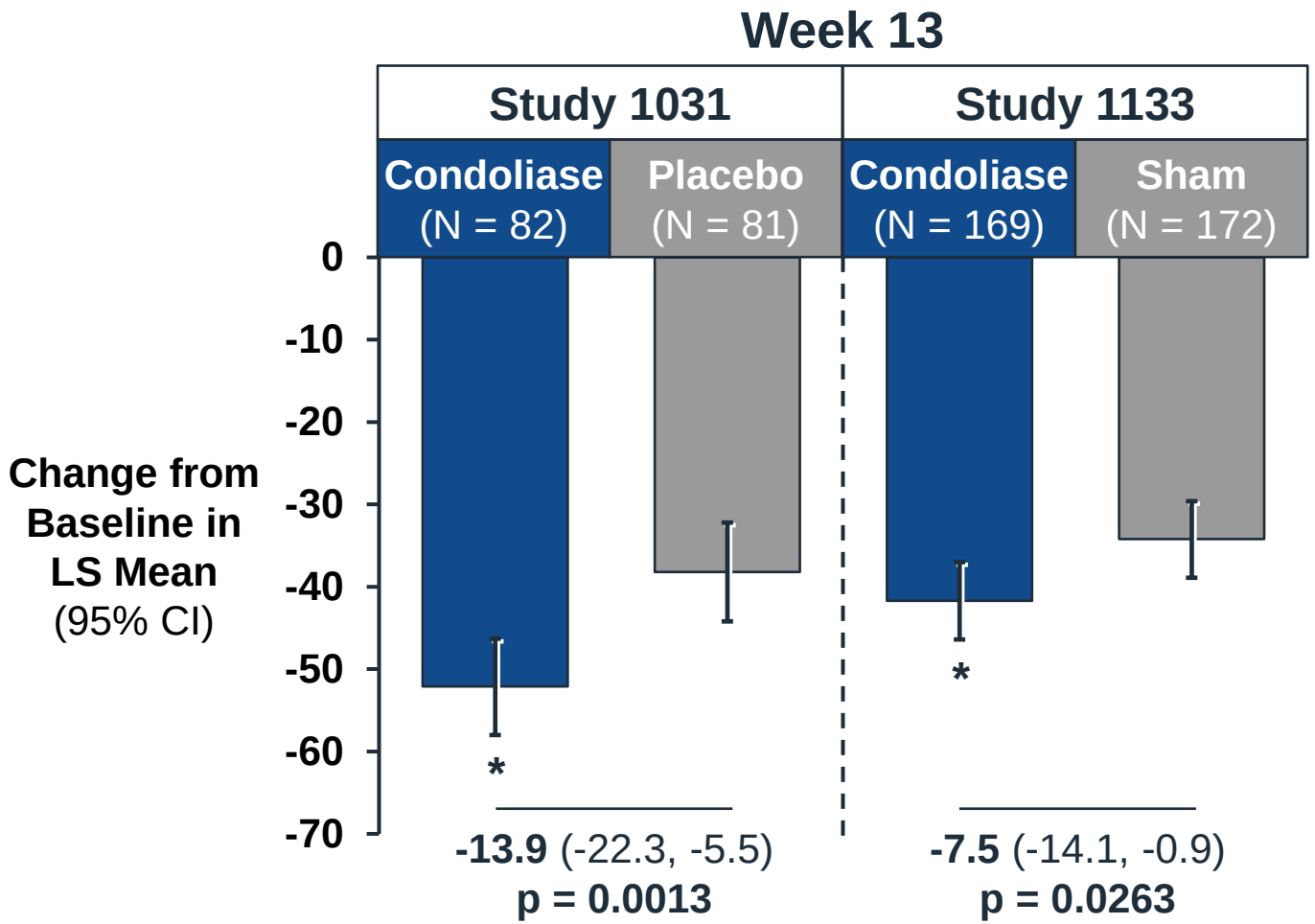


Oswestry Disability Index (ODI) Domains

- Questionnaire contains 10 items of daily living
  - Pain intensity
  - Personal care
  - Lifting
  - Walking
  - Sitting
  - Standing
  - Sleeping
  - Sex
  - Social
  - Travel
- Each item has 6 statements that are scored 0 to 5
  - 0 = least disability; 5 = greatest disability
- Total score = (sum of completed items / max score) * 100
  - Higher score indicates higher disability

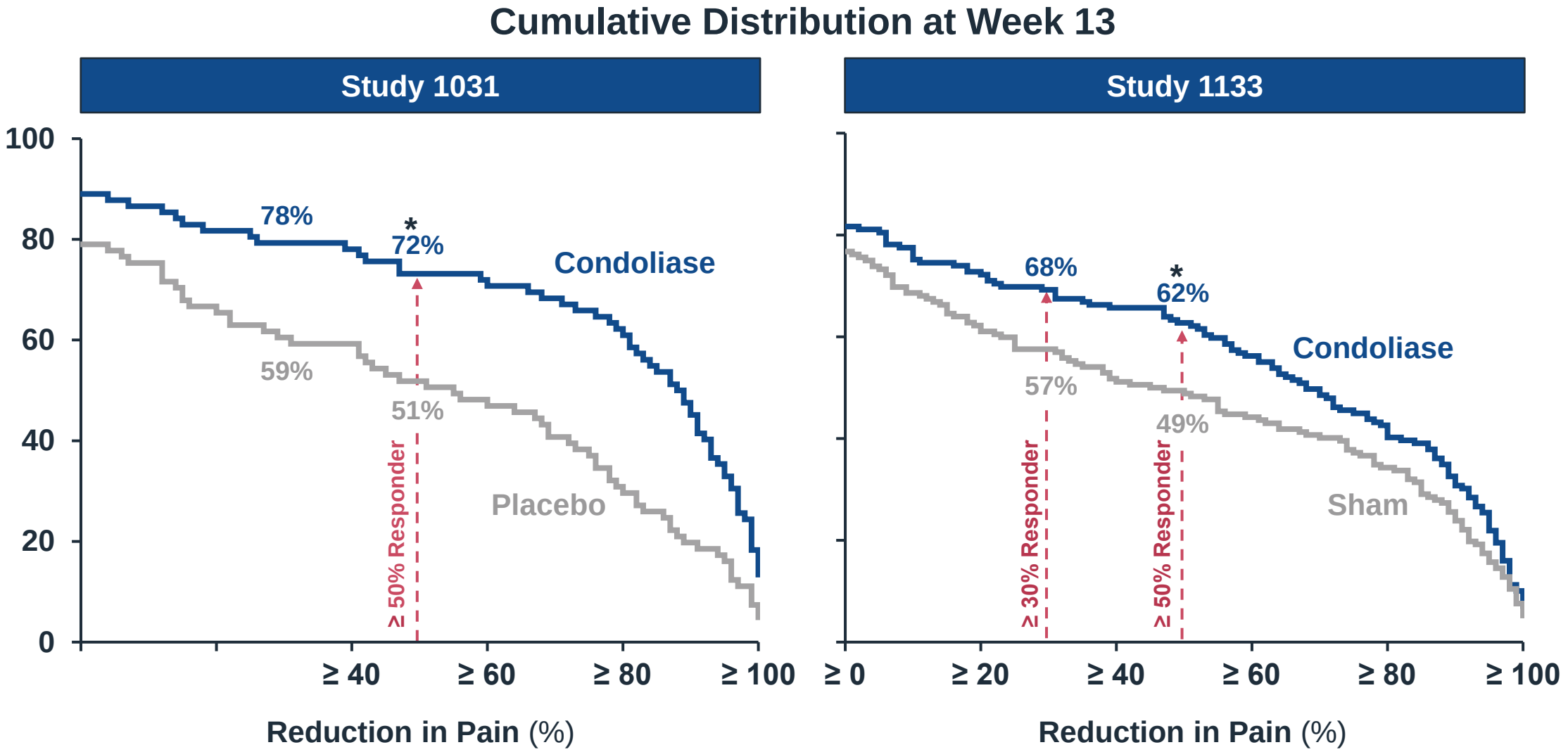
Copy of ODI questionnaire available in Briefing Document

Pivotal Studies: Significant Improvement in Primary Endpoint, Worst Leg Pain at Week 13



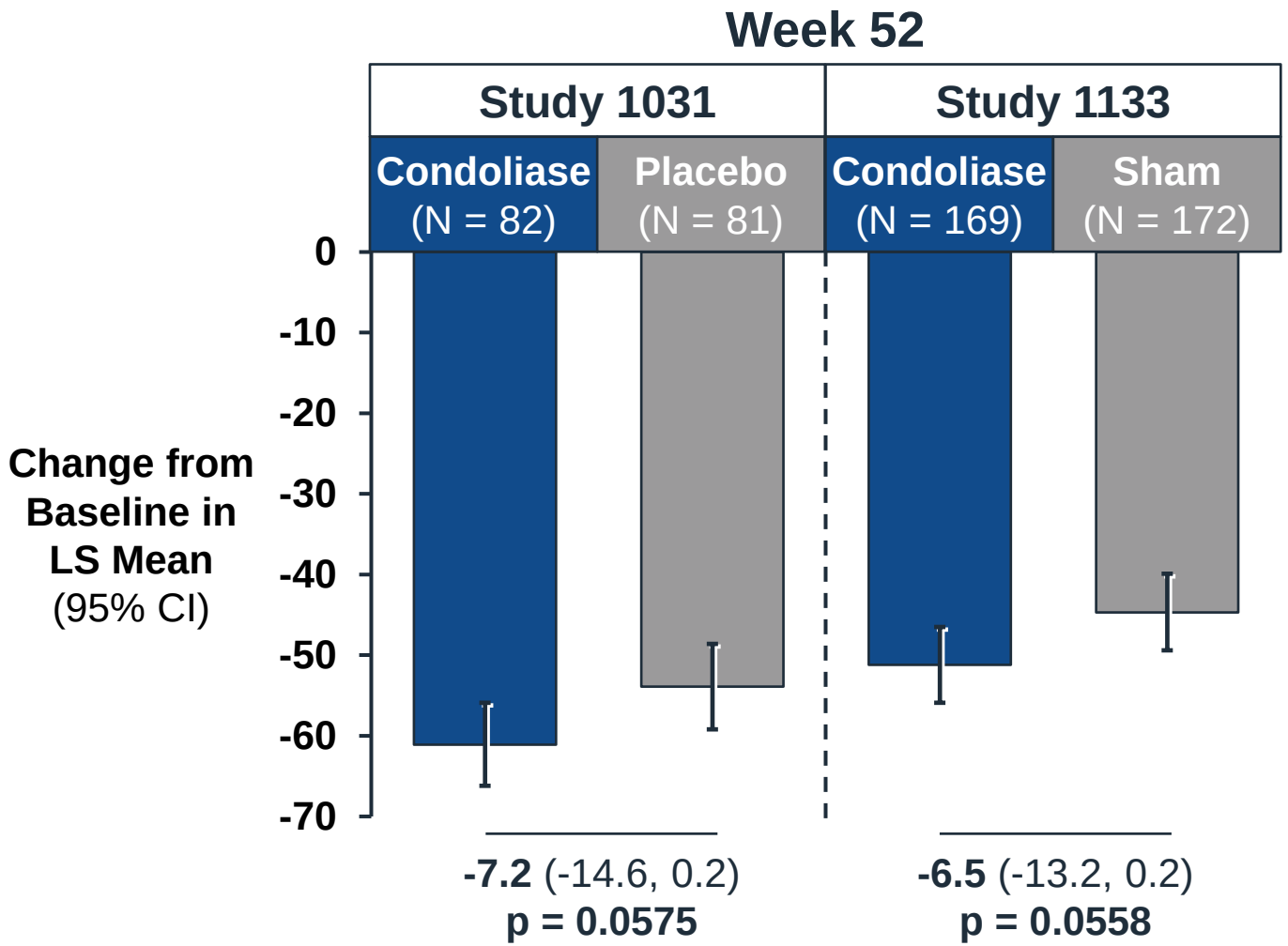
* p-value < 0.05
Worst leg pain was evaluated using 100 mm VAS

Pivotal Studies: Improvement in Weekly Averages of Worst Leg Pain from Baseline at Week 13



