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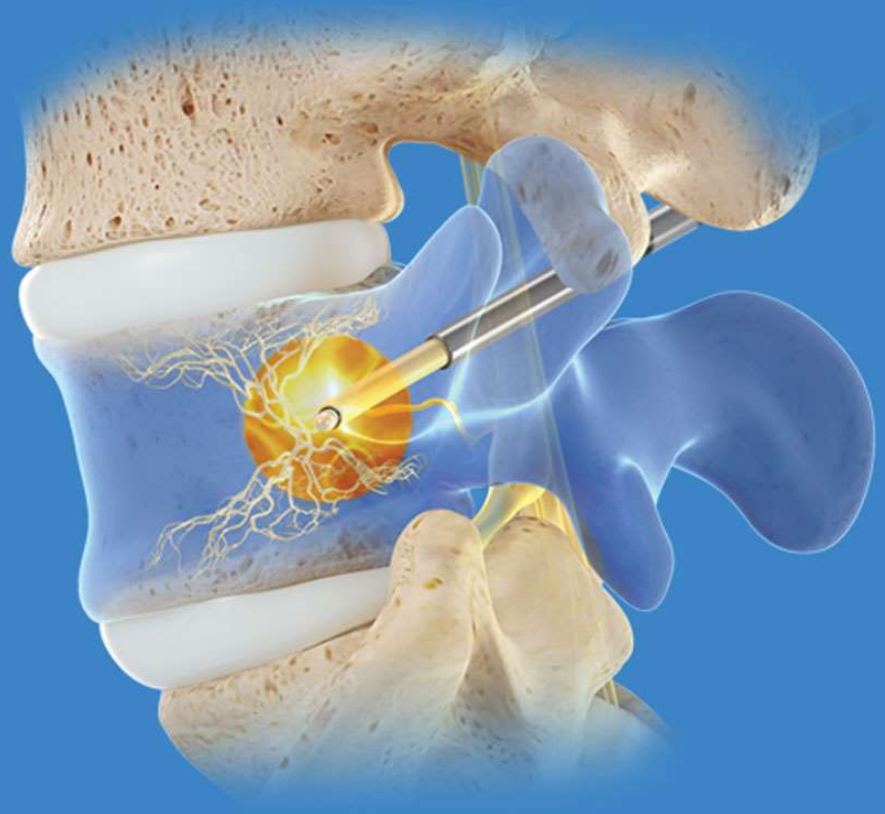
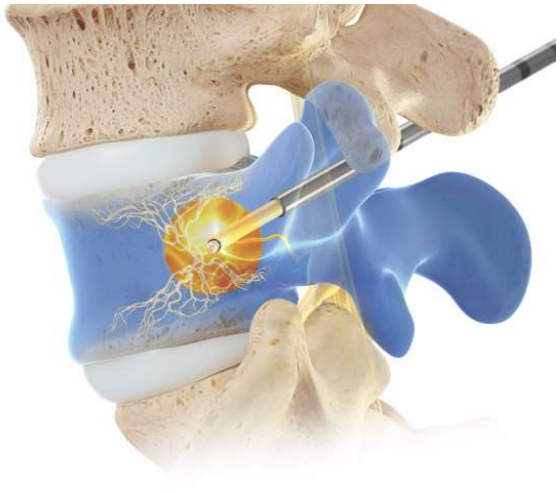
The Intracept® Procedure for the Relief of Chronic Vertebrogenic Low Back Pain



Agenda

- Relievant Medsystems
- Chronic Low Back Pain Overview
- Science of Vertebrogenic Pain
- Intracept Procedure
- Clinical Evidence
- Practice Support and Resources



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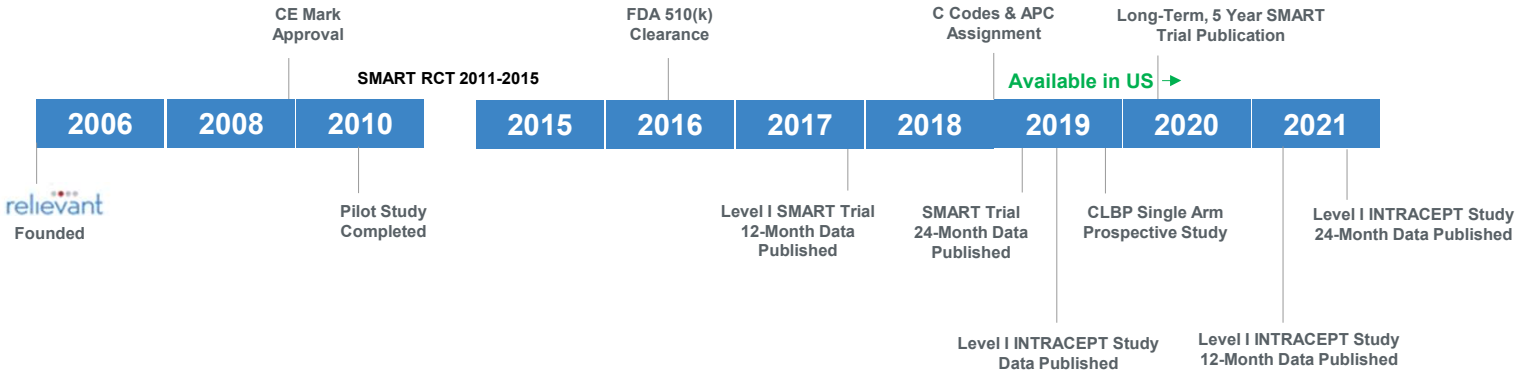
Intracept Procedure Built Upon Extensive Research

- BVN ablation is based on 30 years of research surrounding the impact of damaged vertebral endplates on CLBP
- Relievant Medsystems developed the Intracept Procedure for basivertebral nerve (BVN) ablation more than a decade ago
- Intracept Procedure is FDA cleared and currently available in the US
- Clinical safety, effectiveness, and treatment durability have been proven in a portfolio of clinical trials:
  - Two Level 1 RCTs demonstrate statistically significant, clinically meaningful improvements
  - Long-term data confirms treatment effect durability lasting more than 5 years post-procedure
  - Excellent safety profile and high patient satisfaction
  - Similar improvements reported across studies indicate reproducible outcomes



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Proven & Experienced Management Team

Tyler Binney	President & CEO	Teleflex, neotract, Acclarent, Cordis
Chris Geyen	Chief Financial Officer	Ethicon, NeuWave Medical, Celleration, Restore Medical, EY
Ray Baker, MD	Chief Operating Officer & Chief Medical Officer	NASS, EvergreenHealth, SIS
Steve Augustine	VP, Human Resources	Coloplast, ev3, Boston Scientific
Brian Donovan	VP, R&D and Operations	Medtronic, Kyphon, AviaraDx, Incubic
Mary Hailey	VP, Health Economics & Reimbursement	Penumbra, Neuronetics, Medtronic, Kyphon
Patrick Lyon	VP, Marketing	Medtronic, frankelgroup
Diane Sahr, RN	VP, Clinical Affairs	Boston Scientific, HyperMed, Celleration, AMS, Medtronic
Tom Slater	VP, Quality and Regulatory Affairs	Medtronic, Kyphon

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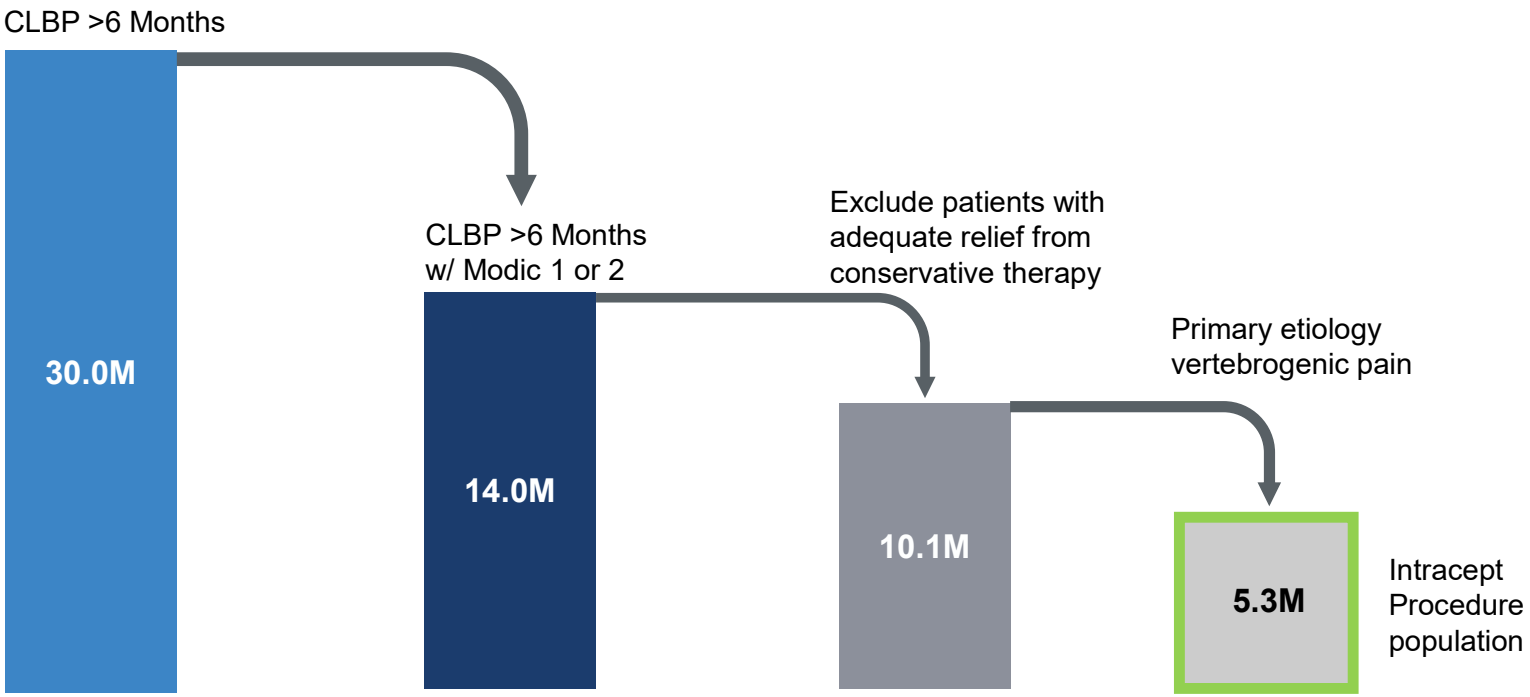
Chronic Low Back Pain Overview

Well-Defined Subset of the Chronic Low Back Pain Population



*Navigant research, 2019

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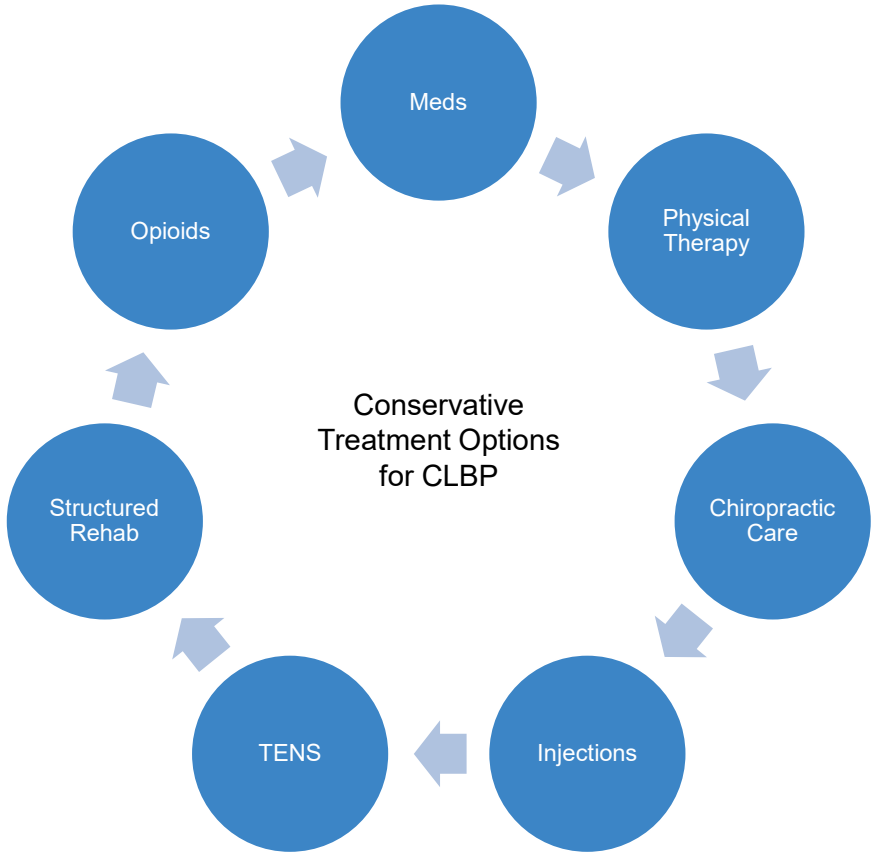
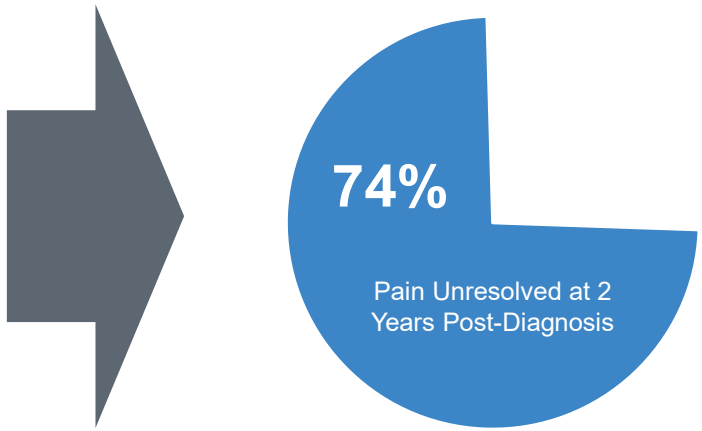
Majority of CLBP Patients Still Seeking Relief Two Years Post-Diagnosis





*Truven Marketscan 2015-2017 – Navigant Research

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Science of Vertebrogenic Pain

Vertebrogenic Pain is a Paradigm Shift in the Science of CLBP

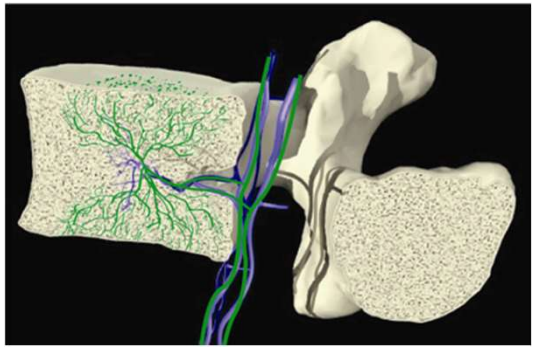
For decades, treatments ignored the endplates and focused on the disc

Vertebral endplates are more innervated than intervertebral discs[1]

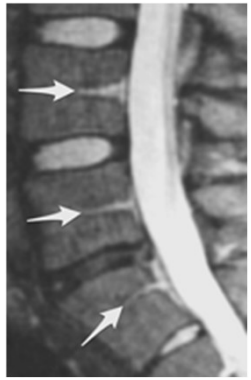
Protein gene product 9.5 (PGP 9.5) positive nociceptors confirmed at the vertebral endplates[2]

Basivertebral nerve (BVN) innervates the endplates and transmits pain signals from the vertebral endplates to the CNS[2]

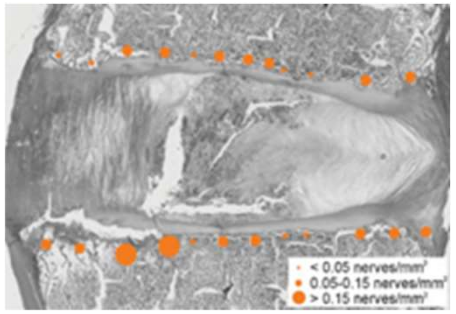
Distribution of the basivertebral nerve



Basivertebral Foramen



Distribution of PGP+ nerve fibers across endplate



[1]Fields AJ, Liebenberg EC, Lotz JC. The Spine Journal 2014;14(3):513-521.
[2]Bailey JF, Liebenberg E, Degmetich S, Lotz JC. Innervation patterns of PGP 9.5-positive nerve fibers within the human lumbar vertebra. Journal of Anatomy 2011;218(3):263-70.

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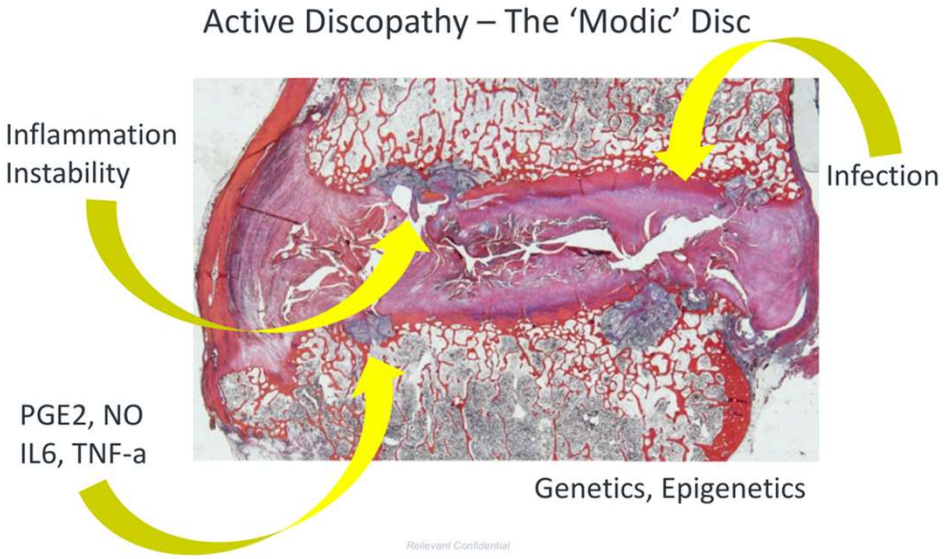
Extensive Independent Research Supports Pathobiology of Vertebrogenic Pain

Endplate defects allow proinflammatory disc tissue to leak into the bone marrow, inciting an inflammatory response

Chronic endplate inflammation leads to Modic changes (MC) on MRI

Prevalence and density of endplate nociceptors higher in vertebral bodies with MC[1]



1. Dudli S, Sing DC, Hu SS, Berven SH, Burch S, Deviren V, Cheng I, Tay BKB, Alamin TF, Ith MAM, Pietras EM, Lotz JC. ISSLS PRIZE IN BASIC SCIENCE 2017: Intervertebral disc/bone marrow cross-talk with Modic changes. Eur Spine J. 2017 May;26(5):1362-1373. doi: 10.1007/s00586-017-4955-4.

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Modic Changes are Correlated with Severe CLBP

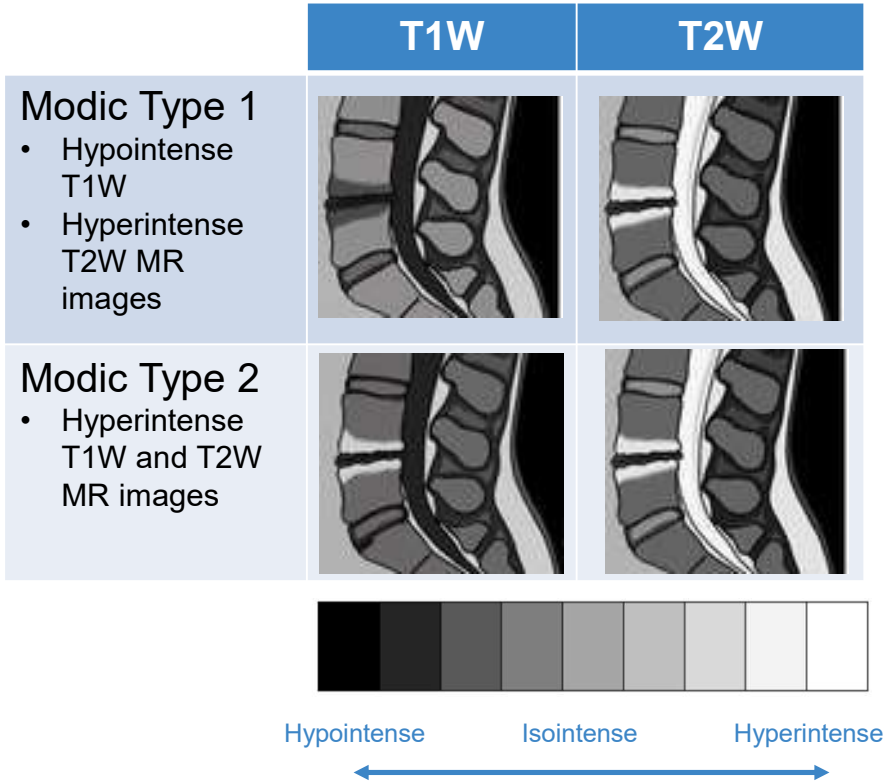
Research Findings:

Association between discography and moderate to severe Type 1 and Type 2 Modic changes[1]

- 38% sensitivity
- 88% specificity with moderate Modic 1 and 2
- 100% specificity with severe Modic 1 and 2

Modic Changes were associated with historical LBP, and with severity and duration of symptoms ($p<.05$)[2]

Patients with Type 1 Modic Changes seek care more often and have poor outcomes with conservative treatment[3,4]



[1] Weishaupt D et al. Radiology; 2001
[2] Mok F et al. The Spine Journal; 2016
[3] Jensen OK et al. The Spine Journal; 2014
[4] Jensen RK et al. BMC Musculoskelet Disord; 2011

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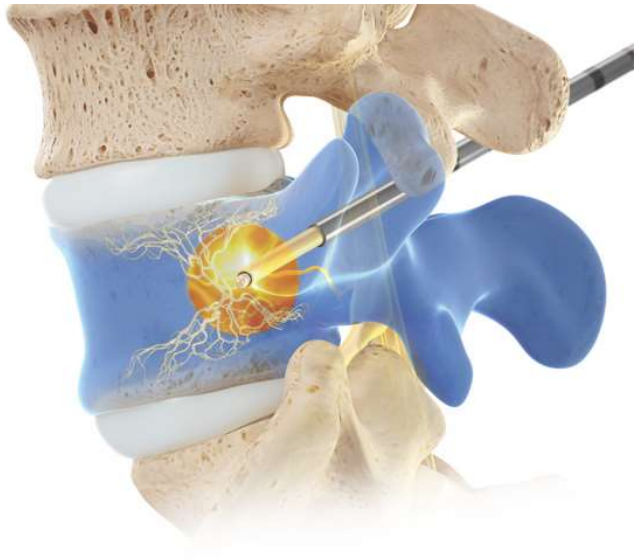
Intracept Procedure Overview

Intracept Procedure Provides Durable Relief of Vertebrogenic CLBP

The Intracept Procedure is a minimally invasive procedure that targets **the basivertebral nerve** for the relief of chronic low back pain.

Key Benefits of Intracept Procedure:

- Provides a treatment option for patients who have not responded to conservative therapy
- Minimally invasive, outpatient procedure
- Implant-free and preserves all future treatment options
- Provides durable[1] relief of vertebrogenic CLBP



1. Fischgrund JS, Rhyne A, Macadaeg K, Moore G, Kamrava E, Yeung C, et al. Long-term outcomes following intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 5-year treatment arm results from a prospective randomized double-blind sham-controlled multi-center study. Eur Spine J. epub May 25, 2020. https://doi.org/10.