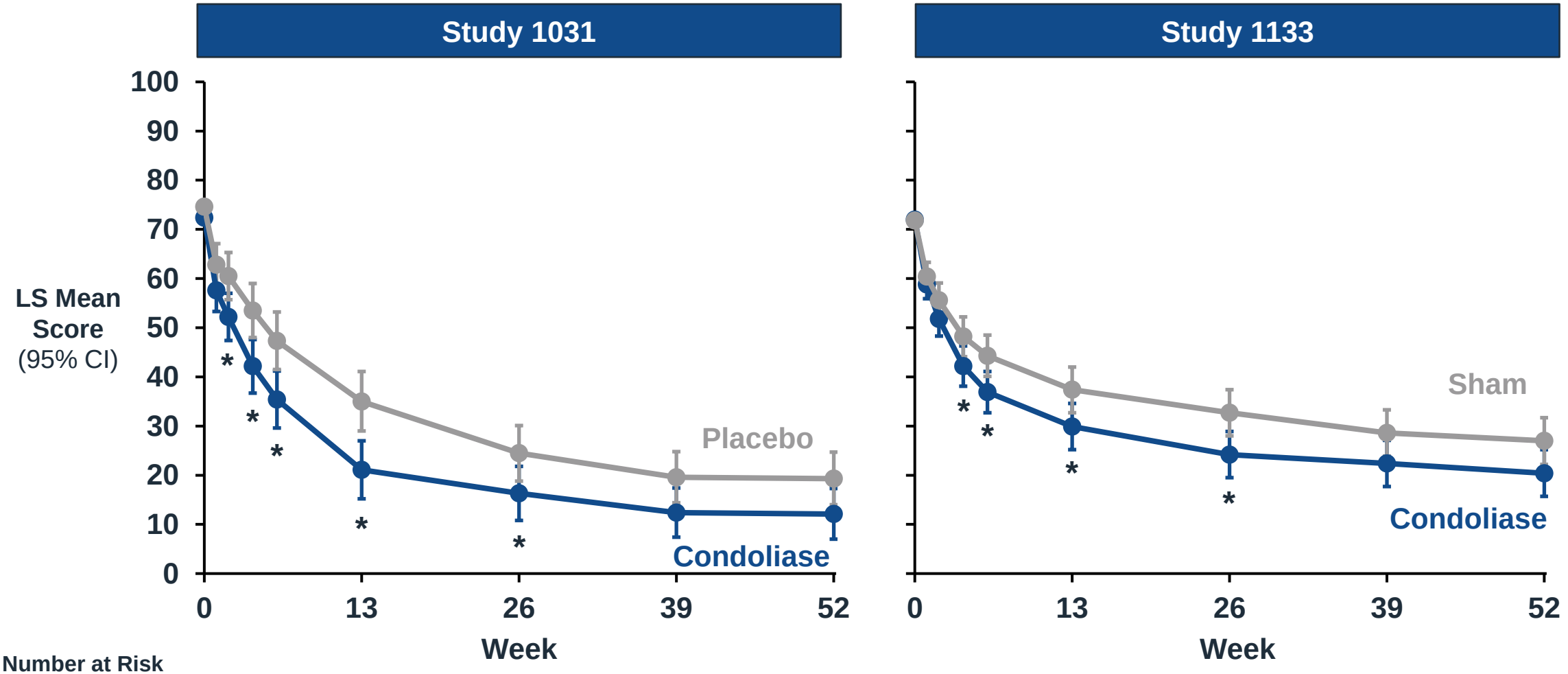
* Nominal p-value < 0.05

Pivotal Studies: Improvement in Secondary Endpoint, Worst Leg Pain at Week 52



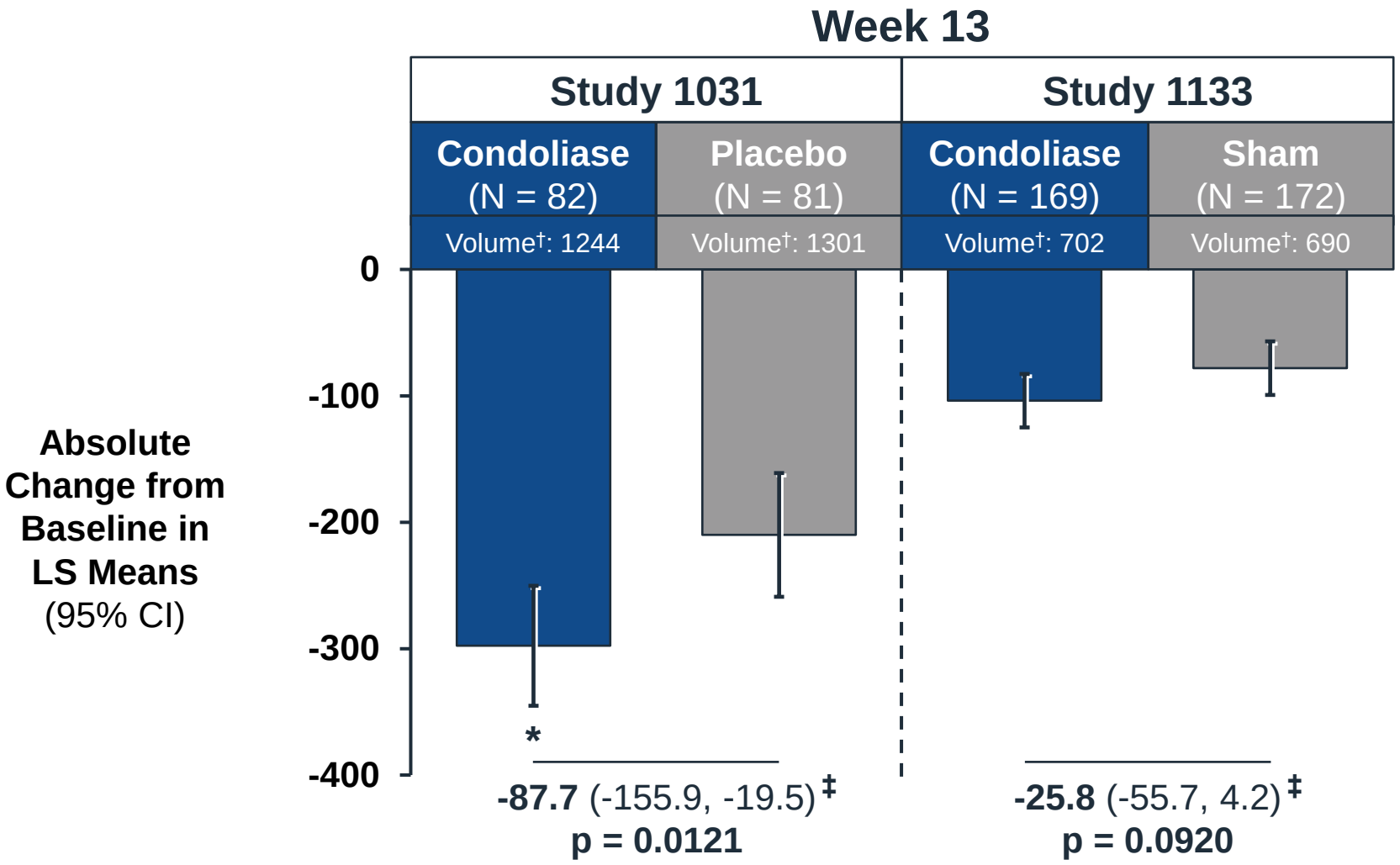
Worst leg pain was evaluated using 100 mm VAS

Pivotal Studies: Change in Weekly Averages of Worst Leg Pain Through Week 52



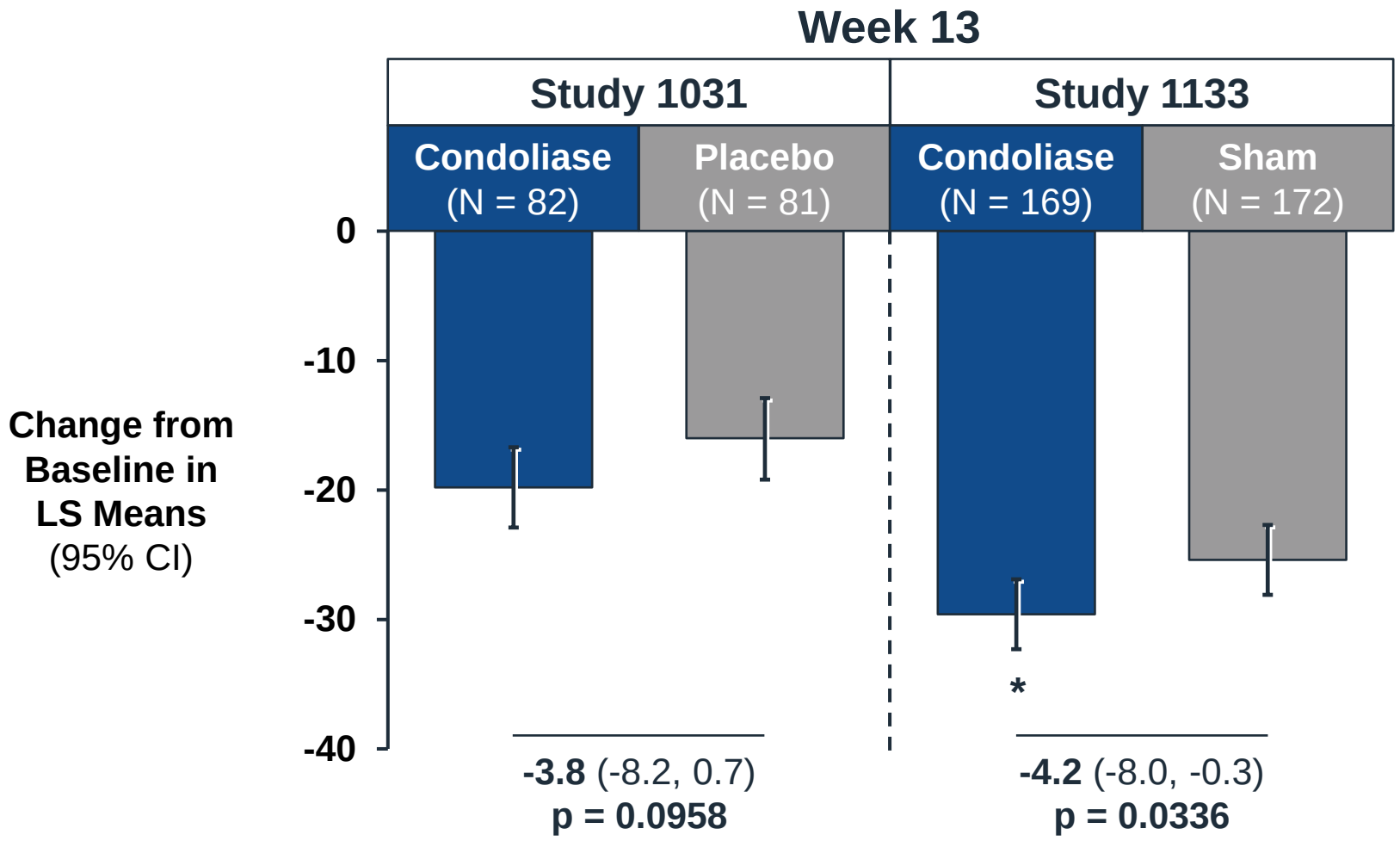
* Nominal p-value < 0.05

Pivotal Studies: Improvement Observed in Herniation Volume at Week 13



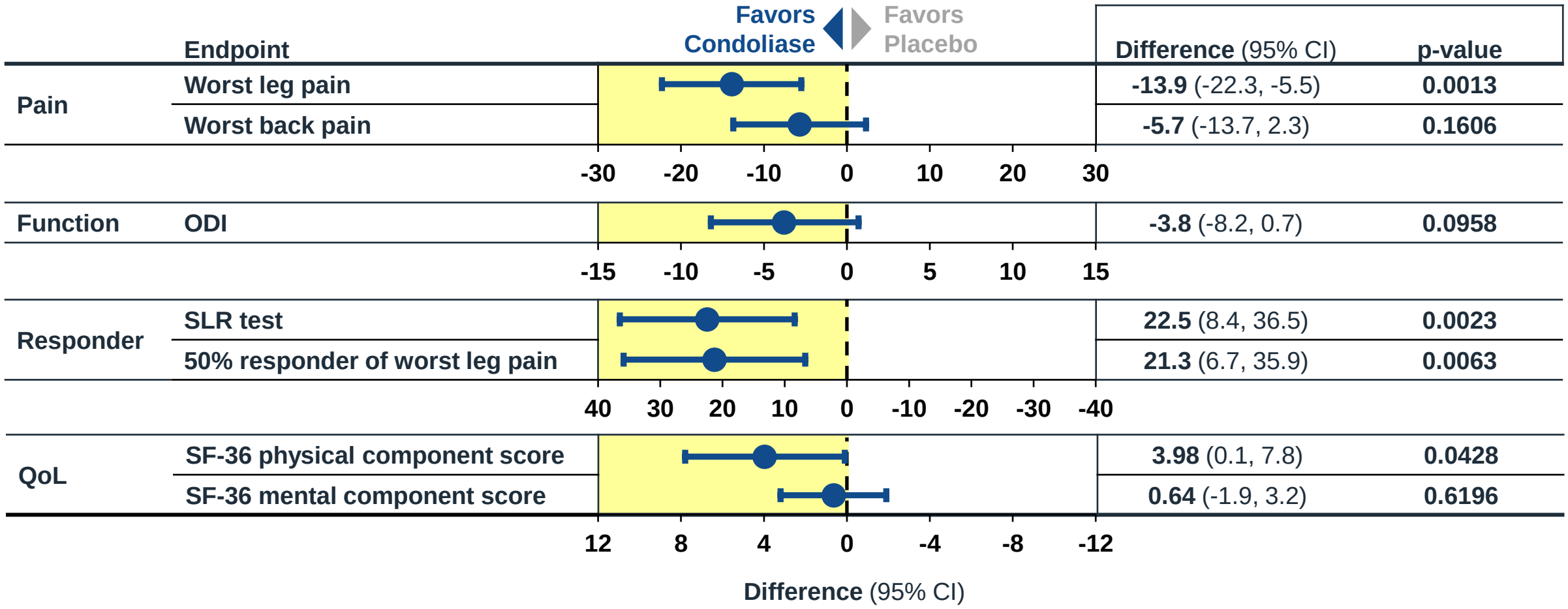
* Nominal p-value < 0.05; † Baseline herniation volume (mm^3); ‡ Studies 1031 and 1133 had difference in average baseline herniation volume

Pivotal Studies: Trends Toward Improvement Observed in ODI Score at Week 13



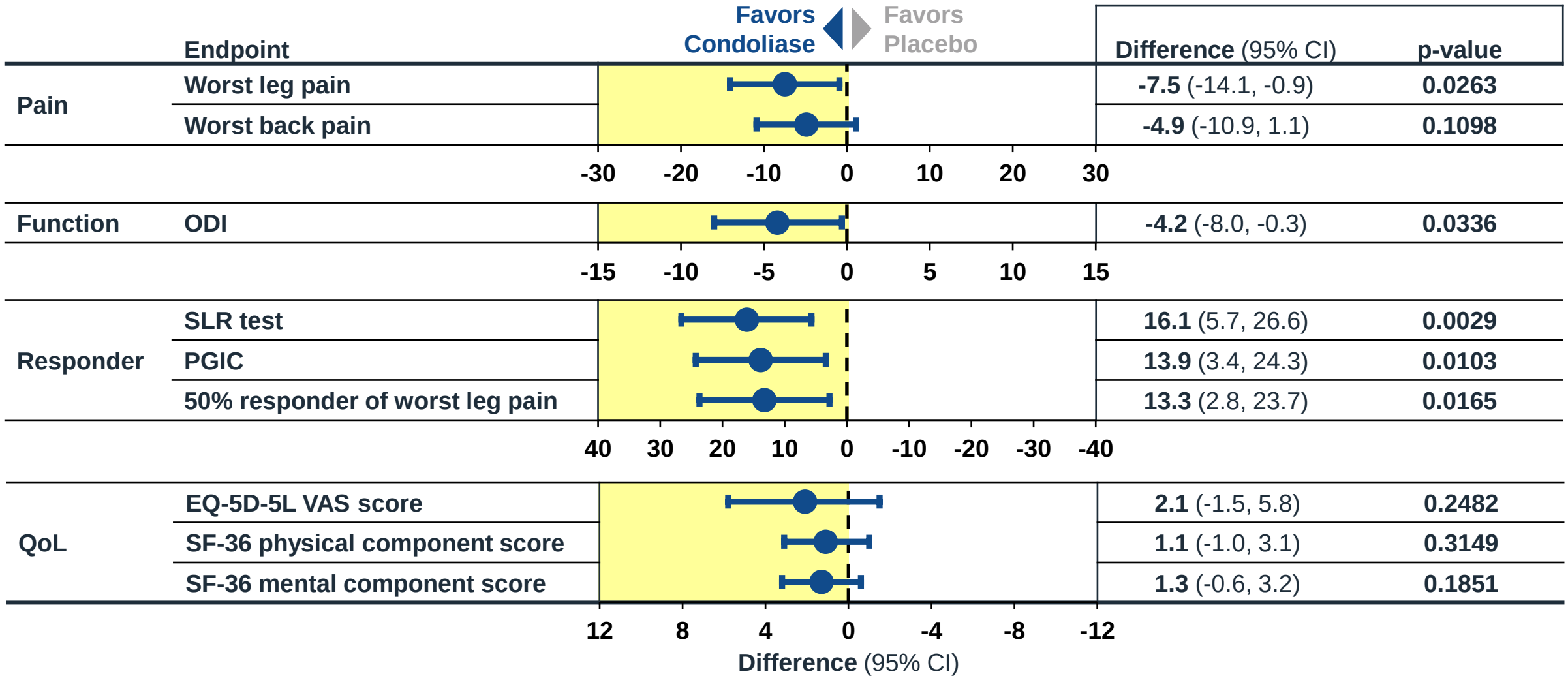
* Nominal p-value < 0.05

Study 1031: Efficacy Endpoints at Week 13 Consistently Favor Condoliase



ODI = Oswestry Disability Index, SLR = Straight Leg Raise

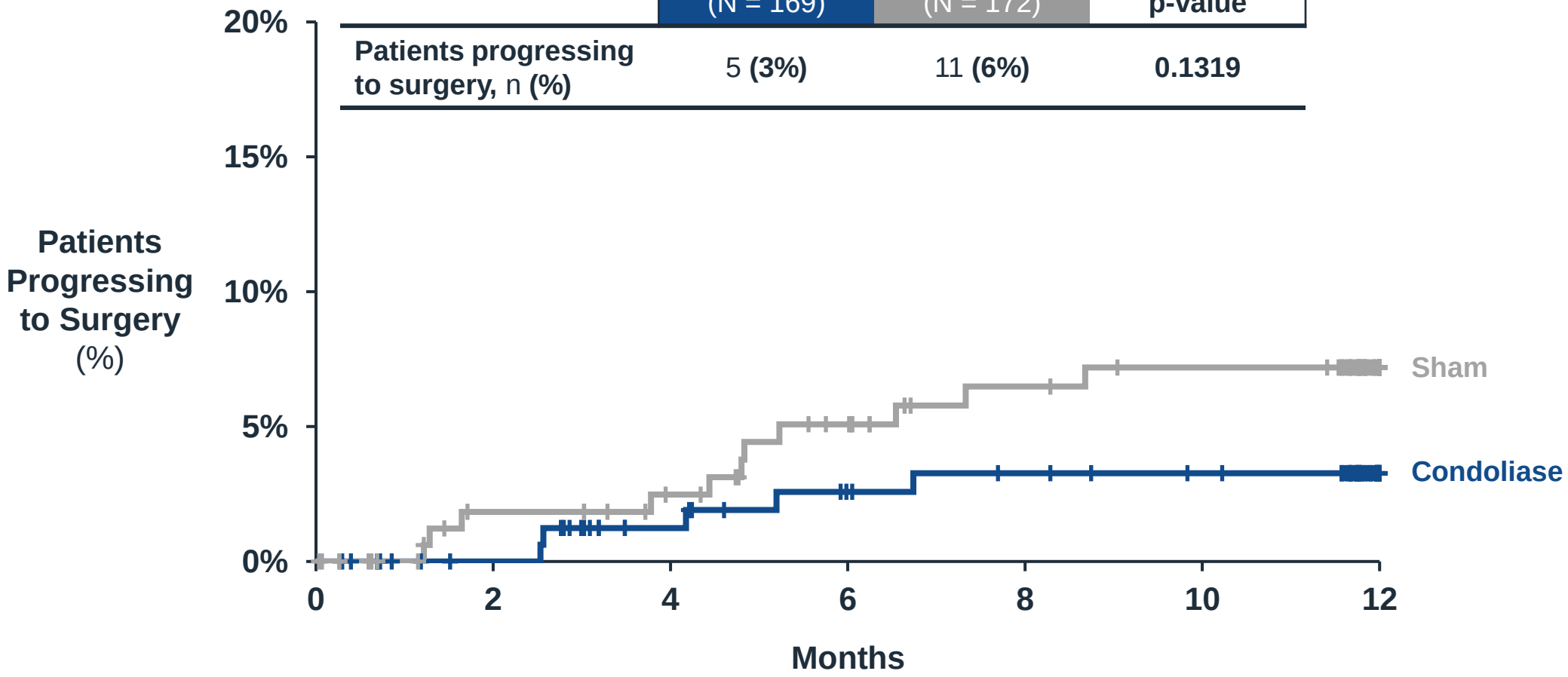
Study 1133: Efficacy Endpoints at Week 13 Consistently Favor Condoliase