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Intracept Procedure System: Designed Specifically For BVN Ablation

Innovative and Intuitive Instrumentation Designed Specifically for BVN Ablation

RF Generator

Bi-Polar RF Probe

Access Instruments

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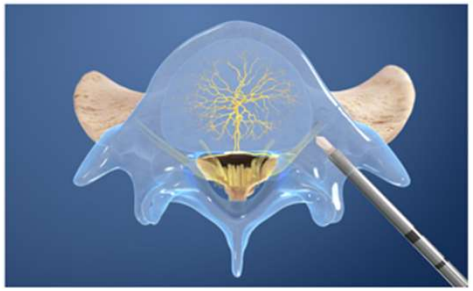
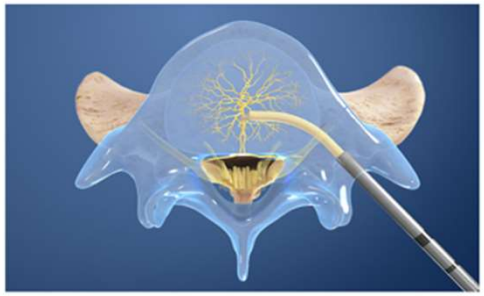
Straightforward Procedure Steps

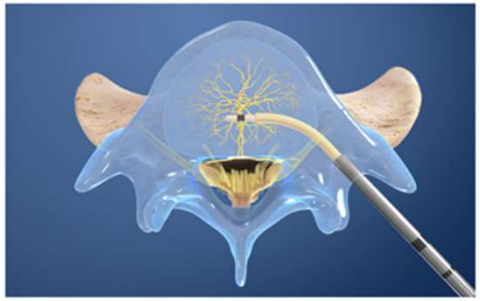
1. Access the Pedicle



2. Create the Channel



3. Place the Radiofrequency Probe



4. Ablate the BVN

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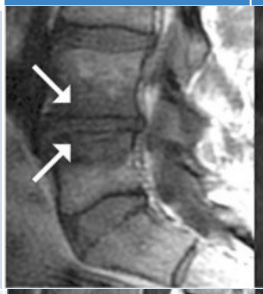
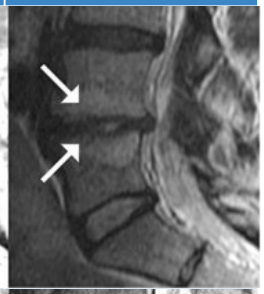
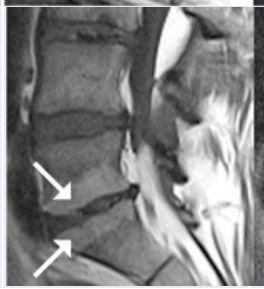
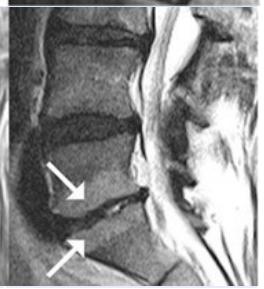
Intracept Procedure Patient Indications

- Chronic Low Back Pain of at least 6 months duration; and
- Failure to respond to at least 6 months of conservative care; and
- MRI demonstrated Modic Type 1 or Type 2 changes at one or more levels from L3 to S1

	T1W	T2W
Modic Type 1 • Hypointense T1W • Hyperintense T2W MR images		
Modic Type 2 • Hyperintense T1W and T2W MR images		

Indications for Use: The Intracept Intraosseous Nerve Ablation System is intended to be used in conjunction with radiofrequency (RF) generators for the ablation of basivertebral nerves of the L3 through S1 vertebrae for the relief of chronic low back pain of at least six months duration that has not responded to at least six months of conservative care, and is also accompanied by features consistent with Type 1 or Type 2 Modic changes on an MRI such as inflammation, edema, vertebral endplate changes, disruption and fissuring of the endplate, vascularized fibrous tissues within the adjacent marrow, hypointensive signals (Type 1 Modic change), and changes to the vertebral body marrow including replacement of normal bone marrow by fat, and hyperintensive signals (Type 2 Modic change).

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Intracept Procedure Contraindications and Risks

Use of the Intracept Intraosseous Nerve Ablation System is contraindicated in:

- Patients with severe cardiac or pulmonary compromise
- Patients where the targeted ablation zone is < 10 mm away from a sensitive structure not intended to be ablated, including the vertebral foramen (spinal canal)
- Patients with active systemic infection or local infection in the area to be treated
- Patients who are pregnant
- Skeletally immature patients (generally < 18 years of age)
- Patients with implantable pulse generators (e.g., pacemakers, defibrillators) or other electronic implants
- Situations where unintended tissue damage may result, based on the clinical assessment by the physician
- Application with electrosurgical instruments NOT tested and specified for use with the Relievant RFG

As with any surgical procedure, there are risks and considerations associated with the Intracept Procedure. To review the contraindications, warnings and precautions visit: https://www.relievant.com/intracept-procedure/procedure/#icr

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Clinical Evidence

Strong Clinical Foundation Supporting the Intracept Procedure

	Trial	Lead Author	# of Subjects	Publication
SMART	SMART Pivotal RCT vs Sham	Fischgrund	225 (147/78)	European Spine Journal
	SMART 2 Year BVN Arm Outcomes	Fischgrund	106	Int'l Journal of Spine Surgery
	SMART 5 Year BVN Arm Outcomes	Fischgrund	100 (n=US PP)	European Spine Journal
INTRACEPT	INTRACEPT Pivotal RCT vs Standard Care	Khalil	140 (66/74) *Interim Analysis* 104 (51/53)	The Spine Journal
	INTRACEPT 1 Year Outcomes BVN Arm + 6 Mo Outcomes on Crossover Arm	Smuck	127	Regional Anesthesia and Pain Management
	INTRACEPT 2 Year Outcomes BVN Arm	Koreckij	58	NASSJ
Prospective, Single-Arm Study	Prospective, Single-Arm Study 3 mo Clinical Results	Truumees	28	European Spine Journal
	Prospective, Single-Arm Study 12 mo Clinical Results	Macadaeg	47	NASSJ

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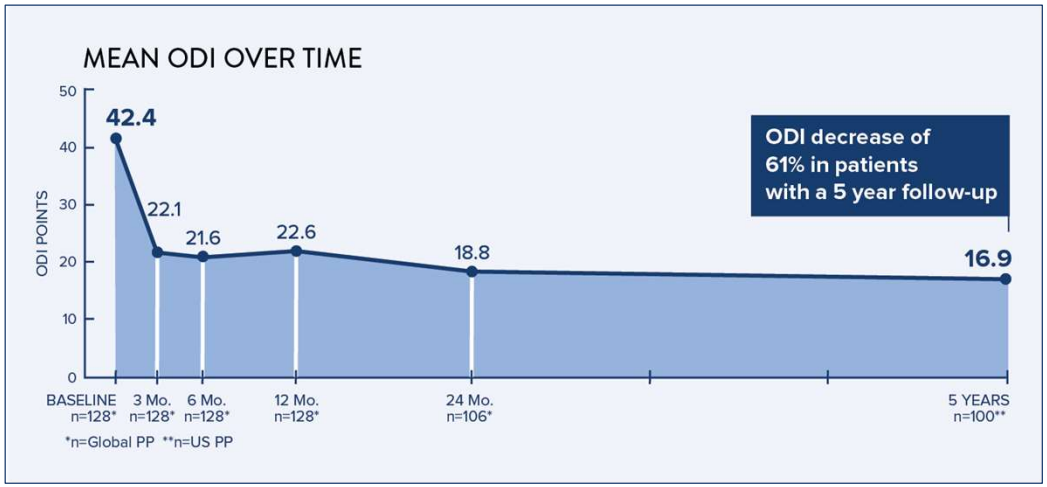
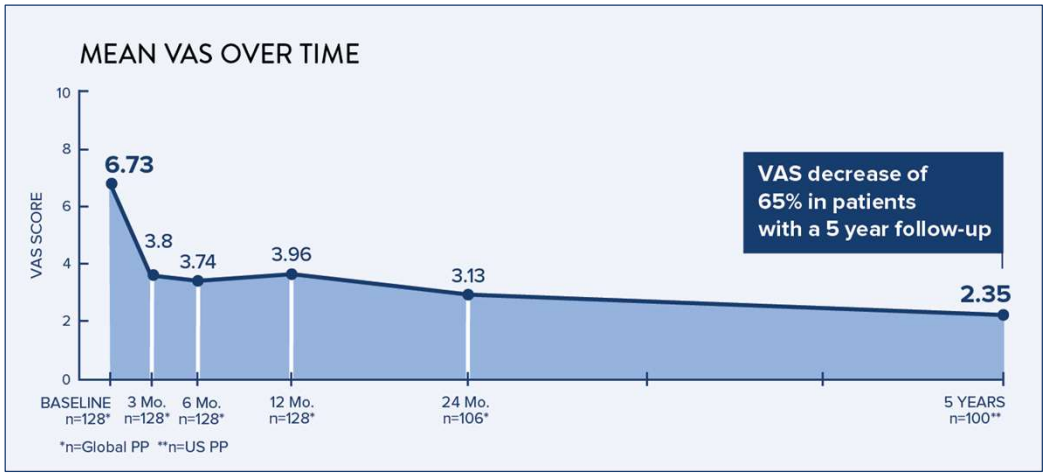
SMART 5+ Year Data: Sustained Improvements in Pain and Function Long-Term

- Study Design
  - Five-year follow-up of the SMART US treatment arm
  - US PP BVN ablated patients; 85% retention rate (100/117)
  - Mean follow-up 6.4 years (range 5.4 to 7.8 years)
  - Mean age was 47 years; majority ≥5 yrs with CLBP

- Key Findings
  - Improvements in pain and function maintained more than 5 years post-procedure (ODI, VAS)
  - 75% responder rate (defined as patients reporting both a ≥15 pt ODI and ≥2 point VAS improvement)





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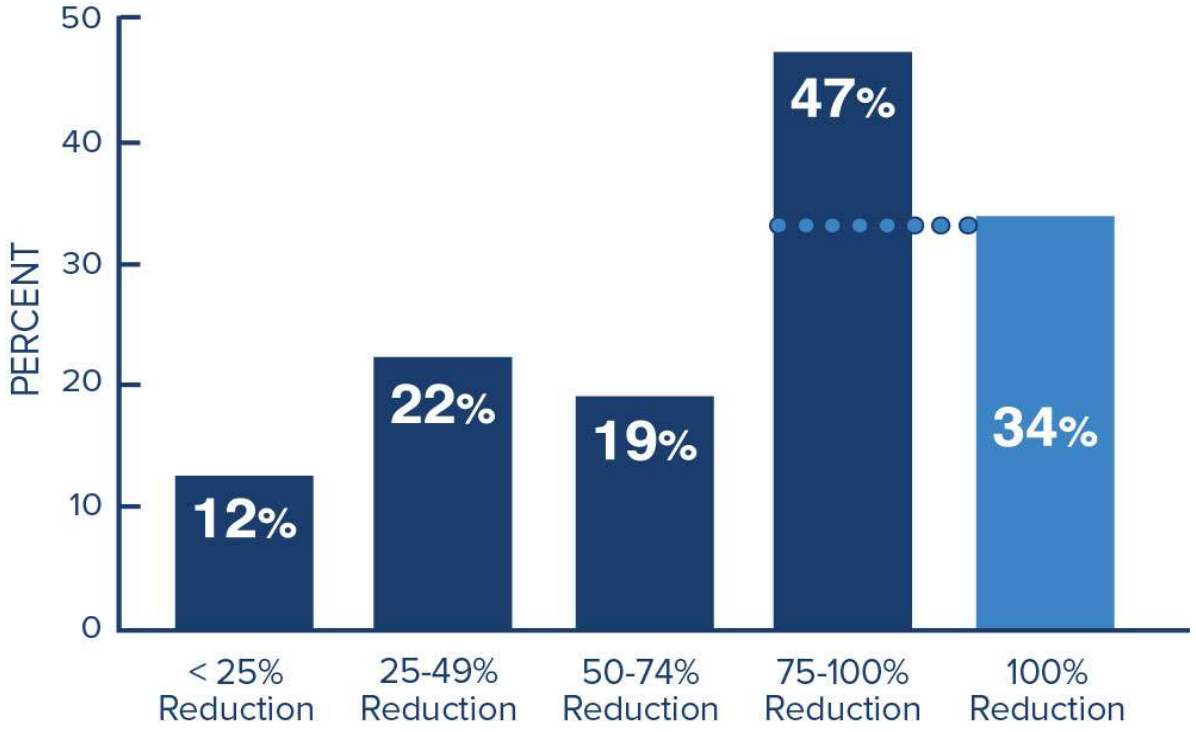
SMART Data: Significant Reductions in VAS from Baseline to 5+ Years



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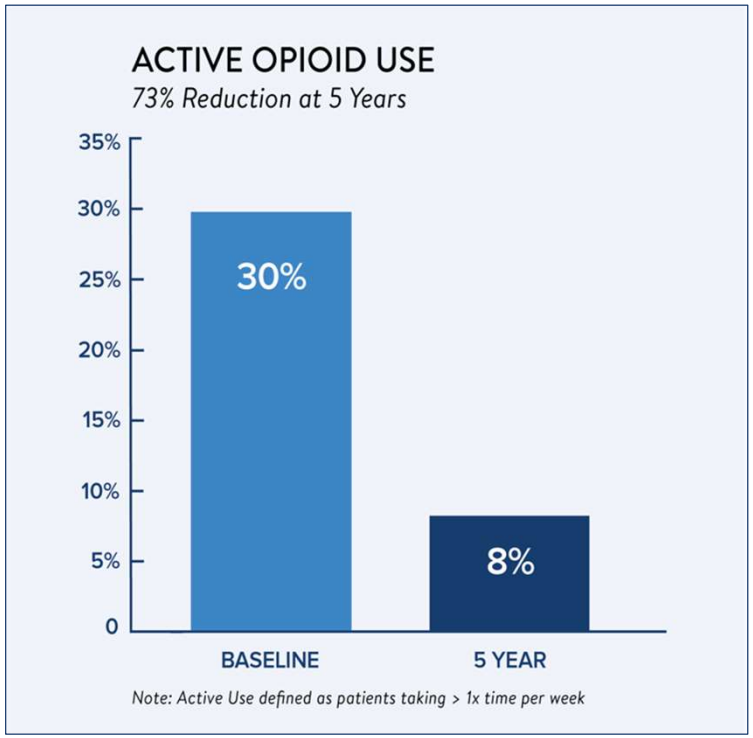
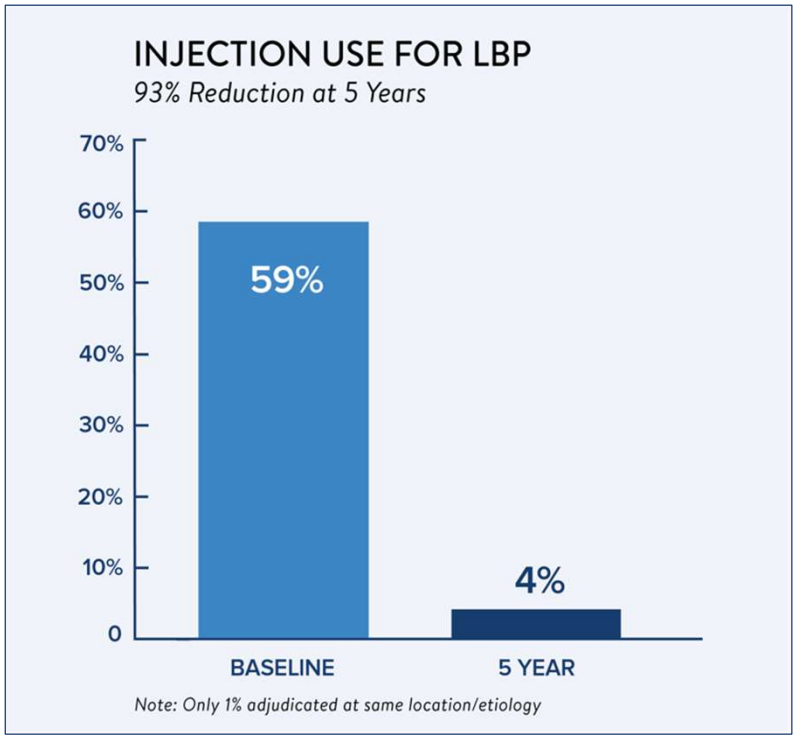
SMART 5+ Year Data: Reduction in Opioids & Injection Utilization (US PP)





* Injection(s) received in the prior 12 months

Fischgrund JS, Rhyne A, Macadaeg K, Moore G, Kamrava E, Yeung C, et al. Long-term outcomes following intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 5-year treatment arm results from a prospective randomized double-blind sham-controlled multi-center study. Eur Spine J. 2020 Aug;29(8):1925-1934. DOI: 10.1007/s00586-020-06448-x

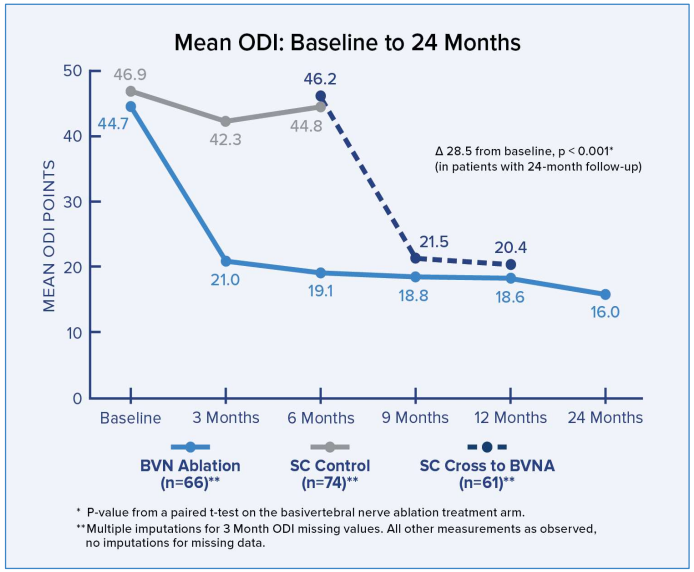
INTRACEPT Study: Sustained Relief at 24 Months

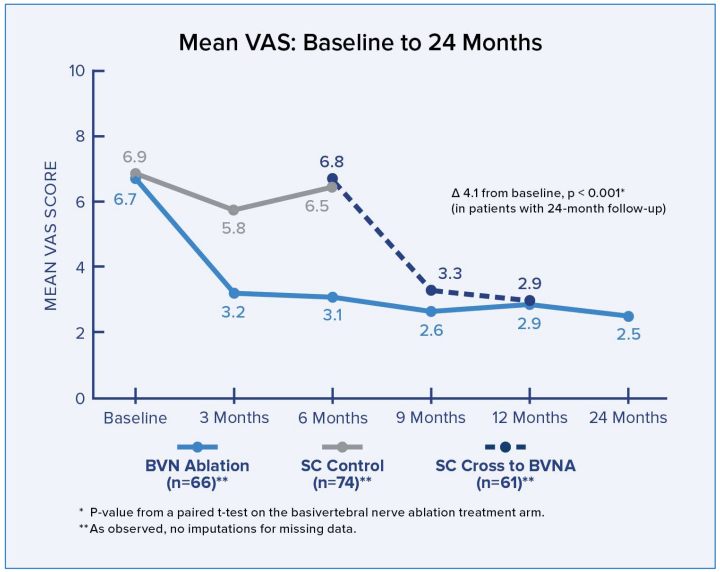
Study Design

- 2nd RCT evaluating BVN ablation; n=140 (interim analysis included 104)
- Allowed treatment of 4 VBs and also previous discectomy
- Mean age was 50.4 years; majority ≥5 yrs with CLBP

Key Findings - Significant Improvements in Pain and Function at all Timepoints through 2 Years

- Typical of anterior column pain, two-thirds of the patients presented with midline axial low back pain that was exacerbated with sitting, forward flexion and with position changes such as sitting to standing





Koreckij T, Kreiner S, Khalil JG, Smuck M, Markman J, Garfin S. Prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 24-month treatment arm results. NASSJ. Published online October 26, 2021. DOI: https://doi.org/10.1016/j.xnsj.2021.100089

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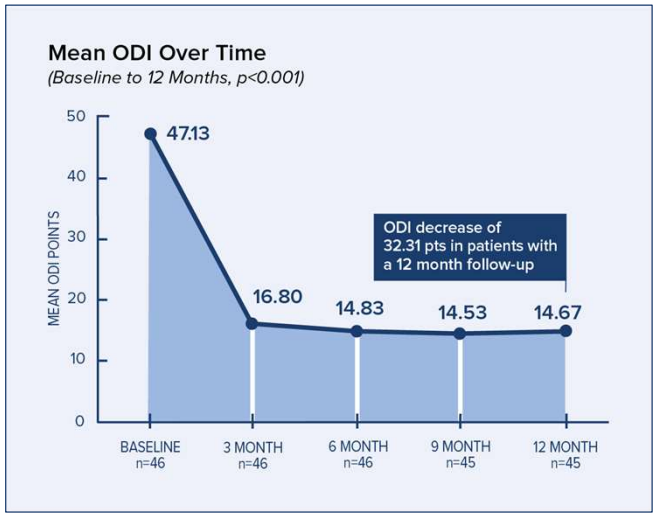
12-Month Case Series: Effectiveness Shown in “Real World” Evaluation

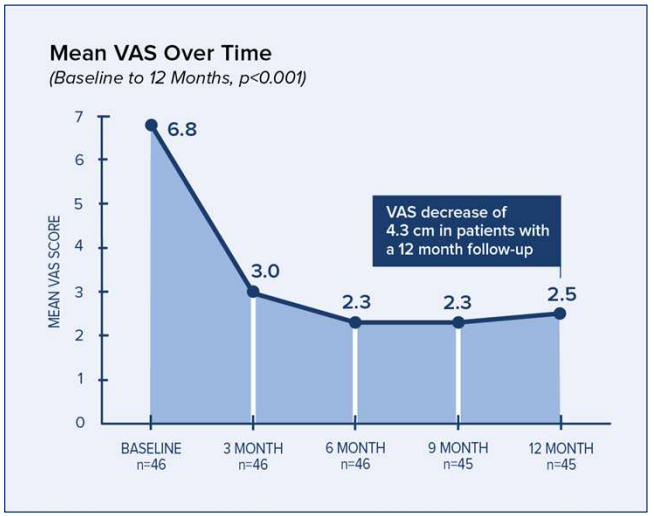
Study Design

- Prospective, single-arm, open label study at 2 typical U.S. spine practices
- 48 patients enrolled consecutively with broader application outside of strict trial inclusion criteria
- Mean age of 44.5 years; majority ≥5 yrs with CLBP

Key Findings – Results Maintained over 12 Months

- Significant improvements at 12 Months (32 point ODI, 4.3 cm VAS)
- Strong 12-month responder rates (over 75% of patients with >20 ODI and >2 VAS improvement)

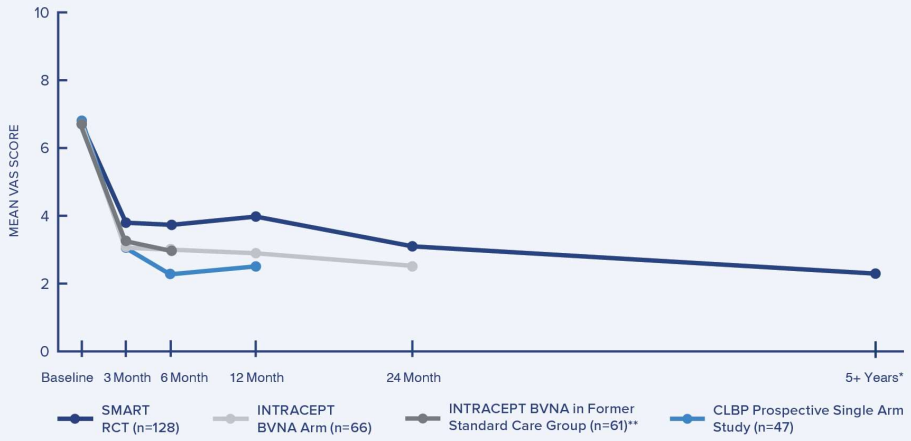




Macadaeg K, Truumees E, Boody B, Pena E, Arbuckle A., Gentile, J, et al. A prospective, open-label, single-arm, multi-center study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 12-month results. NASSJ 2020;3(100030). https://doi.org/10.1016/j.xnsj.2020.100030

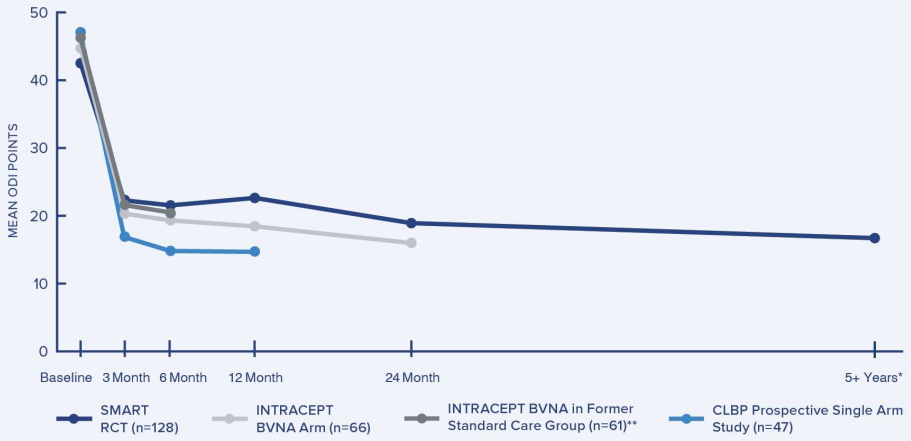
Similar Improvements in ODI and VAS Across Studies Post-Intracept Procedure

BVN Ablation Treatment in Multiple Studies:
Mean Visual Analog Scale (VAS) Over Time



* SMART RCT US per protocol treatment arm at mean of 6.4 years
** Standard arm re-baselined and offered active treatment at a median of 5.8 months

BVN Ablation Treatment in Multiple Studies:
Mean Oswestry Disability Index (ODI) Over Time



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Smuck M, Khalil J, Barrette K, et al. Reg Anesth Pain Med Epub ahead of print: May 24, 2021. doi:10.1136/rapm-2020-102259
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Strong Safety Profile Reported Across Clinical Studies

- Safety data has been collected in 473 clinical trial[1] patients treated with the Intracept procedure

- There has been 1 serious device procedure-related event reported **(0.2%)**

  (Vertebral compression fracture in a sham-control crossover patient w/ osteopenia, taking hormone therapy. Fracture healed spontaneously by 8 weeks.)