ODI = Oswestry Disability Index; SLR = Straight Leg Raise; PGIC = Patient Global Impression of Change

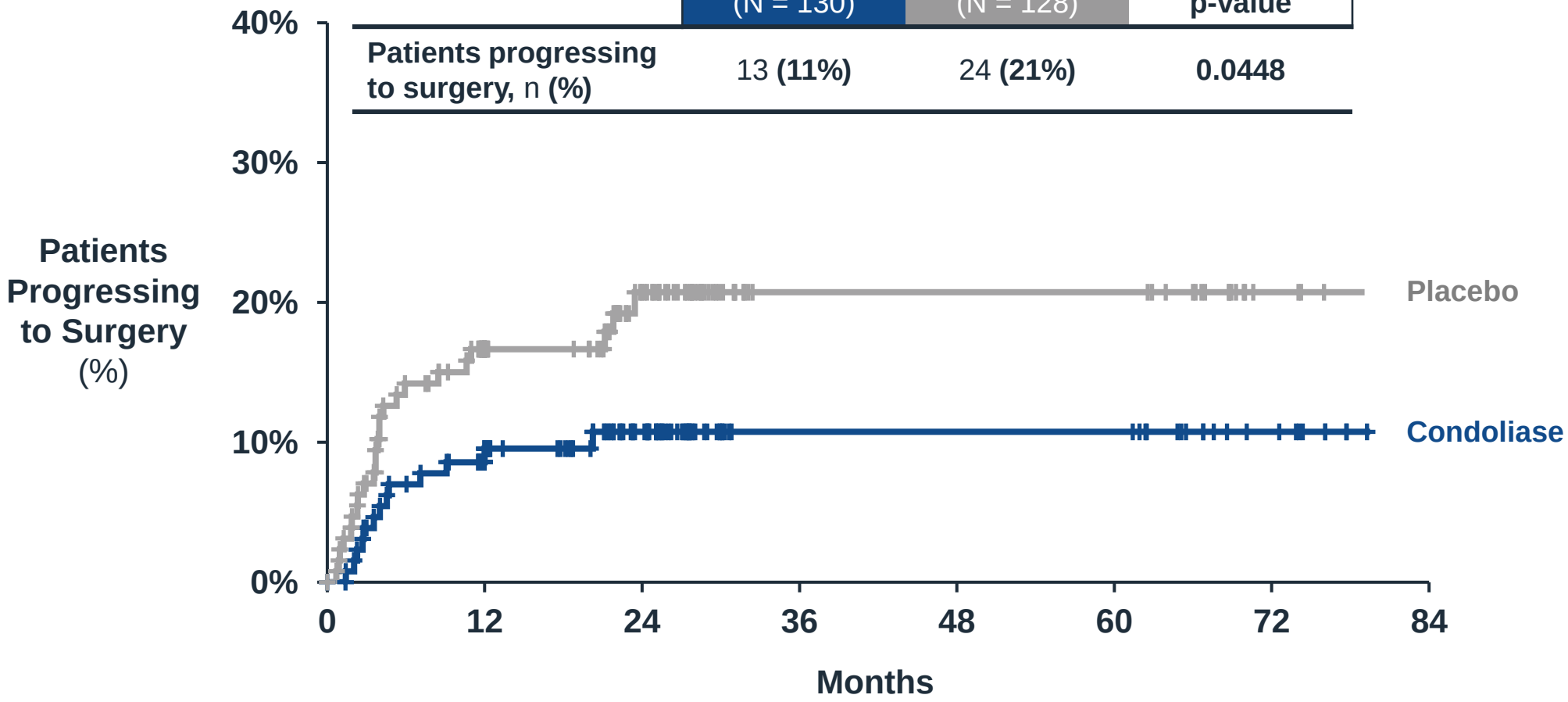
Study 1133: Fewer Condoliase Treated Patients Went on to Surgery for LDH at Target Level Within First Year

	Condoliase (N = 169)	Sham (N = 172)	Log rank p-value
Patients progressing to surgery, n (%)	5 **(3%)**	11 **(6%)**	**0.1319**



Survey of Patients in Studies 1021 and 1031: Time to Surgery for LDH at Target Level

	Condoliase (N = 130)	Placebo (N = 128)	Log rank p-value
Patients progressing to surgery, n (%)	13 **(11%)**	24 **(21%)**	**0.0448**



Patients with LDH administered Condoliase 1.25 U or placebo in Studies 1021 or 1031 conducted in Japan [Median study duration: 5 yrs 3 mos or 2 yrs]
Matsuyama et al., 2023

Condoliase Provides Meaningful Efficacy for Patients that Want to Avoid Surgery

- Statistically significant pain relief demonstrated on primary endpoint in 2 pivotal studies
- Durable relief of worst leg pain
- Reduction in herniation volume
- Improved function in ODI

Condoliase provides patients with significant and clinically meaningful benefits as an alternative to surgical intervention

Condoliase Safety

Diane Martire, MD, MPH

Safety Advisor

Seikagaku

Condoliase Safety Database Meets FDA Requirement for Exposures and Duration

Phase	Countries	Study	Design	Exposure to Condoliase ≥ 1.25 U	Follow up Duration		
					≥ 26 weeks	≥ 52 weeks	≥ 104 weeks
2	US	1121	Open-label	12	–	–	–
2 / 3	Japan	1021	Double-blind, Placebo-control	147	–	–	–
3	Japan	1031	Double-blind, Placebo-control	82	–	–	–
3	US	1131	Double-blind, Sham injection-control	280	253	231	204
3	US and EU	1132	Open-label	991	703	–	–
3	US	1133	Double-blind, Sham injection-control	167	145	95	–
Total				1,679	1,101	326	204
FDA Requirement				1,500	1,000	300	150

Four Phase 2/3 RCTs Support Safety

Study 1021

Phase 2/3
52-Week Study
(Japan)

Supports Safety

Condoliase vs Placebo

1.25 U (N = 49)	Saline (N = 47)
2.5 U (N = 50)	
5.0 U (N = 49)	

Study 1031

Phase 3
52-Week Study
(Japan)

Supports Efficacy
Supports Safety

Condoliase vs Placebo

1.25 U (N = 84)	Saline (N = 82)

Study 1131

Phase 3
104-Week Study
(US)

Supports Safety

Condoliase vs Sham

1.25 U (N = 290)	**-** (N = 95)

Study 1133

Phase 3
52-Week Study
(US)

Supports Efficacy
Supports Safety

Condoliase vs Sham

1.25 U (N = 176)	**-** (N = 176)

Pooled Ph 2/3 RCTs: Summary of Safety

	Up to Week 13		After Week 13 to Week 26		After Week 26 to Week 52	
	Condoliase (N = 578)	**Placebo / Sham** (N = 396)	**Condoliase** (N = 421)	**Placebo / Sham** (N = 252)	**Condoliase** (N = 388)	**Placebo / Sham** (N = 233)
Any AEs	381 **(66%)**	215 **(54%)**	94 **(22%)**	41 **(16%)**	113 **(29%)**	67 **(29%)**
Treatment-related AEs	149 **(26%)**	52 **(13%)**	6 **(1%)**	2 **(0.8%)**	11 **(3%)**	3 **(1%)**
Severe AEs	33 **(6%)**	19 **(5%)**	9 **(2%)**	7 **(3%)**	8 **(2%)**	4 **(2%)**
SAEs	15 **(3%)**	13 **(3%)**	9 **(2%)**	6 **(2%)**	14 **(3%)**	6 **(2%)**
Treatment-related SAEs	1 **(0.2%)**	0	0	0	0	0
AEs leading to discontinuation	3 **(0.5%)**	9 **(2%)**	3 **(0.7%)**	2 **(0.8%)**	0	1 **(0.4%)**
Deaths	0	0	1 **(0.2%)**	1 **(0.4%)**	1 **(0.3%)**	0

Phase 2/3 RCTs: Studies 1021, 1031, 1131, 1133; For 1021 and 1031, only SAEs and AEs related to IV disc were recorded after Week 13. Therefore, subjects at risk for SAEs (>13 to 26 weeks) were 538 for condoliase and 359 for control; subjects at risk for SAEs (>26 to 52 weeks) were 493 for condoliase and 333 for control. Control includes pooled results from placebo and sham injection.

Pooled Ph 2/3 RCTs: AEs Occurring Up to Week 13 (≥ 3% of Patients)

Preferred Term	Up to Week 13	
	Condoliase (N = 578)	Placebo / Sham (N = 396)
Any AE	381 **(66%)**	215 **(54%)**
Back pain	133 **(23%)**	59 **(15%)**
MRI spinal abnormal (Modic changes)	107 **(19%)**	12 **(3%)**
Pain in extremity	65 **(11%)**	48 **(12%)**
Nasopharyngitis	34 **(6%)**	16 **(4%)**
Spinal x-ray abnormal	29 **(5%)**	7 **(2%)**
Injection site pain	27 **(5%)**	16 **(4%)**
Arthralgia	24 **(4%)**	12 **(3%)**

Phase 2/3 RCTs: Studies 1021, 1031, 1131, 1133

Pooled Ph 2/3 RCTs: Back Pain AEs by Time of Onset

	Condoliase (N = 578)	Placebo / Sham (N = 396)
At least one back pain AE at any time	157 **(27%)**	87 **(22%)**
Onset ≤ 7 days after injection	88 **(15%)**	30 **(8%)**
Onset > 7 days after injection	94 **(16%)**	63 **(16%)**

Pooled Ph 2/3 RCTs: AEs Occurring After Week 13 (≥ 3% of Patients)

Preferred Term	After Week 13 to Week 26		After Week 26 to Week 52	
	Condoliase (N = 421)	Placebo / Sham (N = 252)	Condoliase (N = 388)	Placebo / Sham (N = 233)
Any AE	94 **(22%)**	41 **(16%)**	113 **(29%)**	67 **(29%)**
MRI spinal abnormal (Modic changes)	17 **(4%)**	3 **(1%)**	29 **(8%)**	10 **(4%)**
Back pain	4 **(1%)**	7 **(3%)**	9 **(2%)**	7 **(3%)**
Arthralgia	4 **(1%)**	2 **(0.8%)**	4 **(1%)**	7 **(3%)**
COVID-19	4 **(1%)**	4 **(2%)**	3 **(0.8%)**	8 **(3%)**

Phase 2/3 RCTs: Studies 1021, 1031, 1131, 1133

Pooled Ph 2/3 RCTs: SAEs Up to Week 13 (≥ 2 Patients)

Preferred Term	Up to Week 13	
	Condoliase (N = 578)	Placebo / Sham (N = 396)
≥ 1 SAE	15 **(3%)**	13 **(3%)**
Intervertebral disc protrusion	2 **(0.3%)**	3 **(0.8%)**
Back pain	2 **(0.3%)**	0
Lumbar radiculopathy	2 **(0.3%)**	0
Pain in extremity	0	2 **(0.5%)**
Sciatica	0	2 **(0.5%)**

Phase 2/3 RCTs: Studies 1021, 1031, 1131, 1133

Pooled Ph 2/3 RCTs: SAEs After Week 13 (≥ 2 Patients)

Preferred Term	After Week 13 to Week 26		After Week 26 to Week 52	
	Condoliase (N = 538)	Placebo / Sham (N = 359)	Condoliase (N = 493)	Placebo / Sham (N = 333)
Any SAE	9 **(2%)**	6 **(2%)**	14 **(3%)**	6 **(2%)**
Intervertebral disc protrusion	2 **(0.4%)**	2 **(0.6%)**	2 **(0.4%)**	0

Phase 2/3 RCTs: Studies 1021, 1031, 1131, 1133

Pooled Ph 2/3 RCT: Long-Term AEs (≥ 2% of Patients)

Preferred Term	After Week 52	
	Condoliase (N = 229)	Sham (N = 78)
Any AE	75 **(33%)**	20 **(26%)**
MRI spinal abnormal (Modic changes)	19 **(8%)**	8 **(10%)**
Back pain	10 **(4%)**	4 **(5%)**
Spinal x-ray abnormal	5 **(2%)**	1 **(1%)**
Pain in extremity	3 **(1%)**	3 **(4%)**
Hypercholesterolemia	0	2 **(3%)**

After Week 52 only includes Study 1131 which had 104-week observation period

Select Safety Topics of Interest*

Hypersensitivity / Anaphylaxis

Spinal Abnormality AEs

*Prespecified safety topics of interest included:
Anaphylaxis, Discitis, Hematomas, Hypersensitivity, Medication Error, Osteomyelitis, Paresis and Paralysis, Spinal Abnormalities

Pooled Ph 2/3 RCTs: Hypersensitivity AEs: All Time Intervals (≥ 2 Patients)

Preferred Term	Condoliase (N = 578)	Placebo / Sham (N = 396)
Hypersensitivity (SMQ)	22 **(4%)**	13 **(3%)**
Rash	11 **(2%)**	3 **(0.8%)**
Dermatitis contact	3 **(0.5%)**	1 **(0.3%)**
Urticaria	3 **(0.5%)**	1 **(0.3%)**
Toxic skin eruption	2 **(0.3%)**	0
Eczema	0	2 **(0.5%)**
Anaphylactic reaction (SMQ)	0	0

Phase 2/3 RCTs: Studies 1021, 1031, 1131, 1133

Pooled Ph 2/3 RCT: Few Spinal Abnormality AEs Reported

All Time Intervals	Condoliase (N = 578)	Placebo / Sham (N = 396)
Spinal abnormalities of interest	5 **(0.9%)**	5 **(1%)**
Spinal compression fracture	0	2 **(0.5%)**
Spinal osteoarthritis	3 **(0.5%)**	1 **(0.3%)**
Spinal retrolisthesis	1 **(0.2%)**	1 **(0.3%)**
Spondylolisthesis	1 **(0.2%)**	0
Vertebral foraminal stenosis	0	1 **(0.3%)**