- There have been 26 non-serious device-procedure related events reported (5.5%).
  - Most common non-serious events reported: increase in back pain, onset of leg pain
  - All non-serious events were transient in nature with a median time to resolution of 66.5 days
  - All were mild to moderate in severity (typically treated with oral medication)

[1]Intracept Procedure Clinical Evidence References on file.

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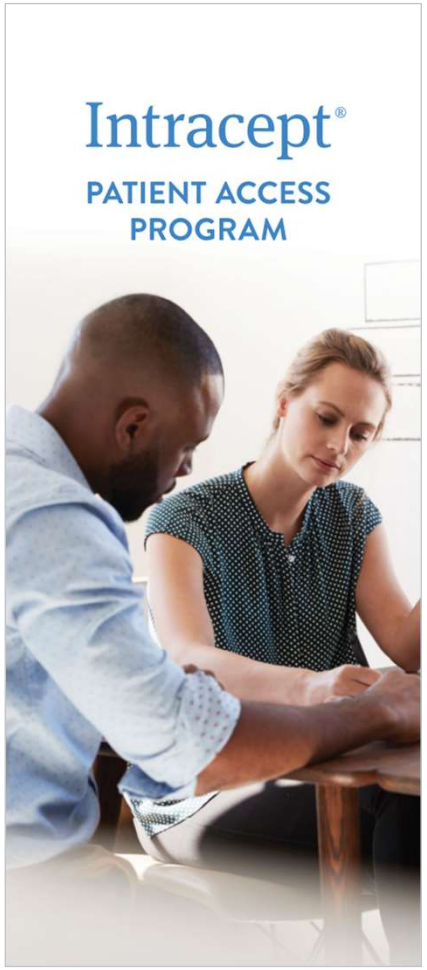
Program Support & Resources

Dedicated Patient Access Team & Program

- Assist patients in obtaining access to care
- Assist with any post service denials
- Experienced team providing support through each step of the commercial appeals process for your patient
- 60% of patients that complete the process are eligible for treatment
- The average time to closure is approximately 80 days

Repeated Patient Authorizations

Builds Foundation for Coverage



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Helpful Marketing Resources

Brochures

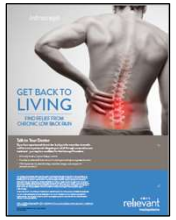
Physician

VAC

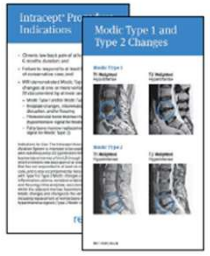
Patient Access Program

Patient

Poster & Indication Card



Poster



Indication Cards

Videos & Webinars

Patient & Physician Testimonials

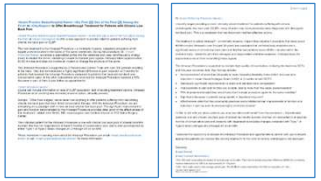
Procedure Animations

Scientific, Clinical Evidence & Procedure Webinars

Program Development

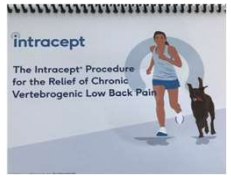
Referrer Presentation

Press Release Template



Internal Communications & Referring Physician Intro Letters

Patient Education



Patient Talk Track Flip Book

Patient Education Symposium Deck

Video Book with Patient Stories

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Best-In-Class Physician, APP and Staff Training Programs

Physician Training

- Live, hands-on training
- Didactic session to review:
  - Anatomy
  - Patient Selection
  - Pathophysiology of Vertebrogenic Pain
  - Intracept Procedure

- Cadaver session for hands on experience with Intracept System and Intracept Procedure
- Certificate of completion will be issued following training course

Staff Training

- Reimbursement team trains physician, APP and office staff on:
  - Patient Access Portal
  - Patient Access Support Materials
- Reimbursement team provides demonstrations for how to use the Patient Access Portal
- Territory Managers educate staff on the Intracept Procedure and patient identification

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Thank You & Next Steps

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Appendix

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Clinical Evidence

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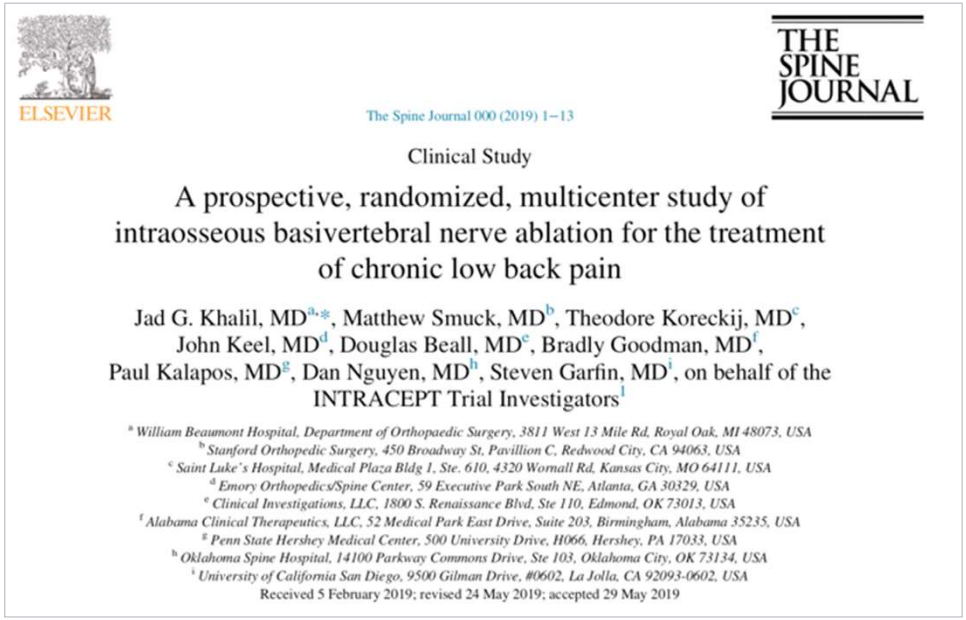
INTRACEPT Study

INTRACEPT Study – Results Published June 2019



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The Spine Journal 000 (2019) 1–13

THE SPINE JOURNAL

Clinical Study

A prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain

Jad G. Khalil, MD[a,*], Matthew Smuck, MD[b], Theodore Koreckij, MD[c], John Keel, MD[d], Douglas Beall, MD[e], Bradly Goodman, MD[f], Paul Kalapos, MD[g], Dan Nguyen, MD[h], Steven Garfin, MD[i], on behalf of the INTRACEPT Trial Investigators[1]

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https://www.thespinejournalonline.com/article/S1529-9430(19)30800-9/fulltext

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INTRACEPT – Study Design

Prospective, Multi-Center, Open Label RCT
Randomized 1:1 Intracept® Procedure (BVN Ablation) vs. Standard Care (SC)

Enrollment Criteria

Primary Inclusion Criteria

- > 6 months lumbar pain
- > 6 months conservative care
- Modic endplate changes (Type 1 or 2) at up to 4 VBs (L3-S1)

Primary Exclusion Criteria

- Other primary sources of LBP including: symptomatic spinal stenosis, radicular pain, instability, ODI < 30, VAS < 4, Modic at levels other than L3 to S1

Effectiveness Endpoints

Primary

- Between arm comparison of the LS Mean change in ODI from baseline to 3 months

Secondary

- Change from baseline in ODI, VAS, SF-36, EQ-5D-5L, and responder rates at 3, 6, 9 and 12 months

Pre-specified Interim Analysis

- Conducted when ≥ 60% of patients reached their 3-month primary endpoint
- DMC stopped enrollments at pre-specified Interim Analysis for superiority and control arm offered early active treatment

Study Population

- N = 140 randomized (66 BVN ablation vs 74 SC) at point of stopping enrollment
- Interim analysis included n=104 (51 BVN ablation, 53 SC)
- 61 (92%) Standard Care patients were rebaselined and then received BVN ablation treatment; they were followed for 6-months post-treatment

Baseline Characteristics (N=140):

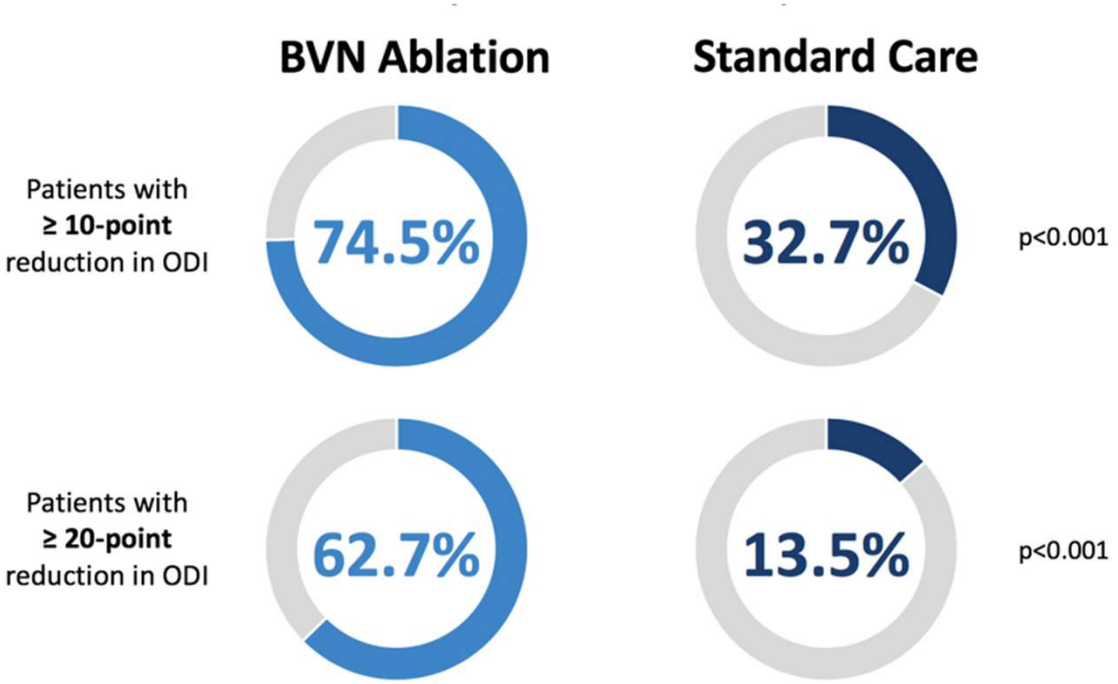
- Mean ODI 45.9
- Mean VAS 6.79
- Mean age 49.7 years
- Duration of symptoms 71.4% ≥ 5 years

INTRACEPT Study Interim Analysis

- Pre-specified Interim Analysis at ≥ 60% of patients at 3-month primary endpoint
- Independent data management committee (DMC) met January 25, 2019
  - Primary endpoint and all secondary endpoints demonstrated statistical significance in favor of the RF ablation arm ($p < 0.001$)
  - DMC recommended to halt randomization and allow early cross-over of SC arm patients
- Study population at time of interim analysis:
  - 140 patients randomized
  - 104 patients at 3-month primary endpoint (51 RB ablation; 53 SC) included in ITT analysis
  - < 1% attrition at primary endpoint

Khalil J, Smuck M, Koreckij T, Keel J, Beall D, Goodman B, Kalapos K, Nguyen D, Garfin S. A Prospective, Randomized, Multi-Center Study of Intraosseous Basivertebral Nerve Ablation for the Treatment of Chronic Low Back Pain presented at the American Society of Spine Radiology Annual Symposium; February 22, 2019; Miami, FL.

ODI Responder Rates: Baseline to 3 Months



N=104

Khalil J, Smuck M, Koreckij T, et al. A prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain, *The Spine Journal*, 2019; 19:1620-1632. https://doi.org/10.1016/j.spinee.2019.05.598.

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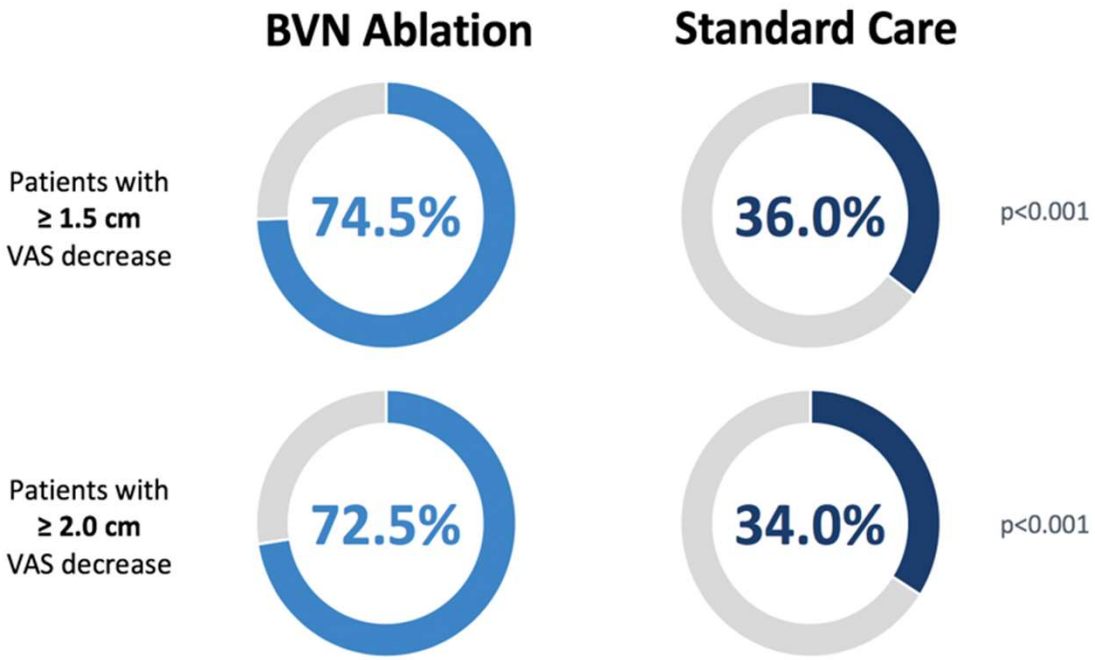
VAS Responder Rates: Baseline to 3 Months



N=104

Khalil J, Smuck M, Koreckij T, et al. A prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain, *The Spine Journal*, 2019; 19:1620-1632. https://doi.org/10.1016/j.spinee.2019.05.598

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INTRACEPT Study
12-Month Results

INTRACEPT Study – 12-Month Results Published May 2021

Original research

OPEN ACCESS

Prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 12-month results

Matthew Smuck,[1] Jad Khalil,[2] Kevin Barrette,[3] Joshua Adam Hirsch,[4] Scott Kreiner,[5] Theodore Koreckij,[6] Steven Garfin,[7] Nagy Mekhail,[8] INTRACEPT Trial Investigators

ABSTRACT

Introduction Vertebral endplates, innervated by the basivertebral nerve (BVN), are a source of chronic low back pain correlated with Modic changes. A randomized trial comparing BVN ablation to standard care (SC) recently reported results of an interim analysis. Here, we report the results of the full randomized trial, including the 3-month and 6-month between-arm comparisons, 12-month treatment arm results, and 6-month outcomes of BVN ablation in the former SC arm.

Methods Prospective, open label, 1:1 randomized controlled trial of BVN ablation versus SC in 23 US sites with follow-up at 6 weeks, 3, 6, 9, and 12 months. SC patients were re-baselined and followed up for 6 months post BVN ablation. The primary endpoint was the between-arm comparison of mean Oswestry Disability Index (ODI) change from baseline. Secondary endpoints were Visual Analog Scale (VAS), Short Form (SF-36), EuroQual Group 5 Dimension 5-Level Quality of Life (EQ-5D-5L), responder rates, and rates of continued opioid use.

Results 140 were randomized. Results from BVN ablation (n=66) were superior to SC (n=74) at 3 months for the primary endpoint (mean ODI reduction, difference between arms of −20.3 (CI −25.9 to −14.7 points; p<0.001)), VAS pain improvement (difference of −2.5 cm between arms (CI −3.37 to −1.64, p<0.001)) and quality of life outcomes. At 12 months, basivertebral ablation demonstrated a 25.7±18.5 point reduction in mean ODI (p<0.001), and a 3.8±2.7 cm VAS reduction (p<0.001) from baseline, with 64% demonstrating ≥50% reduction and 29% pain free. Similarly, the former SC patients who elected BVN ablation (92%) demonstrated a 25.9±15.5 point mean ODI reduction (p<0.001) from baseline. The proportion of opioid use did not change in either group (p=0.56).

Discussion/Conclusion BVN ablation demonstrates significant improvements in pain and function over SC, with treatment results sustained through 12 months in patients with chronic low back pain of vertebrogenic origin.

INTRODUCTION

Clinicians who treat chronic low back pain (CLBP) are challenged by the varied and complex causes and by low effect sizes of treatments.[1] They have long recognized that better subgrouping of patients is necessary for more targeted and effective treatments. One such subgroup is vertebrogenic CLBP. While this diagnosis represents a newer clinical concept, there is a substantial body of basic science evidence indicating this as an important source of CLBP.[2–6] Furthermore, an association has been established between the presence of type 1 or type 2 Modic changes and CLBP.[6 7] Vertebral endplate nociceptors trace back to the basivertebral nerve (BVN),[3] a potential target for therapeutic radiofrequency ablation of the BVN in the subgroup of patients with vertebrogenic CLBP.

A previous randomized, double-blind, sham-controlled trial demonstrated the efficacy of BVN ablation to treat CLBP in this patient subgroup, with durability of benefits for 2 and 5 years.[8 9] Based on these findings, a new randomized controlled trial (RCT) was designed to evaluate the clinical effectiveness of BVN ablation compared with standard care (SC) for CLBP in patients with Modic type 1 or 2 changes. The outcome from this study's interim analysis was recently published, based on an independent Data Management Committee (DMC) recommendation to halt enrollment and offer the SC arm BVN ablation after re-baseline due to statistical superiority of BVN ablation over SC.[10] Here, we report the outcomes of the entire RCT cohort at the 3-month primary endpoint and at 6 months (point of randomization stop and re-baseline for the SC arm), the 12-month results of the entire BVN ablation arm, and the 6-month results from BVN ablation in the former SC arm.

METHODS

Design

The INTRACEPT trial is a prospective, parallel, open-label RCT of 420 patients recruited at 23 US sites, with 140 eligible patients randomized from September 2017 to January 2019. The trial was registered in August 2017 on ClinicalTrials.gov as NCT03246061 (https://clinicaltrials.gov/ct2/show/NCT03246061) and sponsored by Relievant Medsystems (Minneapolis, Minnesota, USA). The study is Health Insurance Portability and Accountability Act (HIPAA) compliant and was conducted under Institutional Review Board approval and participant informed consent. Enrolled patients were assigned a unique deidentified ID number. Data were source-verified by independent study monitors. Third-party statisticians (Abtrnd., Grand Rapids, Michigan, USA) prepared the computer-generated randomization scheme and conducted

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rapm-2020-102259).

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https://rapm.bmj.com/content/rapm/early/2021/05/23/rapm-2020-102259.full.pdf

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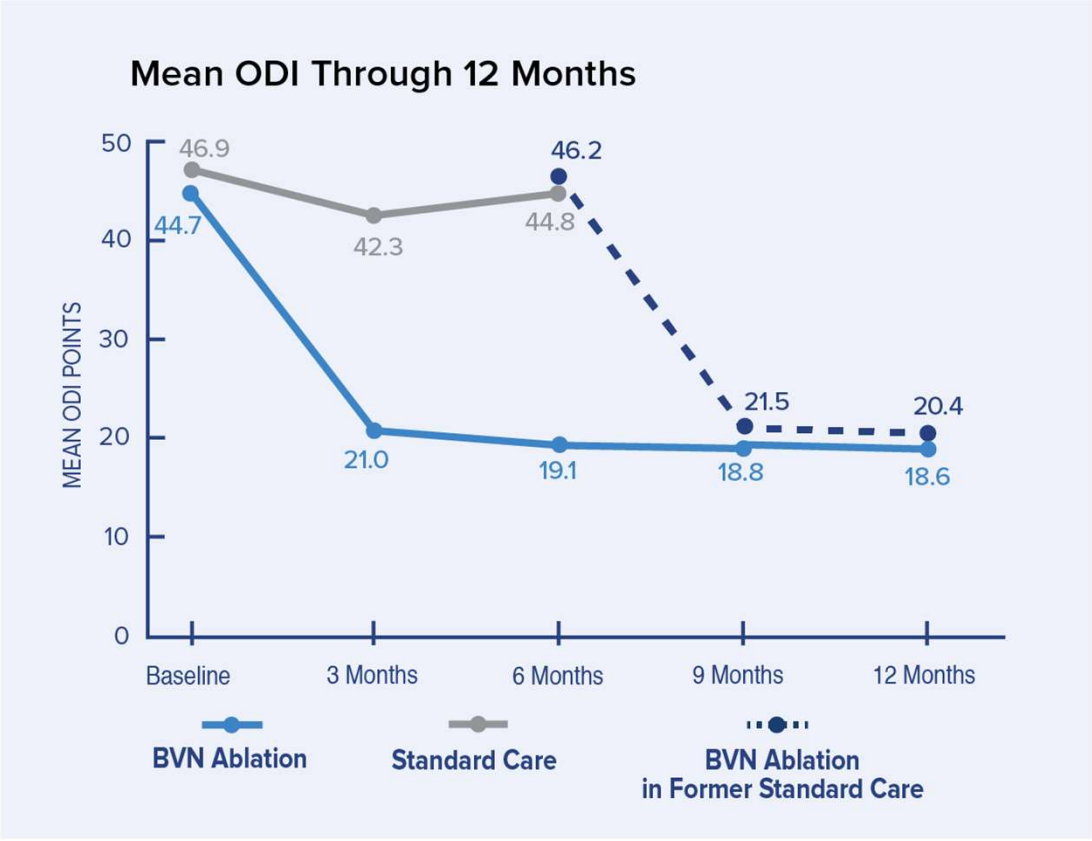
Mean ODI Between Arms



BVN Ablation Arm vs. Standard Care Arm

- Patients in the BVN Ablation Arm demonstrated a statistically significant ($p<0.001$) and clinically meaningful reduction in mean ODI compared to standard care at 3 and 6 months
- Results demonstrated superiority of BVN ablation compared to standard care treatments
- Improvements in function sustained through 12 months in the BVN ablation arm

BVN Ablation in Former Standard Care Group

- Similar trajectory at 3 and 6 months after re-baseline and BVN ablation treatment
- Patients demonstrated a statistically significant ($p<0.001$) and clinically meaningful reduction in mean ODI from re-baseline after BVN ablation treatment
- Results sustained through 6 months

Significant and Sustained ODI Reduction After Treatment in All BVN Patients

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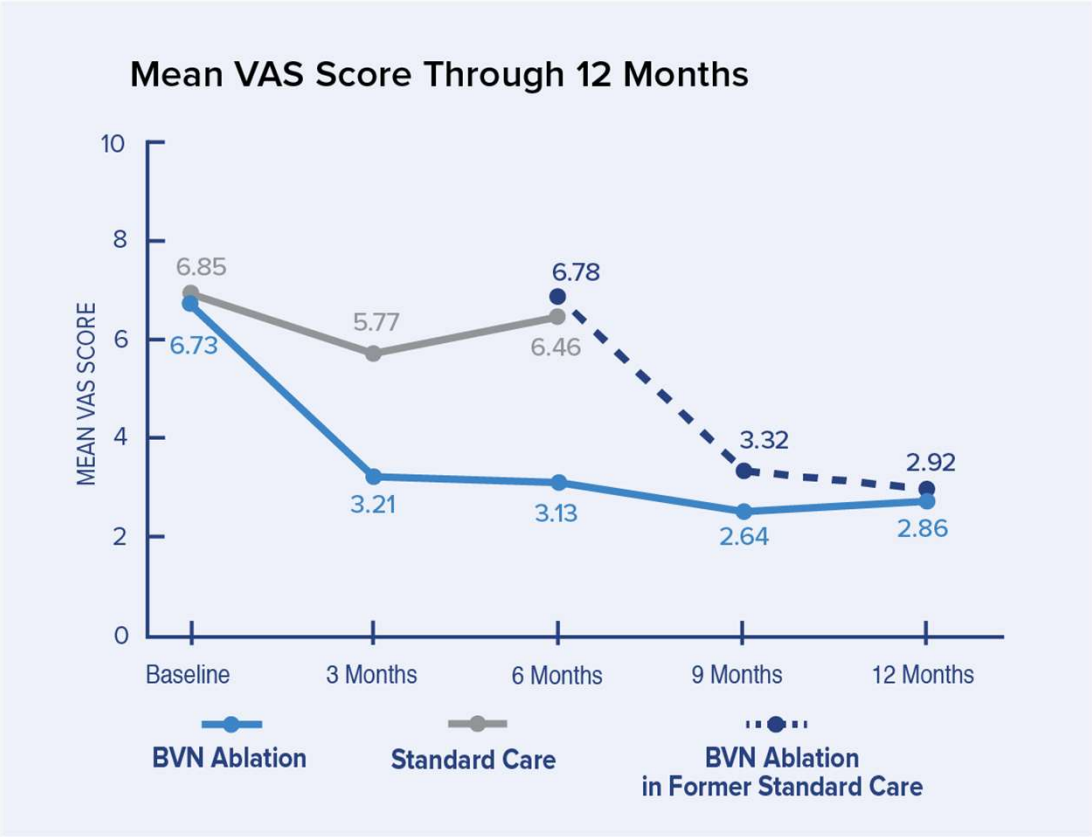
Mean VAS Between Arms



BVN Ablation Arm and Standard Care Arm

- Patients in BVN Ablation Arm demonstrated a statistically significant ($p<0.001$) and clinically meaningful reduction in mean VAS between arms at 3 and 6 months
- Results demonstrated superiority of BVN ablation compared to standard care treatments
- Improvements in pain sustained through 12 months in the BVN ablation arm.