Phase 2/3 RCTs: Studies 1021, 1031, 1131, 1133

Pooled Ph 2/3 RCT: Spinal Abnormality AEs Over Time

	Up to Week 13		After Week 13 to Week 26		After Week 26 to Week 52	
	Condoliase (N = 578)	**Placebo / Sham** (N = 396)	**Condoliase** (N = 421)	**Placebo / Sham** (N = 252)	**Condoliase** (N = 388)	**Placebo / Sham** (N = 233)
Spinal abnormalities of interest	1 **(0.2%)**	0	1 **(0.2%)**	0	1 **(0.3%)**	5 **(2%)**
Spinal osteoarthritis	1 **(0.2%)**	0	1 **(0.2%)**	0	0	1 **(0.4%)**
Spinal compression fracture	0	0	0	0	0	2 **(0.9%)**
Spinal retrolisthesis	0	0	0	0	1 **(0.3%)**	1 **(0.4%)**
Vertebral foraminal stenosis	0	0	0	0	0	1 **(0.4%)**

Phase 2/3 RCTs: Studies 1021, 1031, 1131, 1133

Safety Summary: Condoliase Well-Tolerated in Patients with Radicular Leg Pain Associated with LDH

- Most AEs mild or moderate in severity
- SAE rates consistent between condoliase and control groups
- AEs contained in hypersensitivity SMQ infrequent, with most mild to moderate
- No reports of anaphylaxis

Post-Marketing Safety in ~27,000 Patients[1] Aligns with Safety Profile Observed in Clinical Trials

Preferred Term (≥ 5 Events)	Unsolicited		Solicited	
	Non-Serious	Serious	Non-Serious	Serious
Any Adverse Drug Reaction	176	77	336	80
Rash	45	2	21	1
Back pain	24	7	107	11
Urticaria	21	3	32	2
Pruritus	11	1	4	0
Drug eruption	10	6	13	0
Pain in extremity	9	8	36	12
Erythema	6	1	3	0
Pyrexia	5	2	2	0
Nausea	4	2	3	1
Intervertebral discitis	1	8	3	4
Intervertebral disc protrusion	1	3	23	20
Lumbar spinal stenosis	1	1	4	2
Musculoskeletal pain	0	1	6	1
MRI abnormal	0	1	5	0
Intervertebral disc disorder	0	0	11	2
Intervertebral disc space narrowing	0	0	9	2
Vertebral osteophyte	0	0	6	0

- 3 events in Anaphylactic Reaction (SMQ - Narrow) reported in post-marketing safety

1. Data cutoff March 2024

Patients and Clinicians will be Informed on Risk for Hypersensitivity and Anaphylaxis

- Included in Warnings and Precautions section of label
- Post-injection monitoring consistent with other interventional spinal injections
- Patient leaflet advising patients to seek treatment should they experience rash or serious hypersensitivity symptoms

Disc-Related Imaging Findings

Thomas Fuerst, PhD

Chief Science Officer, Clario

Consultant to Seikagaku

Systematic Evaluation of Disc Images

Screening	Week 13	Week 26	Week 52	Week 104
X-ray & MRI	X-ray & MRI	X-ray & MRI	X-ray & MRI	X-ray & MRI
		Not in Study 1133		*Study 1131 only*

Evaluation of Disc Images to Evaluate Prespecified Changes

- Prespecified imaging assessments by central reader, irrespective of symptomatology
  - X-ray: Decrease in disc height from baseline ≥ 30%
  - X-ray: Intervertebral body angle in flexion ≥ 5°
  - X-ray: Vertebral body translation ≥ 3 mm
  - MRI: Modic change in adjacent vertebral bodies

Modic Type 1	Modic Type 2	Modic Type 3
Inflammation: *Increased signal on fluid-sensitive sequences*	Fat Conversion: *Increased signal on fat-sensitive sequences*	Bony Sclerosis: *Decreased signal on all sequences*

Pooled Ph 2/3 RCT: Disc-Related Imaging Changes on X-Rays

Imaging Change, % of Patients	Week 13		Week 26		Week 52		Week 104	
	Condoliase	Placebo / Sham	Condoliase	Placebo / Sham	Condoliase	Placebo / Sham	Condoliase	Placebo / Sham
Decrease in disc height from baseline ≥ 30%	4% (20 / 512)	0 (0 / 350)	6% (21 / 329)	0 (0 / 176)	6% (27 / 438)	0.3% (1 / 291)	7% (14 / 192)	0 (0 / 71)
Intervertebral body flexion angle ≥ 5°	1% (7 / 514)	0.6% (2 / 349)	2% (8 / 331)	2% (4 / 175)	3% (11 / 437)	2% (7 / 288)	0.5% (1 / 192)	0 (0 / 71)
Vertebral body translation of ≥ 3 mm	0.2% (1 / 512)	1% (5 / 347)	0.9% (3 / 329)	1% (2 / 175)	0.9% (4 / 434)	0.3% (1 / 288)	0.5% (1 / 190)	0 (0 / 71)

Phase 2/3 RCTs: Studies 1021, 1031, 1131, 1133; Week 26 not in Study 1133; Week 104 only includes Study 1131

Pooled Ph 2/3 RCT: New Disc-Related Imaging Changes by Modic Type

	Pre-Existing Modic		New Modic Changes Since Baseline							
	Baseline		Week 13		Week 26		Week 52		Week 104	
% of Patients	Condoliase	Placebo / Sham	Condoliase	Placebo / Sham	Condoliase	Placebo / Sham	Condoliase	Placebo / Sham	Condoliase	Placebo / Sham
Modic Type 1	24% (137 / 577)	18% (73 / 396)	27% (104 / 391)	5% (13 / 286)	30% (75 / 253)	10% (14 / 147)	32% (106 / 334)	15% (34 / 232)	28% (41 / 146)	12% (6 / 50)
Modic Type 2	17% (98 / 577)	19% (75 / 396)	0.5% (2 / 432)	0 (0 / 286)	2% (6 / 270)	0 (0 / 139)	4% (15 / 358)	0.9% (2 / 232)	12% (18 / 147)	10% (5 / 48)
Modic Type 3	0.7% (4 / 577)	0.8% (3 / 396)	0 (0 / 518)	0 (0 / 348)	0 (0 / 333)	0 (0 / 177)	0 (0 / 436)	0 (0 / 288)	0 (0 / 192)	0 (0 / 67)

No consistent relationship between Modic changes and leg or back pain

Phase 2/3 RCTs: Studies 1021, 1031, 1131, 1133; Week 26 not in Study 1133; Week 104 only includes Study 1131

Condoliase Imaging Changes Similar to Discectomy at 1 Year

Imaging Finding	Discectomy	Condoliase
New Modic Type 1 incidence	25% [1]	32%
New Modic Type 2 incidence	13% [1]	4%
New Modic Type 3 incidence	1% [1]	0
Mean disc height loss, CFB	5 – 21% [2]	15%

1. Bostelmann et al., 2019; 2. Chen et al., 2021; CFB = change from baseline

Clinical Perspective

Kee D Kim, MD

Professor of Neurological Surgery

Chief, Spinal Neurosurgery

Co-Director, UC Davis Spine Center

Independent Evaluation of Imaging

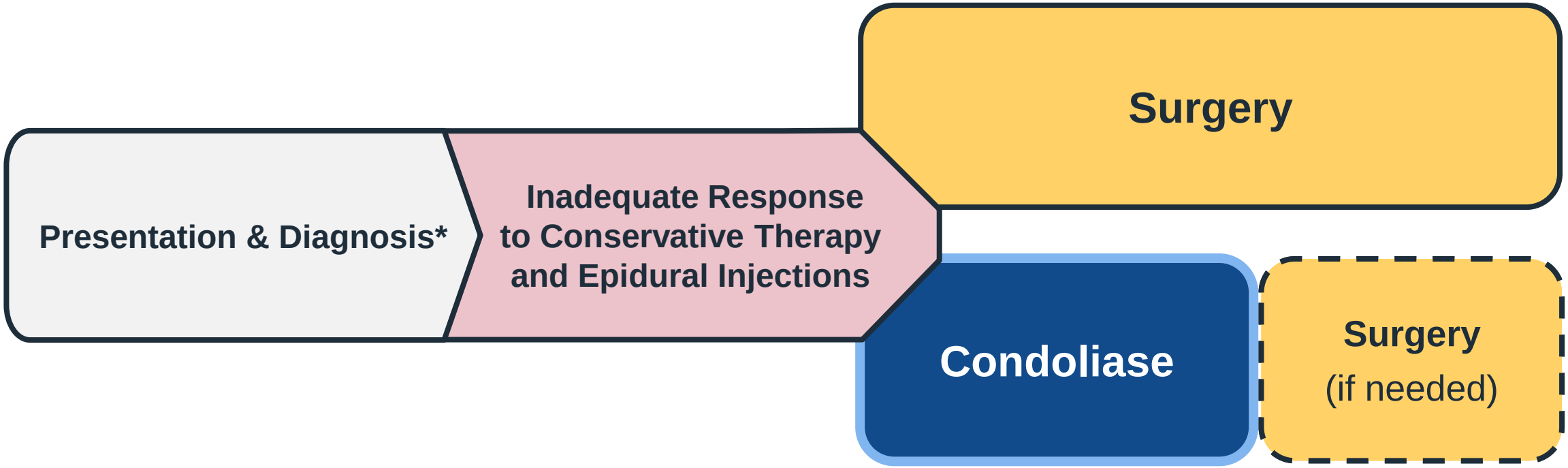
- Reviewed patient profiles for all cases exceeding prespecified thresholds (n = 326)*
  - Decrease in disc height from baseline ≥ 30%
  - Intervertebral posterior angle flexion ≥ 5°
  - Vertebral body translation of ≥ 3 mm
  - Modic change (Type 1 – 3)
- All patients who had lumbar spine surgery at treated level (n = 56)
- Reviewed demographics, concomitant medications, medical history, AEs, neurological exams, ODI, leg and back pain VAS plots

*Includes Studies 1021, 1031, 1131, 1133

Imaging Findings Not Linked to Risk for Incremental Pain or Loss of Function

- Disc height loss and new Modic changes may occur with the natural history of LDH
  - Individual variation regarding patient outcomes
- No clear association between imaging findings and clinical outcomes
  - No differences in worst leg pain or ODI through 1 year
    - Continued through post-study follow-up out to 5 years
  - Some patients with Modic Type 1 changes had concurrent back pain in both treatment groups
- Observed change align with condoliase MoA and natural course
  - Magnitude not predictive of functional impairment

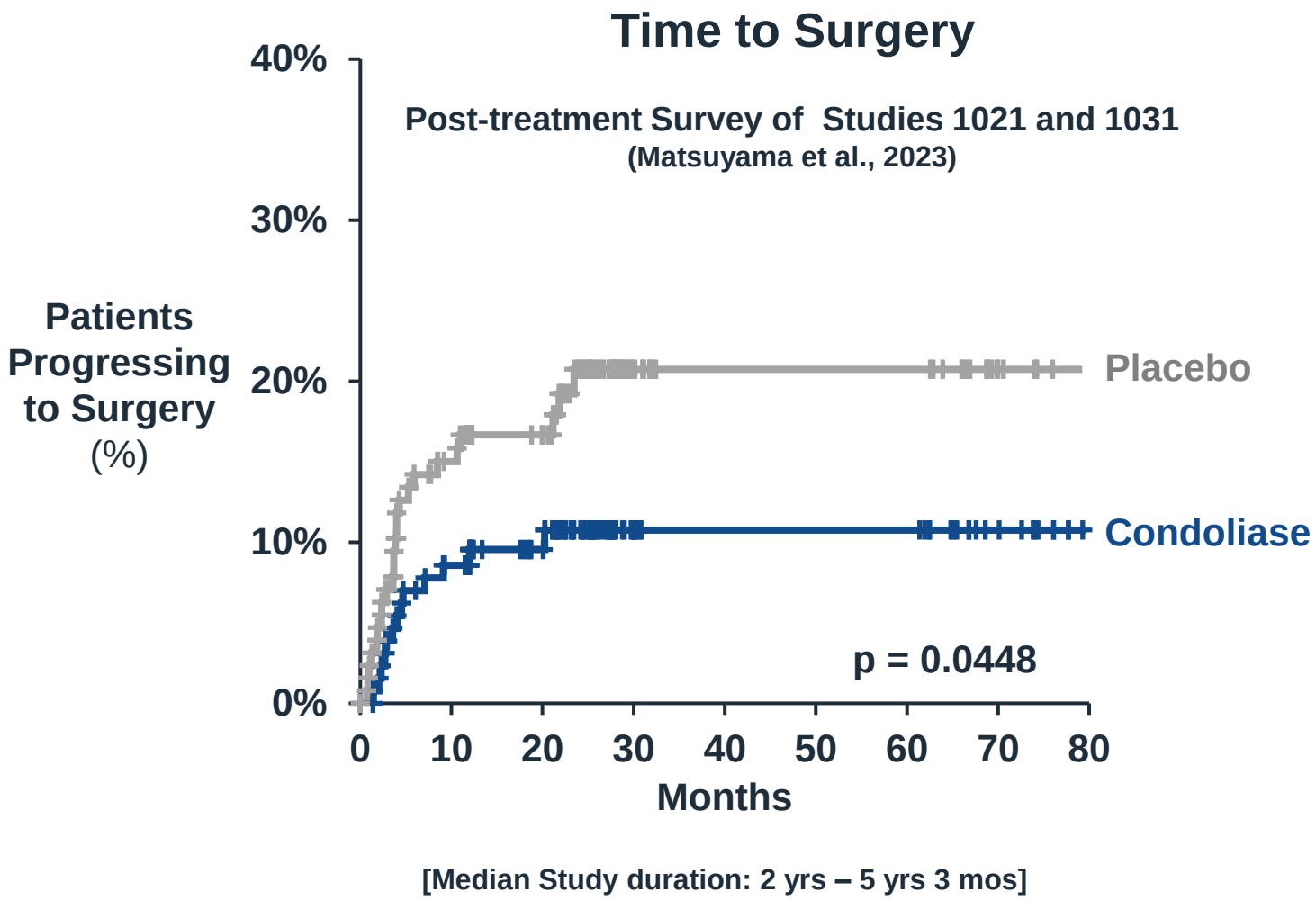
Patients with Inadequate Response to Conservative Therapy Need Non-Surgical Option



*Patients with significant motor deficit and/or cauda equina syndrome should be promptly evaluated for surgery

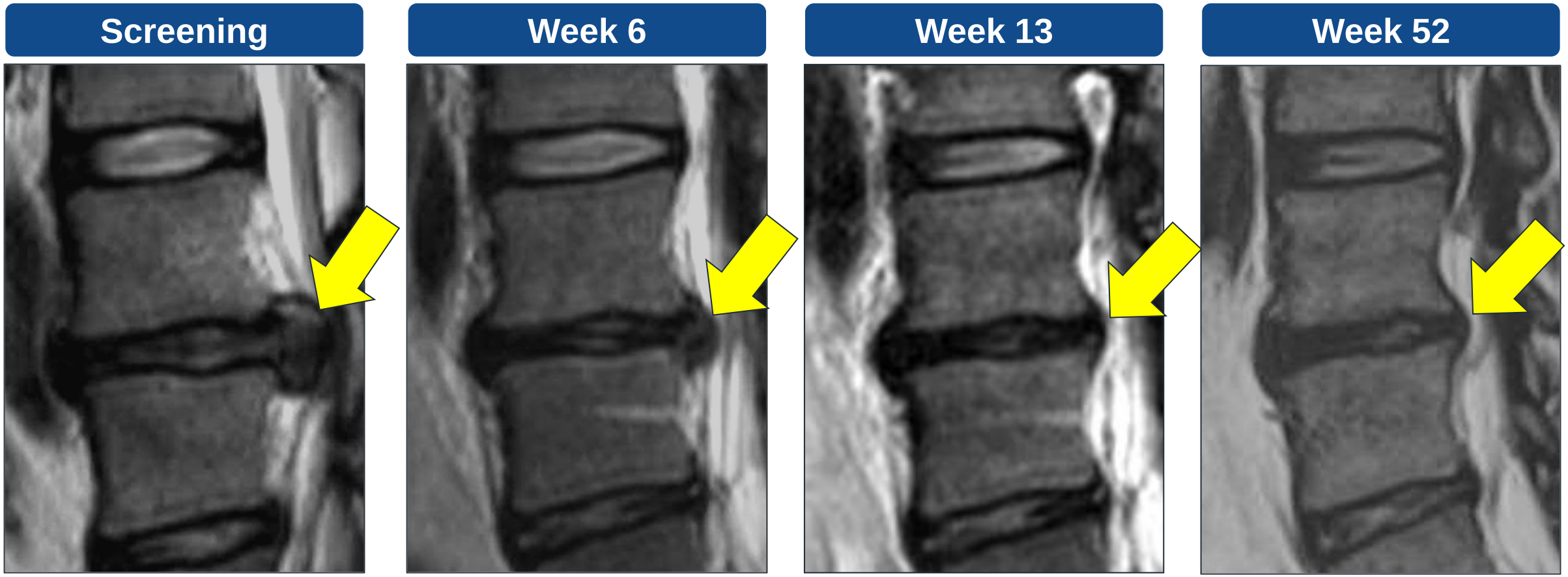
Avoidance of Surgery is Important Goal for Many Patients with Leg Pain due to LDH