BVN Ablation in Former Standard Care Group

- Similar trajectory at 3 and 6 months after re-baseline and BVN ablation treatment
- Patients demonstrated a statistically significant ($p<0.001$) and clinically meaningful reduction in mean VAS after BVN ablation treatment
- Results sustained through 6 months

Significant and Sustained VAS Pain Improvement After Treatment in All BVN Patients

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INTRACEPT Study
24-Month Results

INTRACEPT Study – 24-Month Results Published October 2021

North American Spine Society Journal (NASSJ) 8 (2021) 100089

Contents lists available at ScienceDirect

North American Spine Society Journal (NASSJ)

journal homepage: www.elsevier.com/locate/xnsj

Clinical Studies

Prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 24-Month treatment arm results

Theodore Koreckij[a,*], Scott Kreiner[b], Jad G. Khalil[c], M. Smuck[d], J. Markman[e], Steven Garfin[f], on behalf of the INTRACEPT Trial Investigators

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ARTICLE INFO

Keywords:
Chronic low back pain
Basivertebral nerve
Basivertebral nerve ablation
Radiofrequency ablation
Modic
Vertebrogenic pain

ABSTRACT

Background: Vertebral endplates, innervated by the basivertebral nerve, can be a source of vertebrogenic low back pain when damaged with inflammation, visible as types 1 or 2 Modic changes. A randomized controlled trial (RCT) compared basivertebral nerve ablation (BVNA) to standard care (SC) showed significant differences between arms at 3 and 6-months. At 12-months, significant improvements were sustained for BVNA. We report results of the BVNA arm at 24-months.

Methods: Prospective, open label, single-arm follow-up of the BVNA treatment arm of a RCT in 20 US sites with visits at 6-weeks, and 3, 6, 9, 12 and 24-months. Paired comparisons to baseline were made for the BVNA arm at each timepoint for Oswestry Disability Index (ODI), Visual Analog Scale (VAS), Short Form Health Survey (SF-36), EQ-5D-5L, and responder rates.

Results: 140 patients were randomized, 66 to BVNA. In the 58 BVNA patients completing a 24-month visit, 67% had back pain for >5 years, 36% were actively taking opioids at baseline, 50% had prior epidural steroid injections, and 12% had prior low back surgery. Improvements in ODI, VAS, SF-36 PCS, and EQ-5D-5L were statistically significant at all timepoints through 2 years. At 24 months, ODI and VAS improved 28.5±16.2 points (from baseline 44.5; $p < 0.001$) and 4.1±2.7 cm (from baseline 6.6; $p < 0.001$), respectively. A combined responder rate of ODI≥15 and VAS≥2 was 73.7%. A ≥50% reduction in pain was reported in 72.4% of patients and 31.0% were pain-free at 2 years. At 24 months, only 3(5%) of patients had BVNA-level steroid injections, and 62% fewer patients were actively taking opioids. There were no serious device or device-procedure related adverse events reported through 24 months.

Conclusion: Intraosseous BVNA demonstrates an excellent safety profile and significant improvements in pain, function, and quality of life that are sustained through 24 months in patients with chronic vertebrogenic low back pain.

Background

Clinicians treating axial chronic low back pain (CLBP) have historically been challenged with limited objective differentiators for pain sources, as well as poor effect sizes and a lack of high-quality evidence for existing treatments [1]. This in turn has resulted in large variations in treatment, including overtreatment, with therapeutic decisions often based on non-specific imaging findings, or diagnoses made by exclusion [2,3]. Advancing science surrounding physiologic and immunohistochemical changes of degenerative disc disease suggests pain result-

Abbreviations: BVN, Basivertebral Nerve; BVNA, Basivertebral Nerve Ablation; CLBP, Chronic Low Back Pain; SC, Standard Care; ODI, Oswestry Disability Index; VAS, Visual Analog Scale; RCT, Randomized Controlled Trial; DMC, Data Management Committee; MCID, Minimal Clinically Important Difference; QOL, Quality of Life; AE, Adverse Events; ANCOVA, Analysis of Covariance; LS, Least Squares; ESI, Epidural Steroid Injection; RDQ, Roland-Morris Disability Questionnaire.

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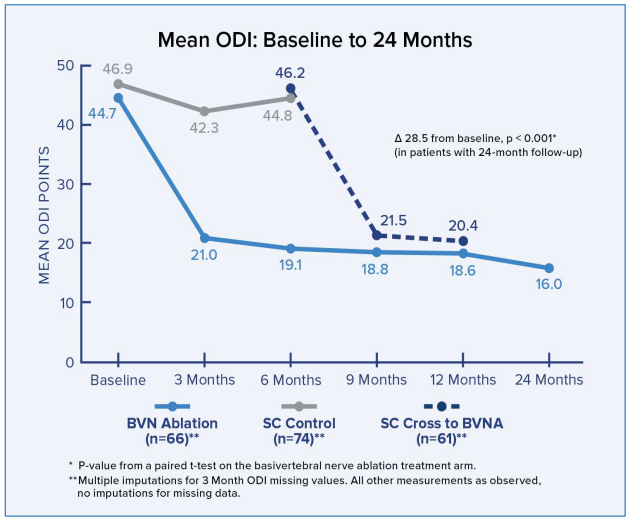
INTRACEPT Study: Sustained Relief at 24 Months

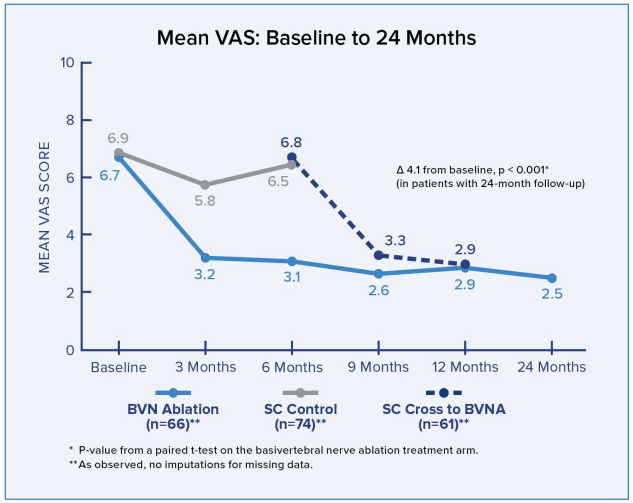
Study Design

- 2nd RCT evaluating BVN ablation; n=140 (interim analysis included 104)
- Allowed treatment of 4 VBs and also previous discectomy
- Mean age was 50.4 years; majority >5 yrs with CLBP
- N=58 patients in the BVN ablation treatment arm were followed 24 months post-treatment (an 88% retention rate)

Key Findings

- Statistically significant and clinically meaningful differences in mean ODI and mean VAS were observed from baseline/re-baseline for each timepoint through 24 months in patients treated with BVN ablation, including control arm patients that crossed to active treatment
  - At 24 months, 28.5 point (p<0.001) reduction in mean ODI; 4.1 cm reduction in mean VAS (p<0.001)
- Typical of anterior column pain, two-thirds of the patients presented with midline axial low back pain that was exacerbated with sitting, forward flexion and with position changes such as sitting to standing
- Study demonstrates an excellent safety profile





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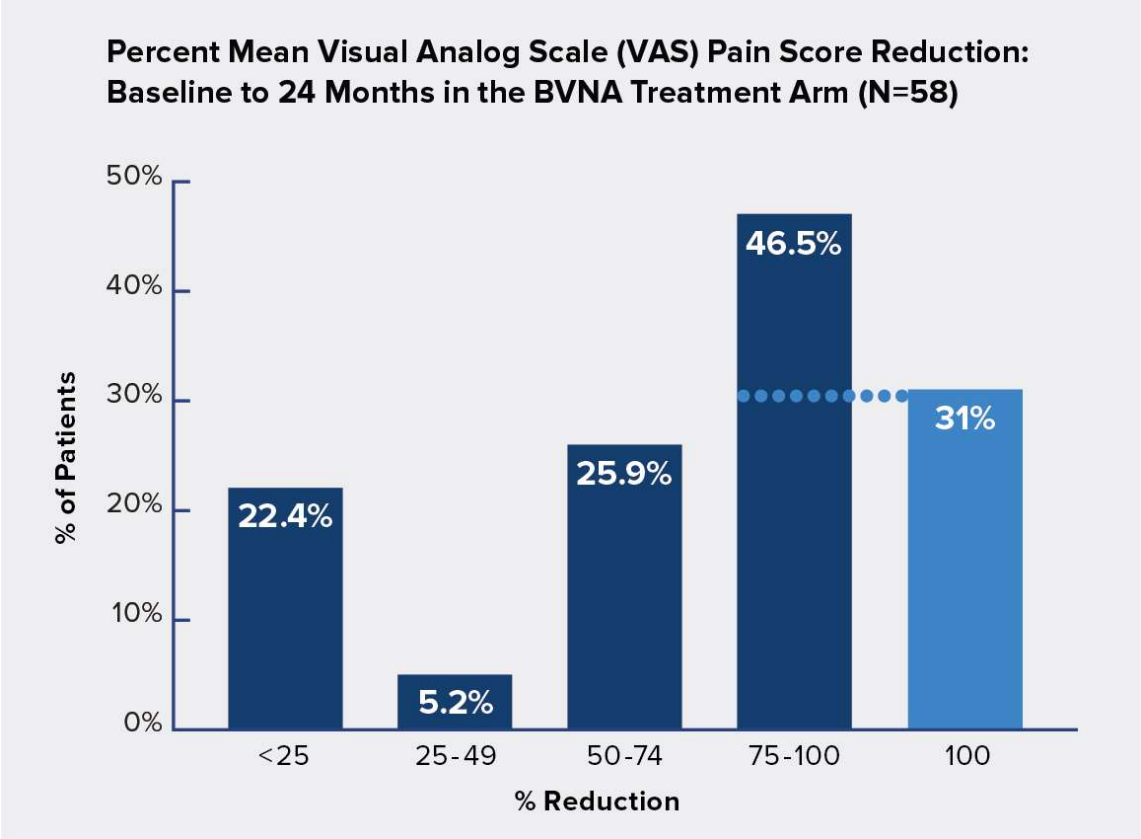
24-Month Results – BVN Ablation Treatment Arm VAS Quadrants



At 24 months post-ablation, 72% of patients reported a > 50% reduction in pain from baseline and 31% were pain free.

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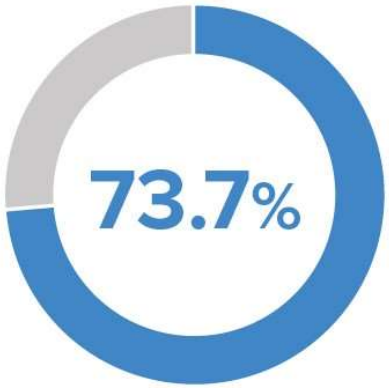
24-Month BVN Ablation Treatment Arm Results – Responder Rates

Combined Responder Rate from Baseline to 24 Months *(p<0.001)*[a]

BVN Ablation Arm *(n=57)*[b,c]



Patients with ≥15-point reduction in ODI and ≥2 cm reduction in VAS

[a] P-value from a Binomial test
[b] As observed with no imputation for missing data
[c] 57 patients with ODI and 58 patients with VAS at 24 months

- Responder rates, using minimal clinically important differences of ≥15-points for ODI and ≥2-cm for VAS, were 77.2% and 79.3%, respectively.