- Some patients don't want surgery or are unwilling to accept risks
- Condoliase provides an effective and well-tolerated option for patients



[Median Study duration: 2 yrs – 5 yrs 3 mos]

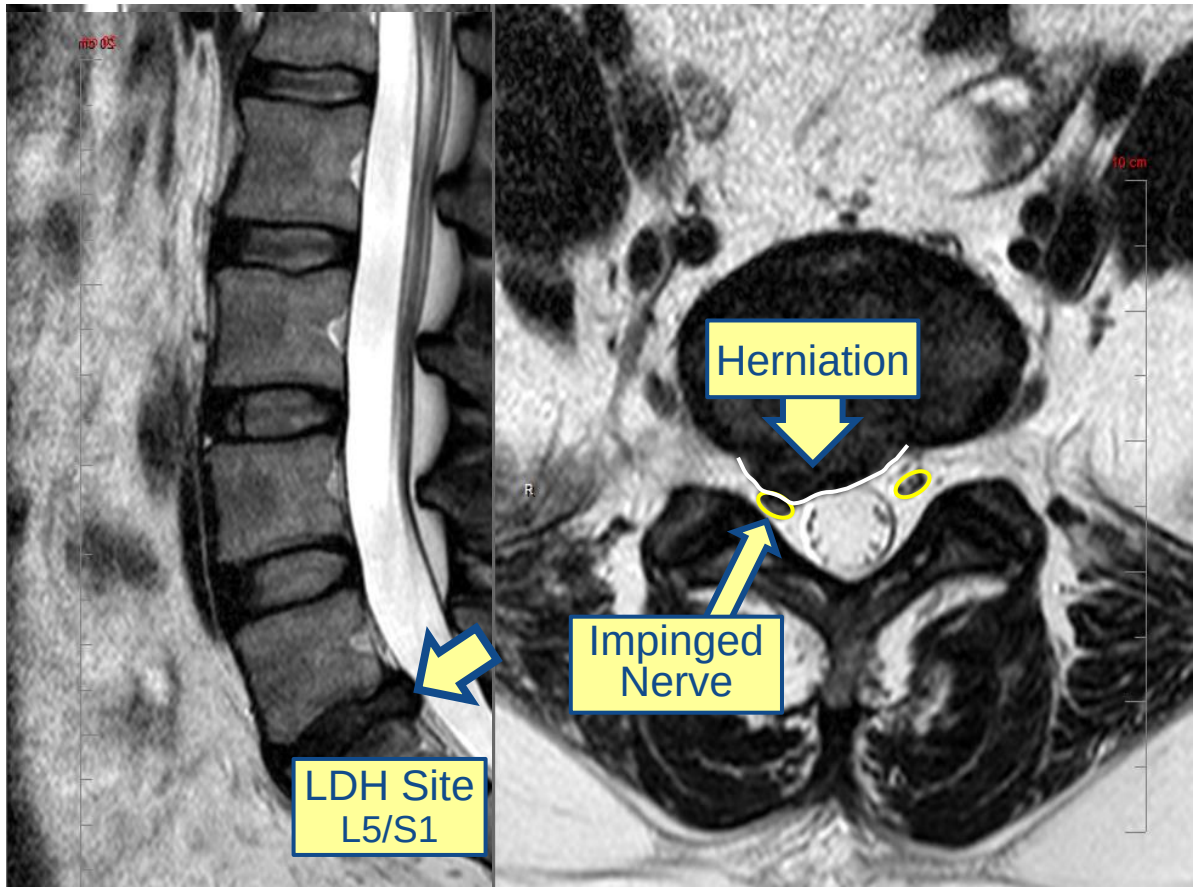
Condoliase Provides Meaningful Improvement by Relieving LDH, Alleviating Radicular Leg Pain



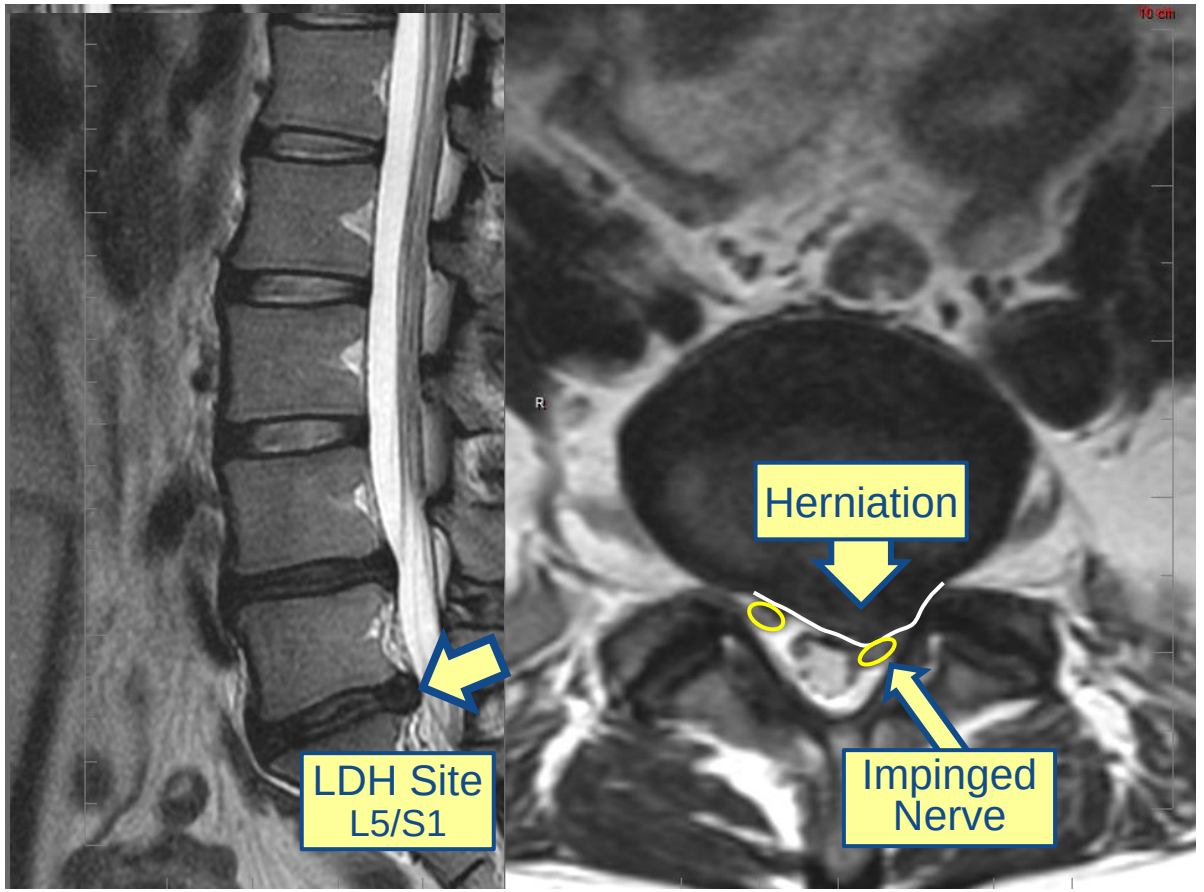
Sagittal T2 FSE (L4/L5); Patient from Study 1031

Confirmation of Visible Nerve Impingement is Important for Patient Selection

Example 1



Example 2



Images from Study 1133

Benefit-Risk Conclusion

Joe Stauffer, DO, MBA, FAPCR

Chief Medical Advisor

Seikagaku

Positive Condoliase Benefit-Risk Assessment

Clear unmet need for effective and safe therapy for radicular leg pain in patients with LDH

Benefits

- Met primary endpoint in 2 pivotal studies
- Significant, clinically meaningful improvement in relief of worst leg pain compared with control
  - Durable up to 12 months
- Reduction in herniation volume and improvement in function at Week 13 that persisted over time

Risks

- Well-tolerated with acceptable safety profile for patients with LDH associated radicular leg pain
  - Hypersensitivity warning, including anaphylaxis
- Safety profile supported by clinical use and post-marketing surveillance in ~ 29,000 patients

Labeling and Awareness of Study Results Will Reinforce Use in Appropriate Patients

- Appropriate patients treated with condoliase have
  - ✓ Inadequate response to conservative therapy
  - ✓ Radiologically confirmed, visible nerve root impingement
- Patients unresponsive to conservative therapy will be treated by trained specialist who is experienced with spine injections
- Awareness that patients without impingement are unlikely to benefit will prompt confirmation of nerve impingement

Condoliase for the Treatment of Radicular Leg Pain Associated with Radiologically Confirmed Nerve Root Impingement Caused by Lumbar Disc Herniation (LDH) in Adults

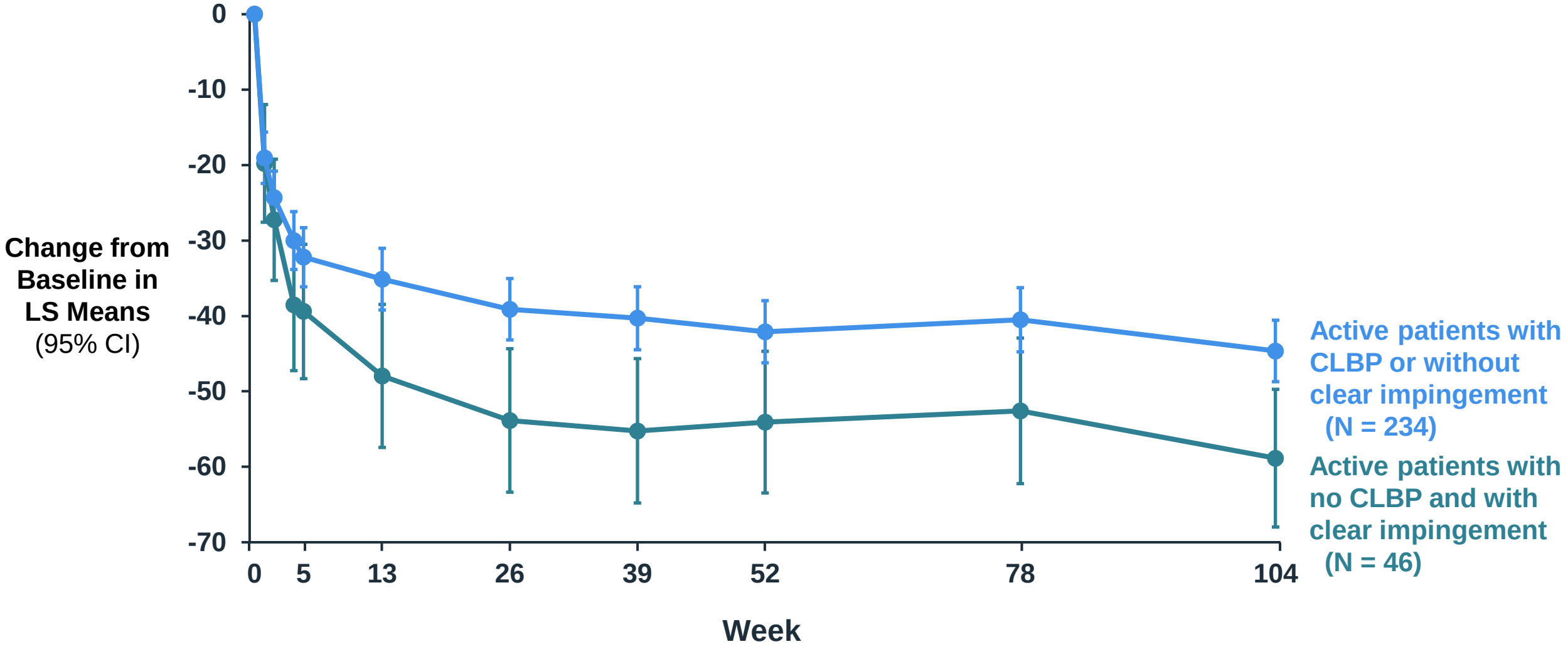
January 10, 2025

Anesthetic and Analgesic Drug Products Advisory Committee

Seikagaku Corp.

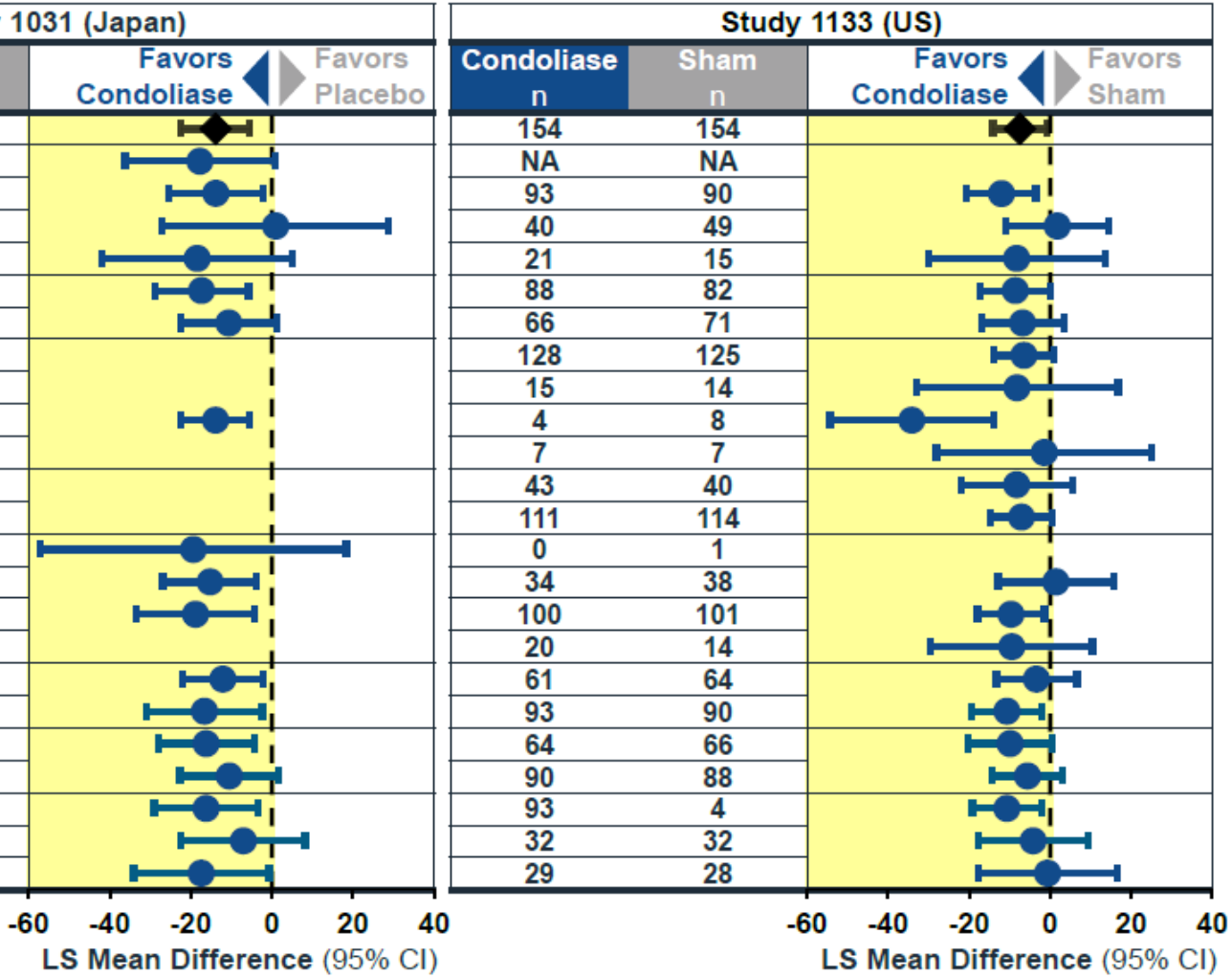
Q&A Slides Shown

Study 1131: Change from Baseline for Worst Leg Pain by Subgroup (CLBP, Impingement)



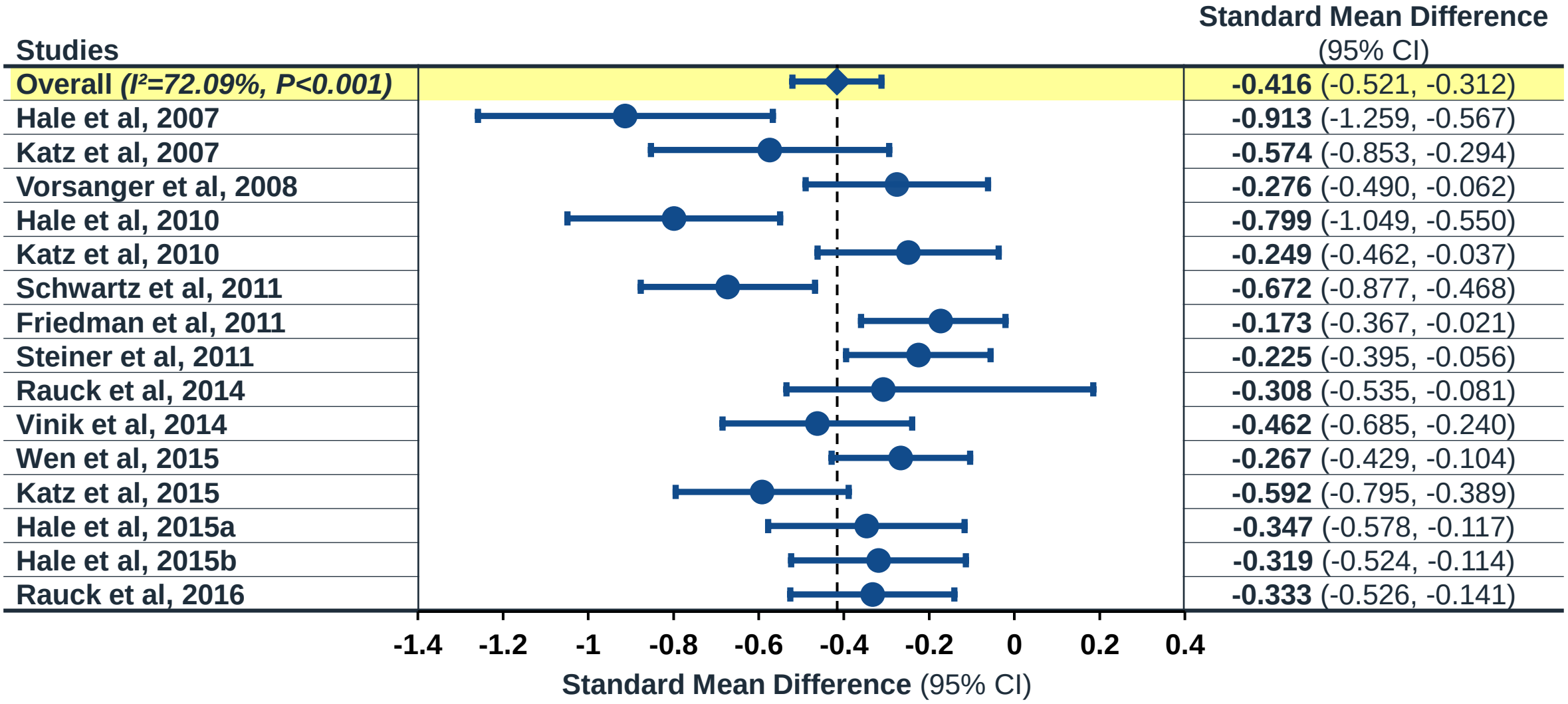
SKK Figure 32: Comparison of Primary Efficacy Results in Subgroups — Pivotal Phase 3 Studies (mITT)

Subgroup		Study 1031 (Japan) Condoliase n	Study 1031 (Japan) Placebo n	Study 1133 (US) Condoliase n	Study 1133 (US) Sham n
Overall		76	70	154	154
Age	20 – 29 years	12	19	NA	NA
	30 – 49 years	48	37	93	90
	50 – 59 years	10	7	40	49
	≥ 60 years	6	7	21	15
Sex	Male	46	40	88	82
	Female	30	30	66	71
Race	White	NA	NA	128	125
	Black or African American	NA	NA	15	14
	Asian	76	70	4	8
	Other	NA	NA	7	7
Ethnicity	Hispanic or Latino	NA	NA	43	40
	Not Hispanic or Latino	NA	NA	111	114
BMI category	< 18.5 kg/m²	4	5	0	1
	18.5 to < 25.0 kg/m²	46	40	34	38
	25.0 to < 35.0 kg/m²	26	25	100	101
	≥ 35 kg/m²	0	0	20	14
Height	< 170 cm	43	39	61	64
	≥ 170 cm	33	31	93	90
Disc level	L4 – L5	42	32	64	66
	L5 – S1/L6	34	38	90	88
Smoking history	Never smoked	36	31	93	4
	Past smoker	24	14	32	32
	Current smoker	16	25	29	28



BMI: body-mass index; CI: confidence interval; LS: least squares; mITT: modified intent to treat; NA: not applicable.

Effect Size (Opioids)



Patients With and Without Modic 1 Type Changes with Back Pain TEAEs Grouped by Time of Onset

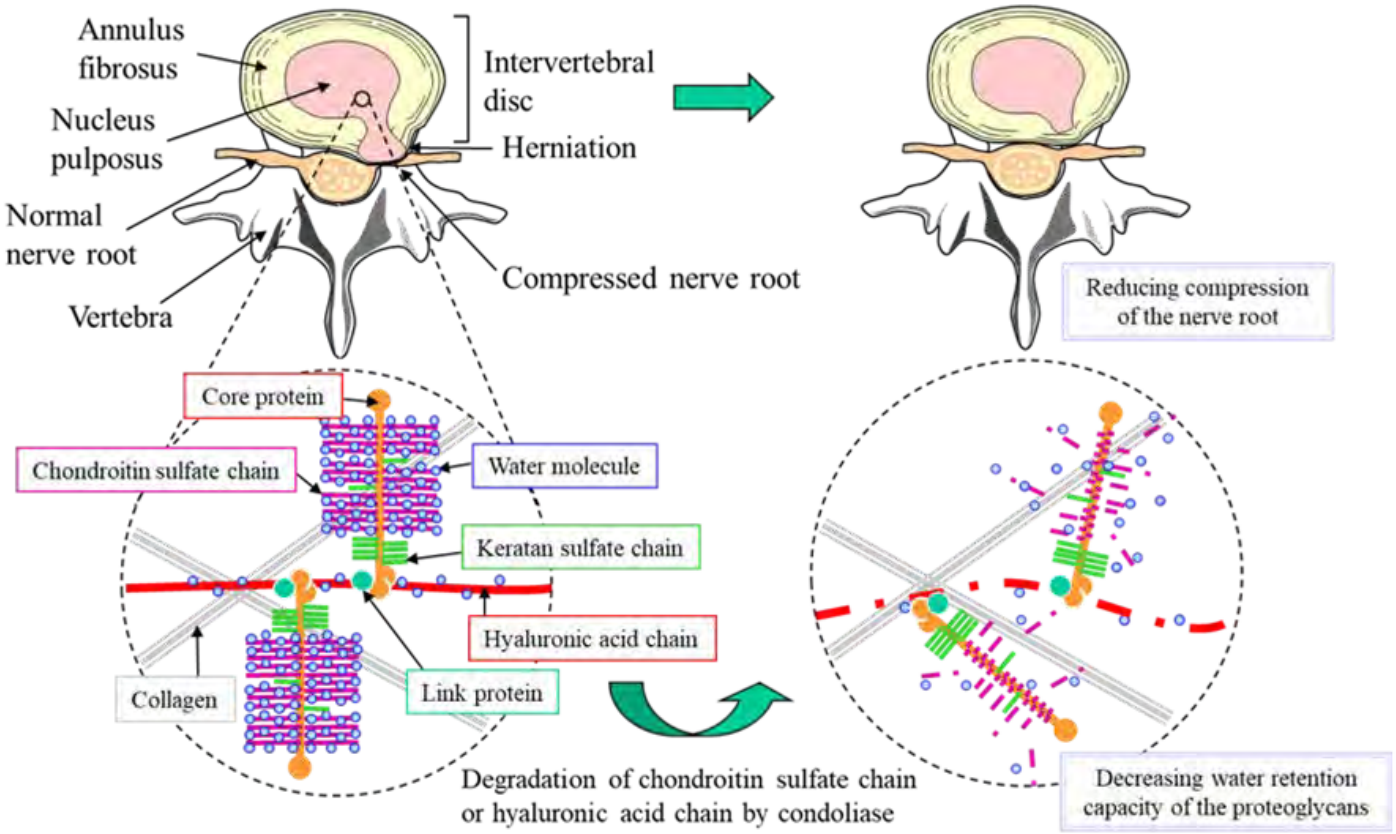
	Condoliase 1.25 U		Placebo / Sham	
	No Modic Type 1 Change (N = 261)	Modic Type 1 Change (N = 140)	No Modic Type 1 Change (N = 244)	Modic Type 1 Change (N = 37)
At least One Back Pain TEAE				
Any Time	70 **(27%)**	42 **(30%)**	48 **(20%)**	10 **(27%)**
Onset ≤ 7 Days after Injection	41 **(16%)**	22 **(16%)**	17 **(7%)**	3 **(8%)**
Onset > 7 Days after Injection	40 **(15%)**	27 **(19%)**	35 **(14%)**	8 **(22%)**

Phase 3 RCTs: Studies 1031, 1131, 1133

Pivotal Studies: Responder Analysis ODI (≥20-point Improvement) at Week 13

	Study 1031 (Japan)		Study 1133 (US)	
	Condoliase (N = 82)	**Placebo** (N = 81)	**Condoliase** (N = 169)	**Sham** (N = 172)
ODI score	38 **(46%)**	30 **(37%)**	111 **(66%)**	97 **(56%)**

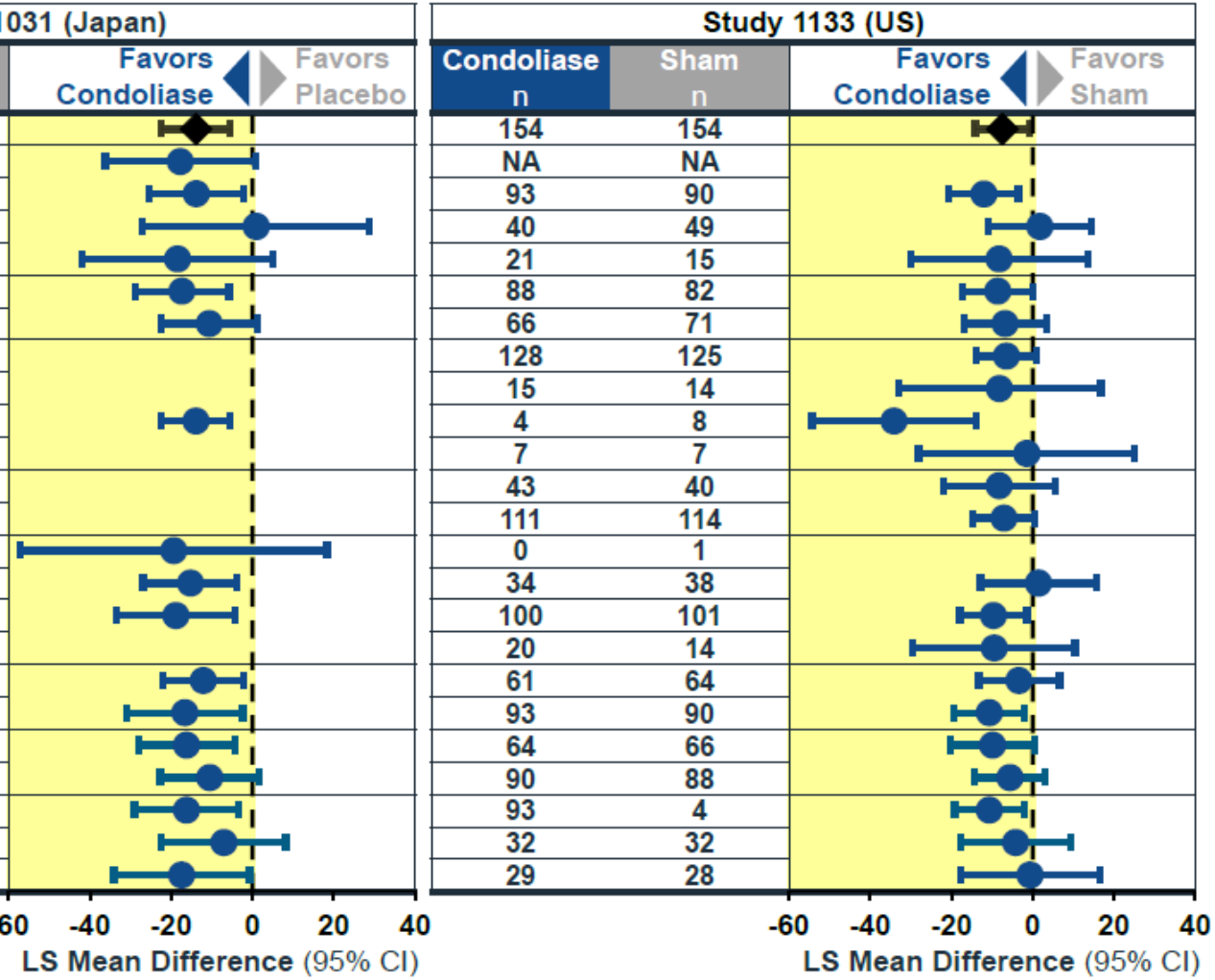
SKK Figure 18: Predicted Effects on Proteoglycan by Condoliase



Left Side: Model of proteoglycan in nucleus pulposus. Proteoglycan is rich in chondroitin sulfate, a component of glycosaminoglycan, which holds a large number of water molecules. From this, nucleus pulposus functions as a shock absorber that absorbs a physical load on the vertebral body.
Right Side: Model of proteoglycan in nucleus pulposus after administration of condoliase. After administration of condoliase, chondroitin sulfate chain and hyaluronic acid chain in proteoglycan of nucleus pulposus are degraded. This degradation reduces high water retention in proteoglycan, suppressing disc pressure and leading to pressure reduction of nerve root in lumbar disc herniation.

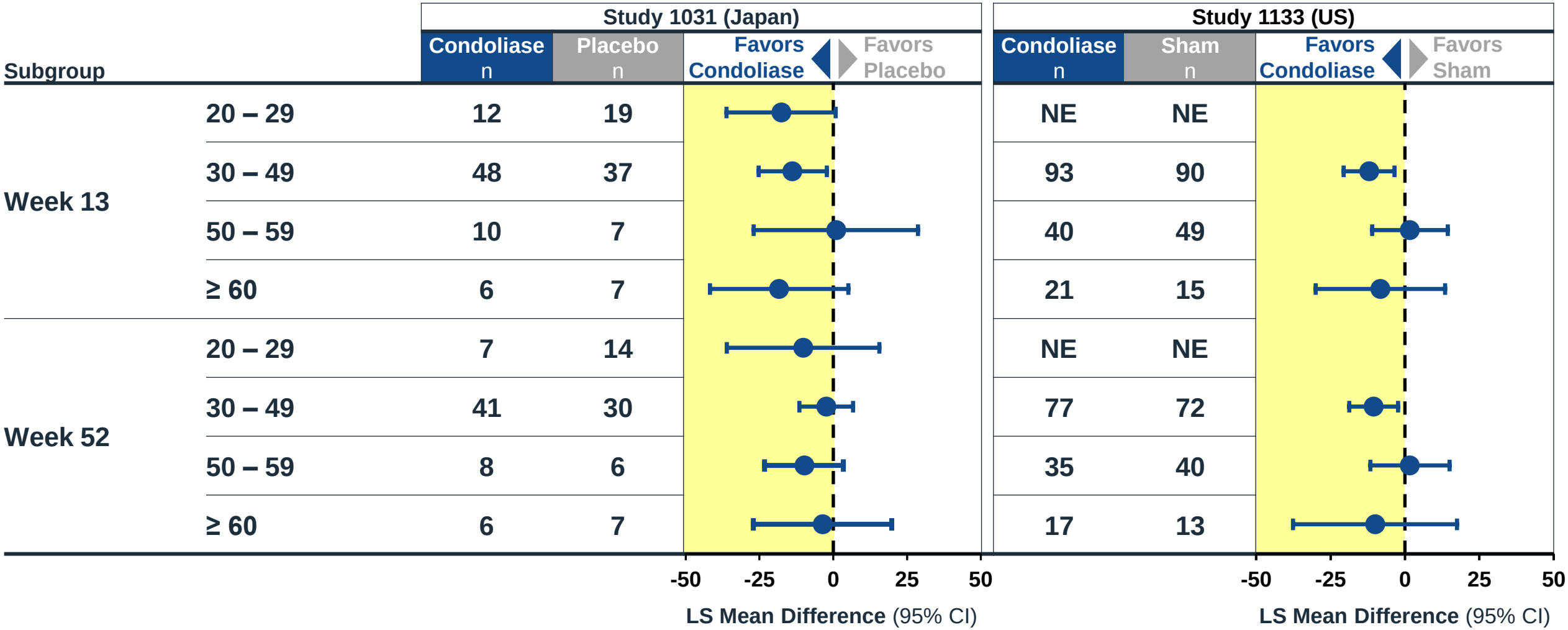
SKK Figure 32: Comparison of Primary Efficacy Results in Subgroups — Pivotal Phase 3 Studies (mITT)

Subgroup		Study 1031 (Japan) Condoliase n	Study 1031 (Japan) Placebo n	Study 1133 (US) Condoliase n	Study 1133 (US) Sham n
Overall		76	70	154	154
Age	20 – 29 years	12	19	NA	NA
	30 – 49 years	48	37	93	90
	50 – 59 years	10	7	40	49
	≥ 60 years	6	7	21	15
Sex	Male	46	40	88	82
	Female	30	30	66	71
Race	White	NA	NA	128	125
	Black or African American	NA	NA	15	14
	Asian	76	70	4	8
	Other	NA	NA	7	7
Ethnicity	Hispanic or Latino	NA	NA	43	40
	Not Hispanic or Latino	NA	NA	111	114
BMI category	< 18.5 kg/m²	4	5	0	1
	18.5 to < 25.0 kg/m²	46	40	34	38
	25.0 to < 35.0 kg/m²	26	25	100	101
	≥ 35 kg/m²	0	0	20	14
Height	< 170 cm	43	39	61	64
	≥ 170 cm	33	31	93	90
Disc level	L4 – L5	42	32	64	66
	L5 – S1/L6	34	38	90	88
Smoking history	Never smoked	36	31	93	4
	Past smoker	24	14	32	32
	Current smoker	16	25	29	28



BMI: body-mass index; CI: confidence interval; LS: least squares; mITT: modified intent to treat; NA: not applicable.

Pivotal Studies: Worst Leg Pain at Week 13 and Week 52 by Age (MMRM)



Condoliase Presence and Enzyme Activity Detectable in Injected Intervertebral Disc up to 30 Days

Retention of Condoliase in Intervertebral Disc Following Single Injection of Condoliase 2 U/disc Into L5/L6 of Dogs and Monkeys

Time After Injection (days)	Retention (% of Dose)			
	Dogs		Monkeys	
	EA	ELISA	EA	ELISA
3	30.9, 87.7	10.5, 28.9	NC, NC	28.4, 1.2
7	NC, NC	4.8, 9.2	NC, 21.7	NC, 33.4
14	NC, 55.1	NC, 27.5	NC, NC	9.7, 13.8
30	NC, NC	7.9, NC	NC, NC	4.3, 0.2
90	NC, NC	NC, NC	NC, NC	NC, NC

EA = enzyme activity; NC = not calculated due to a value below the lower limit of quantification
Expressed as individual values measured by EA and ELISA (n = 2)

Minimal and Reversible Findings Were Identified in Nonclinical Local Irritation Studies

Administration Route	Animal Species	Dose (fold clinical dose)	Results
Intramuscular	Rabbit	**7.5 U/site** (6x)	Slight irritant effect on the muscle tissue was observed. This effects showed a tendency of recovery.[1]
Subarachnoidal	Rabbit	**7.5 U/site** (6x)	No irritation effect due to condoliase[1]
Intradermal	Guinea pig	**8 U/site** (6.4x)	No irritation effect due to condoliase[2]
Spinal nerve root	Rabbit	**50 U/site** (40x)	No irritation effect due to condoliase[1]

[1] 2- and 7- days post-dose, [2] 3- days post-dose

- Slight irritation after intramuscular administration
- No irritation after subarachnoidal, spinal nerve root, or intradermal administration

SKK Table 5: Change from Baseline in Worst Leg Pain at Week 13 Using MMRM (MAR) Analysis — Pivotal Phase 3 Studies (mITT)

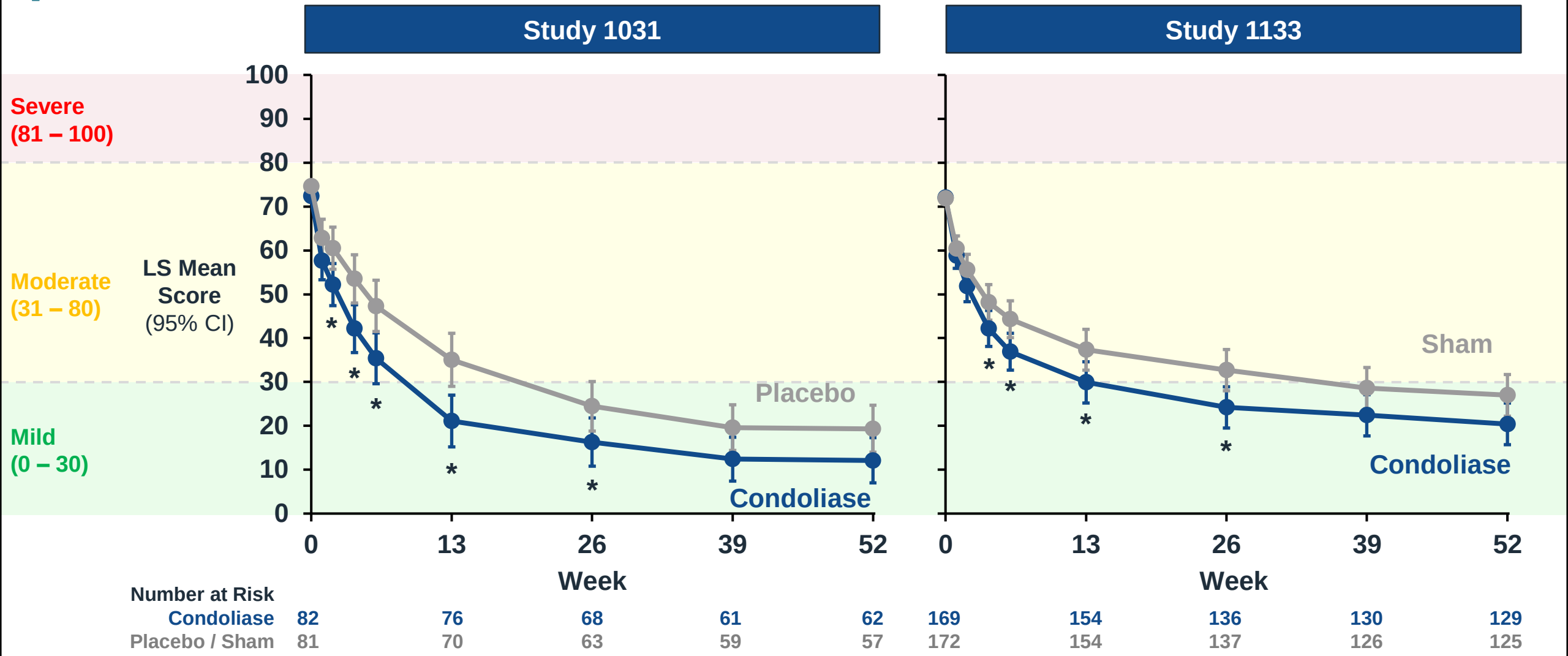
Worst Leg Pain, VAS:	Study 1031 (Japan)		Study 1133 (US)	
	Condoliase (N=82)	Placebo (N=81)	Condoliase (N=169)	Sham (N=172)
Baseline, mean (SD)	72.4 (12.29)	74.6 (12.48)	72.0 (9.55)	71.8 (9.75)
Week 13, LS mean (SE)	21.1 (2.97)	35.0 (3.05)	29.9 (2.38)	37.4 (2.36)
Change from Baseline, LS mean (SE)	-52.1 (2.97)	-38.2 (3.05)	-41.7 (2.38)	-34.2 (2.36)
95% CI	(-58.0, -46.3)	(-44.2, -32.2)	(-46.4, -37.0)	(-38.9, -29.6)
Treatment difference for condoliase vs control				
Difference in LS means (SE)	-13.9 (4.26)		-7.5 (3.35)	
95% CI	(-22.3, -5.5)		(-14.1, -0.9)	
p-value	0.0013		0.0263	

CI: confidence interval; LS: least squares; MAR: missing at random mITT: modified intent to treat; MMRM: mixed methods for repeated measures; SD: standard deviation; SE: standard error; VAS: visual analog scale.

Pivotal Studies: Similar Baseline Medication Use

	Study 1031 (Japan)		Study 1133 (US)	
	Condoliase (N = 82)	**Placebo** (N = 81)	**Condoliase** (N = 169)	**Sham** (N = 172)
Anti-inflammatory and anti-rheumatic products, non-steroids	77 **(94%)**	77 **(95%)**	124 **(73%)**	127 **(74%)**
Other analgesics and antipyretics	19 **(23%)**	19 **(24%)**	54 **(32%)**	64 **(37%)**
Muscle relaxants	15 **(18%)**	12 **(15%)**	24 **(14%)**	17 **(10%)**
Opioids	5 **(6%)**	9 **(11%)**	15 **(9%)**	9 **(5%)**
Antidepressants	2 **(2%)**	3 **(4%)**	15 **(9%)**	18 **(11%)**
Anxiolytics	2 **(2%)**	5 **(6%)**	4 **(2%)**	9 **(5%)**
Antiepileptics	0	1 **(1%)**	1 **(1%)**	2 **(1%)**

Pivotal Studies: Change in Weekly Averages of Worst Leg Pain Through Week 52



* Nominal p-value < 0.05

SKK Table 21: Primary Efficacy Analysis: Change from Baseline to Week 13 in Worst Leg Pain — Study 1131 (mITT)

Worst Leg Pain, VAS:	Condoliase (N=280)	Sham (N=94)
Baseline, n	279	93
Mean (SD)	74.4 (14.03)	76.7 (12.82)
Week 13, n	255	88
Change from Baseline		
LS mean (SE) change from Baseline	-37.7 (2.11)	-39.6 (3.36)
(95% CI)	(-41.8, -33.6)	(-46.2, -33.0)
Treatment difference for condoliase vs placebo		
LS mean (SE) treatment difference	1.9 (3.82)	
(95% CI)	(-5.6, 9.4)	
p-value	0.6212	

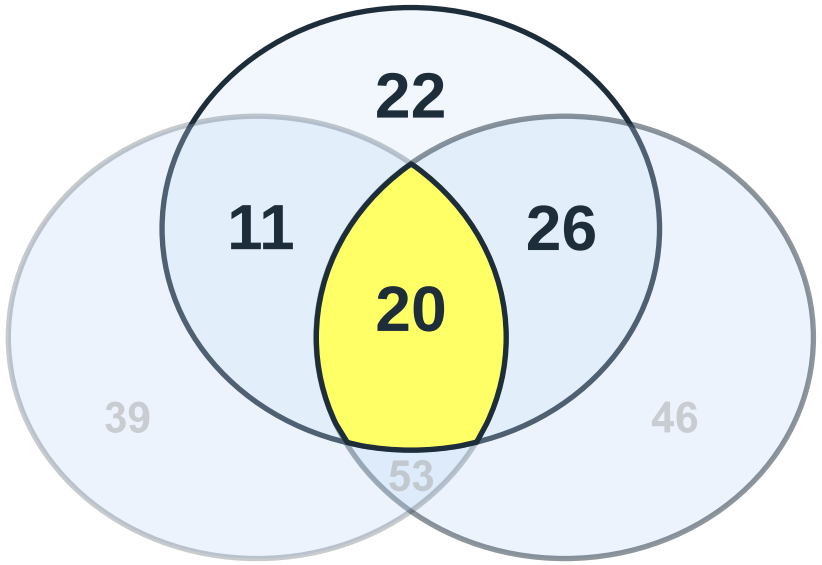
CI: confidence interval; ITT: intent to treat; LS: least square; SD: standard deviation; SE: standard error; VAS: visual analog scale

1. Mixed model: Change from baseline=baseline score, duration of leg pain (< 90 days vs ≥ 90 days), treatment, week, week*treatment. Unstructured covariance matrix for the correlation of the repeated measures within patient.

Study 1131: Concomitant Opioid Use or Used in 30 Days Up to Treatment

Condoliase (N = 280)

Clear Nerve Root Impingement (n = 79)

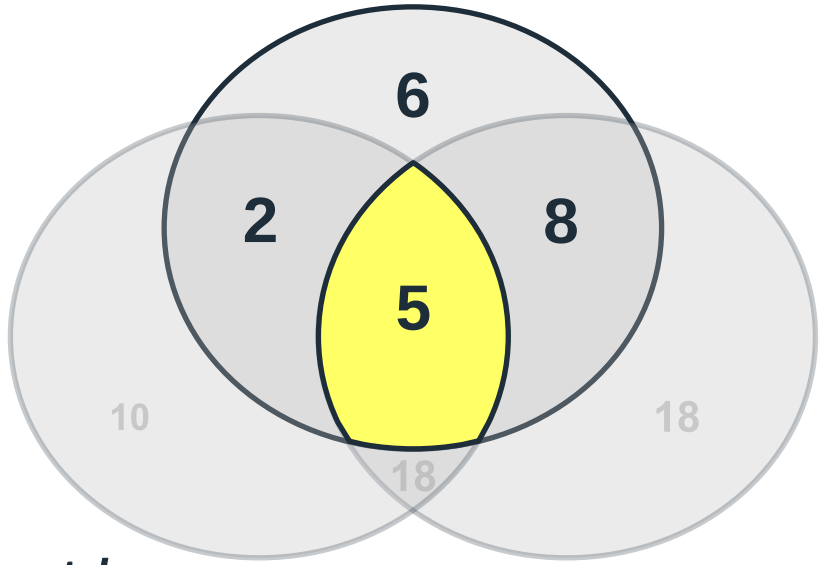


No Recent / Concomitant Opioid Use

No Chronic LBP (≥ 1 year)

Sham (N = 94)

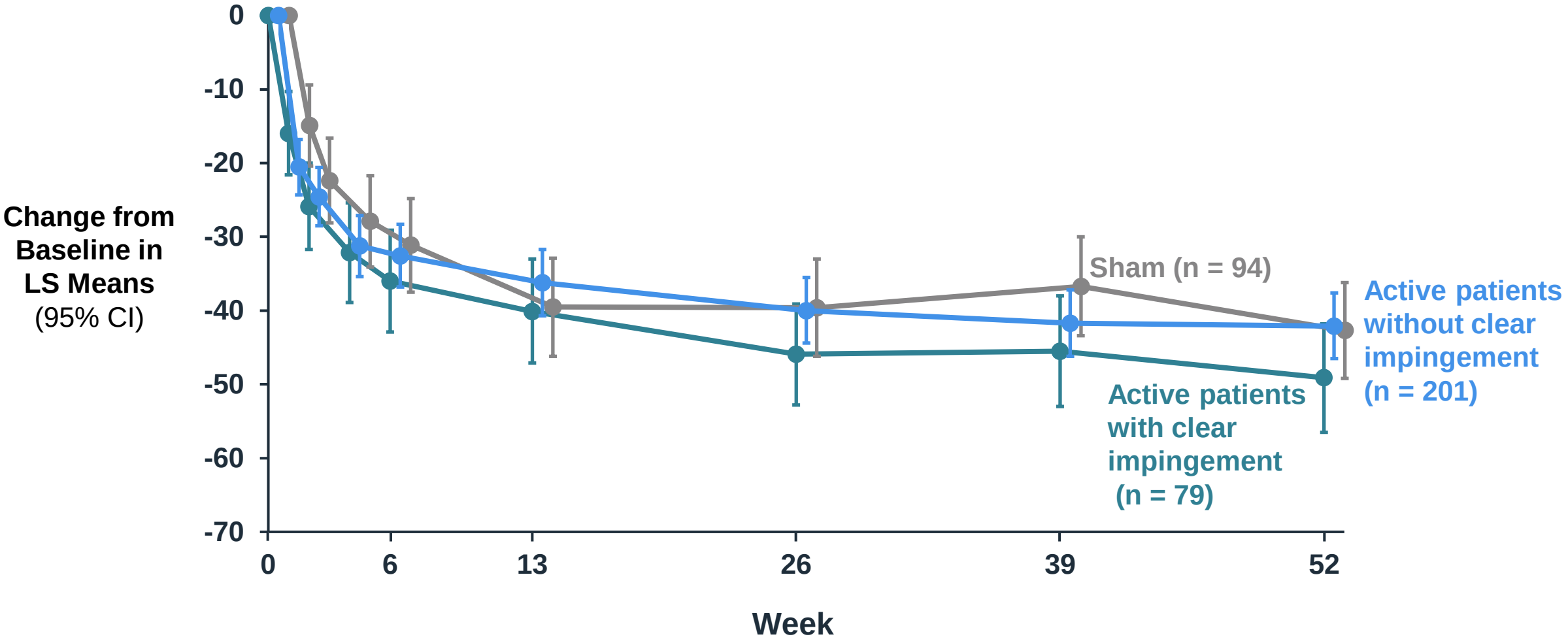
Clear Nerve Root Impingement (n = 21)



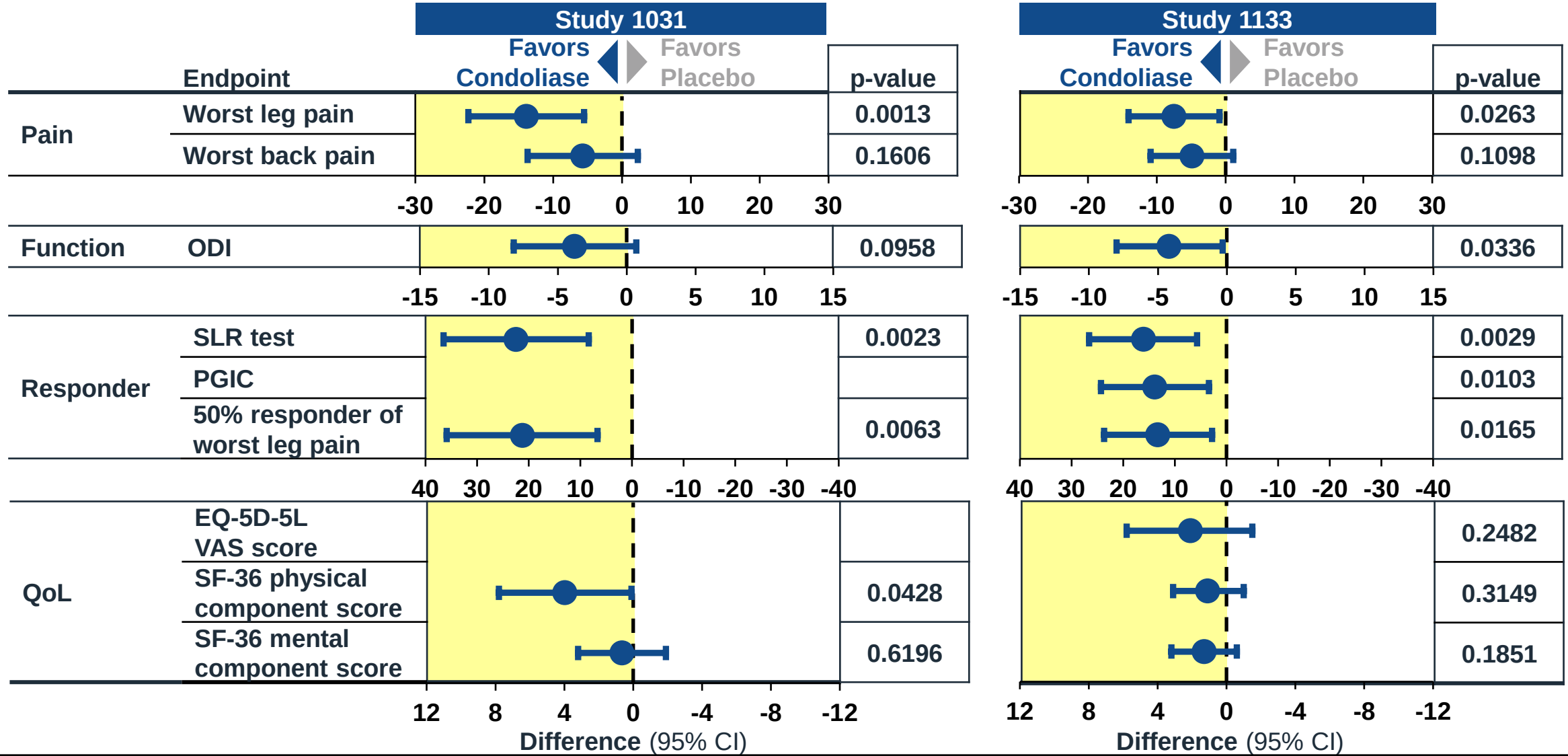
No Recent / Concomitant Opioid Use

No Chronic LBP (≥ 1 year)

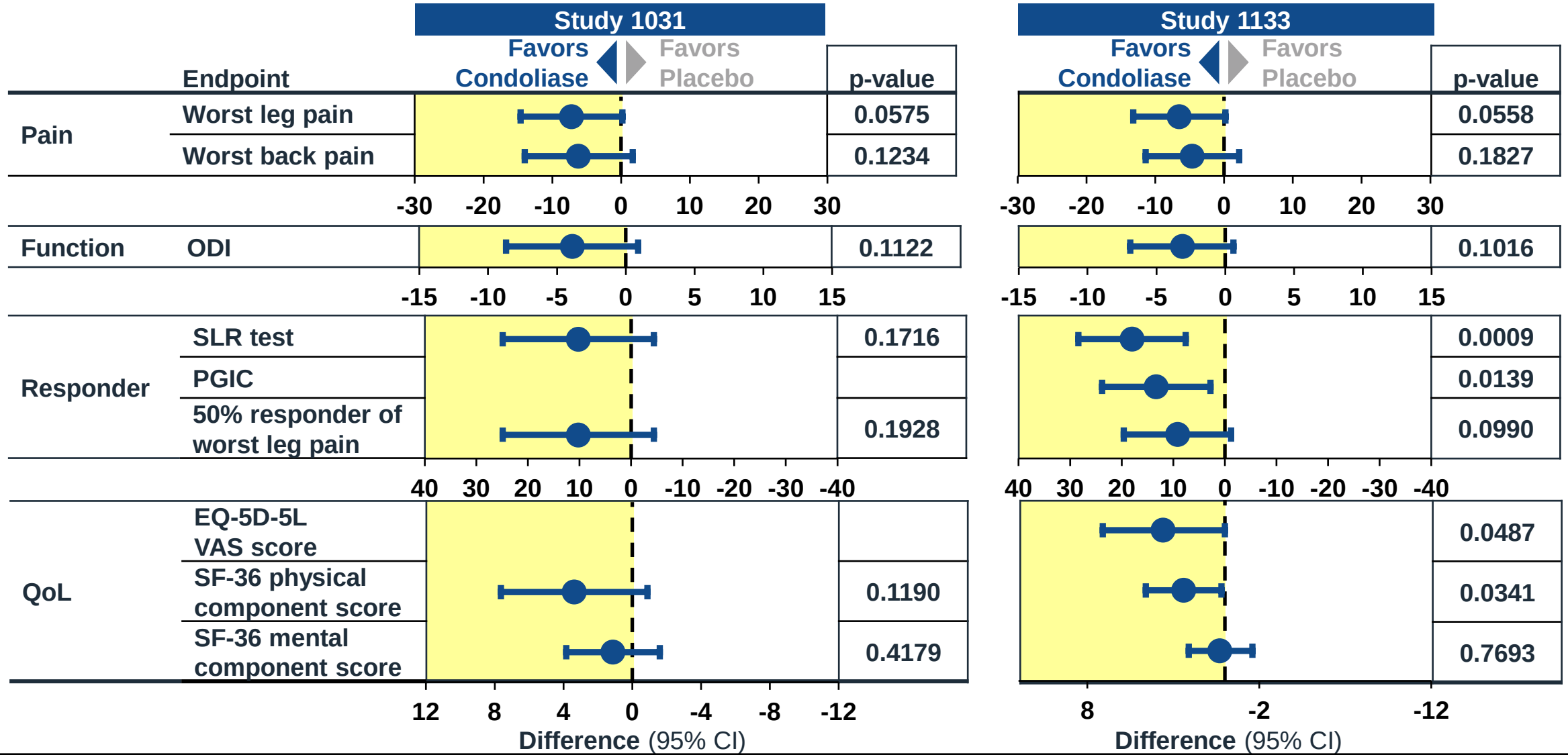
Study 1131: Change from Baseline for Worst Leg Pain by Subgroup (Impingement)



Pivotal Studies: Efficacy Endpoints at Week 13 Consistently Favor Condoliase



Pivotal Studies: Efficacy Endpoints at Week 52 Consistently Favor Condoliase



Condoliase is Highly Selective for Chondroitin Sulfate

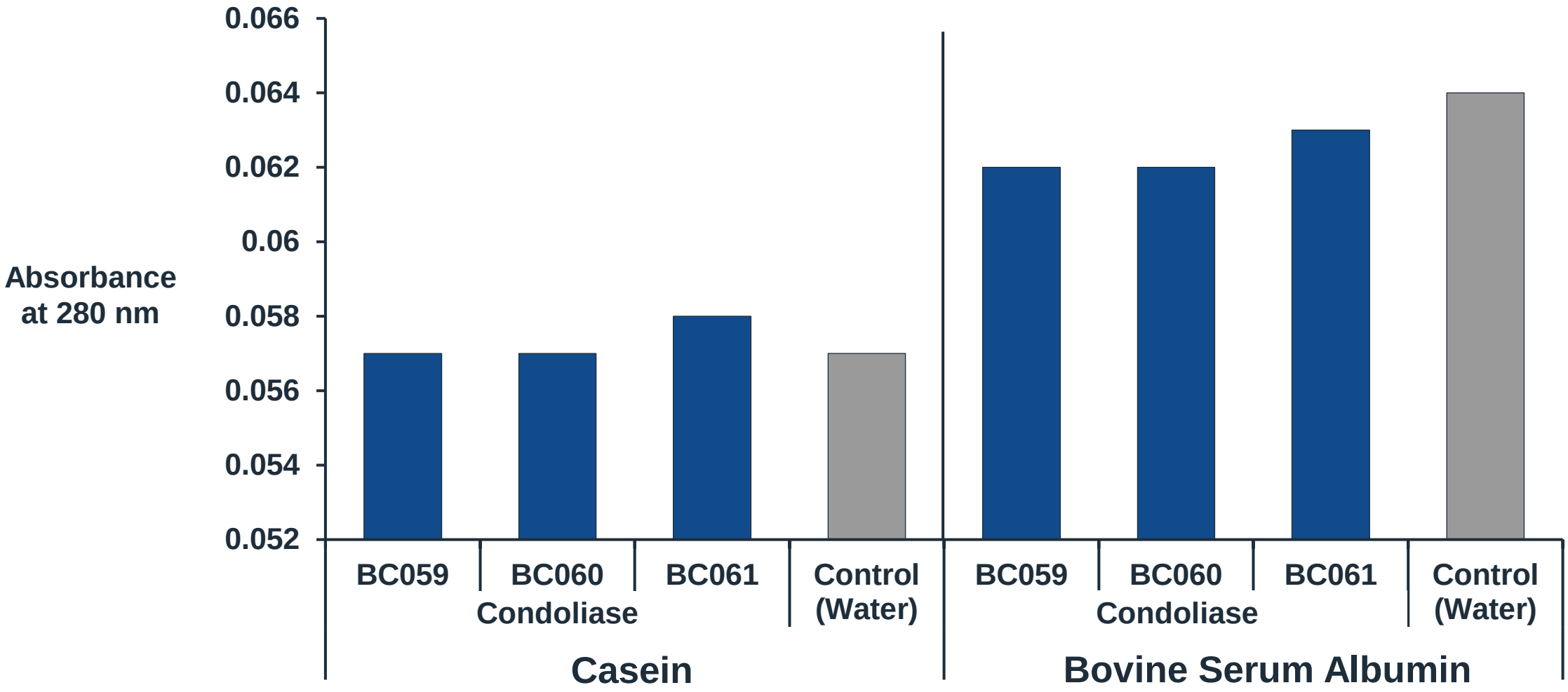
Substrate	Condoliase lot number		
	CLS-001E	CLS-002E	CLS-003E
	Relative activity rate to chondroitin sulfate A condition (%)		
Chondroitin	23	23	25
Chondroitin sulfate A	100	100	100
Chondroitin sulfate B	50	48	51
Chondroitin sulfate C	66	68	67
Sodium chondroitin sulfate CD Seikagaku[1]	82	80	85
Chondroitin sulfate D	54	52	54
Heparan sulfate	4	5	2
Hyaluronic acid	3	4	2
Heparin	3	1	2
Keratan sulfate	ND	ND	ND
Substrate	Collagen degradation activity compared to 0 U reference (U/mL)		
Collagen (100 x dilution sample)	0.0	0.0	0.0
Collagen (10 x dilution sample)	0.0	0.1	0.0
Collagen (1 x dilution sample)	-0.3	-0.3	-0.3

1. Sodium chondroitin sulfate CD Seikagaku is prepared by chemically degrading and purifying chondroitin sulfate extracted from shark cartilage

ND = Not Detected

One Unit (U) of condoliase = the amount of enzyme that produces 1 µmol of unsaturated disaccharide per minute from sodium chondroitin sulfate at 37°C and pH 8.0

Condoliase Does Not Degrade Casein or Bovine Serum Albumin



FDA 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