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Conclusions

- Significant improvements in pain, function, and quality of life at all timepoints through 2 years for BVN ablation arm patients
- Typical of anterior column pain, two-thirds of the patients presented with midline axial low back pain that was exacerbated with sitting or bending
- Study demonstrates an excellent safety profile; consistent for two Level I RCTs
- Results demonstrate utility and clinical impact of intraosseous BVN ablation for patients with vertebrogenic CLBP over existing treatments with published poor effect sizes
- 22% of the patients in this follow-up had one or more BVNA treated motion segments with associated Modic changes that were classified as Pfirrmann grades III or below; suggesting endplate changes may occur alongside less degenerated discs yet contribute to disabling chronic vertebrogenic pain

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SMART Trial

SMART Trial – 24 Month Results Published April 2019

INTERNATIONAL JOURNAL of SPINE SURGERY

Intraosseous Basivertebral Nerve Ablation for the Treatment of Chronic Low Back Pain: 2-Year Results From a Prospective Randomized Double-Blind Sham-Controlled Multicenter Study

Jeffrey S. Fischgrund, Alfred Rhyne, Jörg Franke, Rick Sasso, Scott Kitchel, Hyun Bae, Christopher Yeung, Eeric Truumees, Michael Schaufele, Philip Yuan, Peter Vajkoczy, Michael Depalma, David G. Anderson, Lee Thibodeau and Bernhard Meyer

Int J Spine Surg published online 4 April 2019
http://ijssurgery.com/content/early/2019/04/03/6015

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Fischgrund J et al., Intraosseous Basivertebral Nerve Ablation for the Treatment of Chronic Low Back Pain: 2-Year Results from a Prospective Randomized Double-Blind Sham-Controlled Multicenter Study. International Journal of Spine Surgery, Vol. 13, No. 2, 2019, pp. 1–10.

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SMART Trial Design

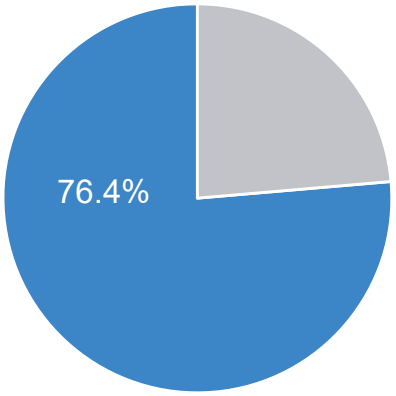
- Randomized, double-blind, sham-controlled
- Multi-Center: 15 US and 3 EU sites
- 225 Patients; Randomized to treatment (147) or sham (78) intervention
- Patients were evaluated preoperatively and at 2 weeks and 6 weeks and 3, 6, 12 and 24 months postoperatively
- Skeletally mature patients with chronic (≥ 6 months), isolated lumbar pain, who had not responded to at least 6 months of non-operative management
- All patients had Type 1 or Type 2 Modic changes of the treated vertebral bodies
- Outcome Measures: ODI, SF-36, and VAS
- Sham patients offered cross-over Intracept Procedure at 12 months

Fischgrund J et al., Intraosseous Basivertebral Nerve Ablation for the Treatment of Chronic Low Back Pain: 2-Year Results from a Prospective Randomized Double-Blind Sham-Controlled Multicenter Study. International Journal of Spine Surgery, Vol. 13, No. 2, 2019, pp. 1–10.

Responder Rates Maintained At 24-Month Follow Up[1]

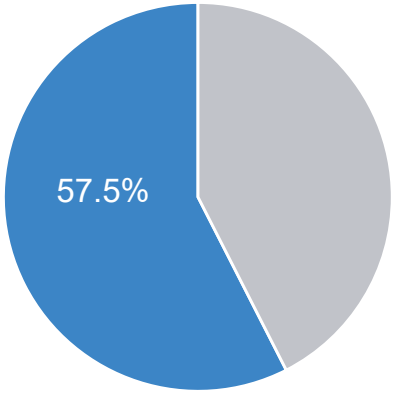
ODI

% of Patients with ≥ 10 Point Improvement in ODI



n=106*

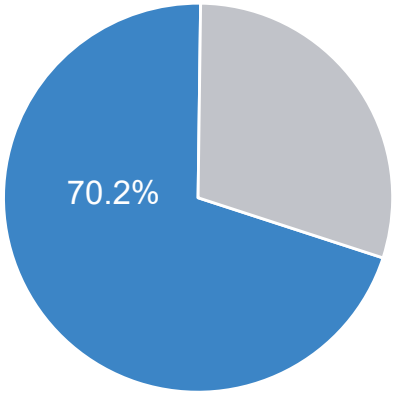
% of Patients with ≥ 20 Point Improvement in ODI



n=106*

VAS

% of Patients with ≥ 1.5cm Improvement in VAS



n=104*

1. Per Protocol Treatment Arm
*All observed data without imputation used

Fischgrund J et al., Intraosseous Basivertebral Nerve Ablation for the Treatment of Chronic Low Back Pain: 2-Year Results from a Prospective Randomized Double-Blind Sham-Controlled Multicenter Study. International Journal of Spine Surgery, Vol. 13, No. 2, 2019, pp. 1–10.

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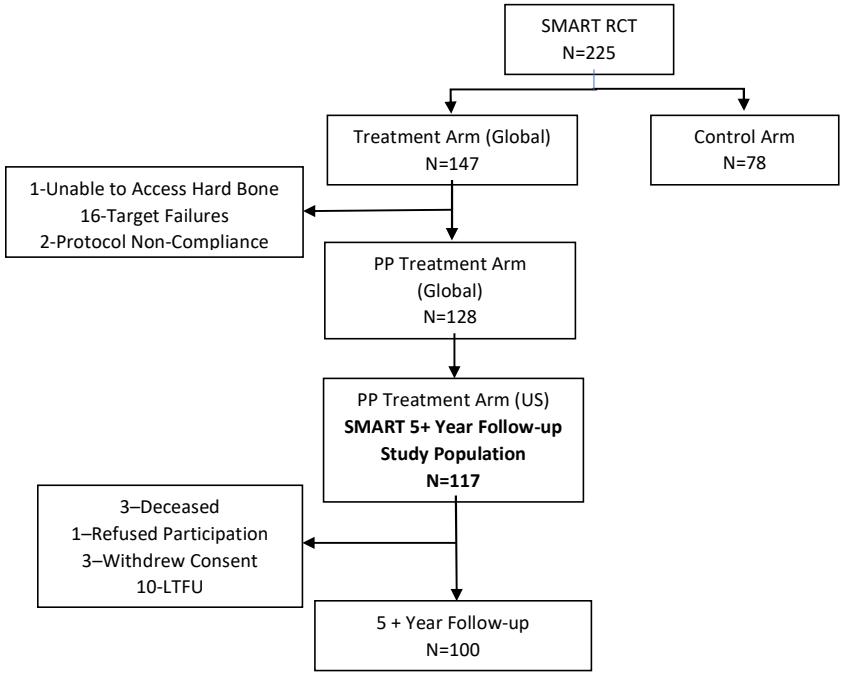
SMART 5-Year Results

SMART 5 Year – Study Design

- US PP BVN Ablated patients
- All 13 US sites that treated patients participated
- Visits completed by an independent clinical research nurse
- 85% U.S. PP retention rate (100/117)
- Mean follow-up 6.4 years (range 5.4 to 7.8 yrs.)



Fischgrund JS, Rhyne A, Macadaeg K, Moore G, Kamrava E, Yeung C, et al. Long-term outcomes following intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 5-year treatment arm results from a prospective randomized double-blind sham-controlled multi-center study. Eur Spine J. epub May 25, 2020. https://doi.org/10.

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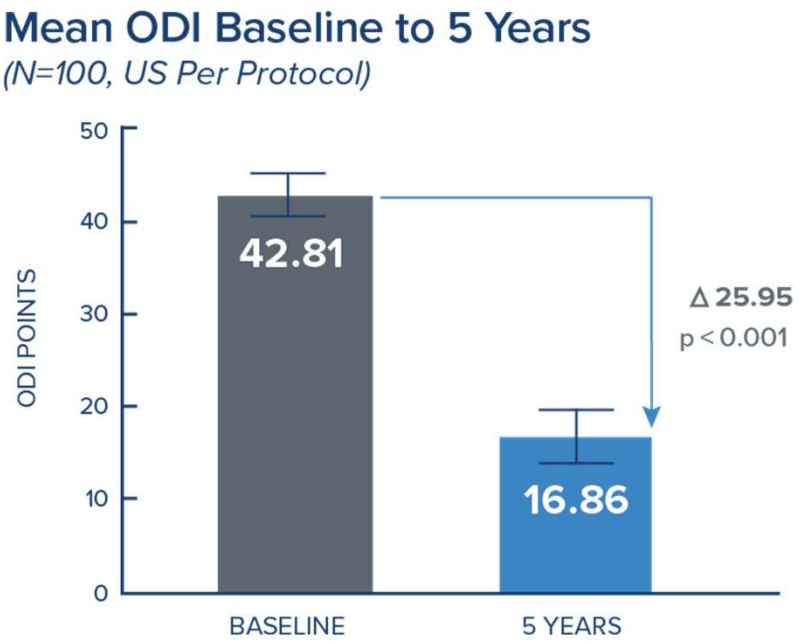
SMART 5 Year – Primary Endpoint Mean ODI Improvement

- ODI improvement of 25.95 points at 5+ years
- Significant difference (p<0.001)
- Narrow, non-overlapping CI



Fischgrund JS, Rhyne A, Macadaeg K, Moore G, Kamrava E, Yeung C, et al. Long-term outcomes following intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 5-year treatment arm results from a prospective randomized double-blind sham-controlled multi-center study. Eur Spine J. epub May 25, 2020. https://doi.org/10.

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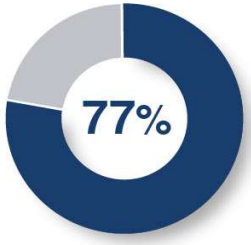
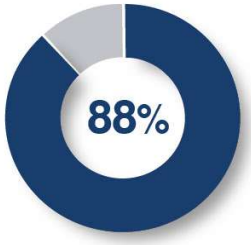
SMART 5 Year – Responder Rates

Responder Rates at 5 Years

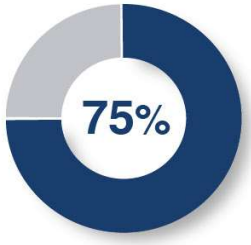


Patients with
≥ 15 Improvement
in ODI



Patients with
≥ 2.0 Reduction
in VAS

Composite Treatment Success



≥ 15 ODI Improvement
≥ 2.0 VAS Reduction

Fischgrund JS, Rhyne A, Macadaeg K, Moore G, Kamrava E, Yeung C, et al. Long-term outcomes following intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 5-year treatment arm results from a prospective randomized double-blind sham-controlled multi-center study. Eur Spine J. epub May 25, 2020. https://doi.org/10.

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CLBP Single Arm Prospective Study

CLBP Single Arm Prospective Study – Published 2020

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Clinical Studies

A prospective, single arm study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 12-month results

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ABSTRACT

Background: The basivertebral nerve (BVN) has been a recently discovered target as a potential source for vertebrogenic chronic low back pain (CLBP). Prior randomized controlled trials have demonstrated safety and efficacy of BVN ablation for vertebrogenic CLBP, but minimal data exists regarding BVN ablation's clinical effectiveness with broader application outside of strict trial inclusion criteria.

Methods: Prospective, single arm, open label effectiveness trial of 48 patients from community spine and pain practices treated with BVN ablation. Inclusion criteria required more than 6 months of CLBP and type 1 or 2 Modic changes on MRI to be enrolled. Patients were followed post procedure for 12 months using ODI, VAS, EQ-5D-5L and SF-36 patient reported outcome metrics.*Results:* 47 patients successfully received BVN ablation and 45 patients completed 12 months of follow up. Mean reduction in ODI at 12 months was 32.31 +/- 14.07 ($p<0.001$) with 88.89% (40/45) patients reporting a ≥15 point ODI decrease at 12 months. Mean VAS pain score decrease was 4.31 +/-2.51 at 12 months ($p<0.001$) and more than 69% reported a 50% reduction in VAS pain scale. Similarly, SF-36 and EQ-5D-5L scores improved 26.27 +/-17.19 and 0.22 +/-0.15 (each $p<0.001$).

Conclusions: This data supports the clinical effectiveness of BVN ablation in the community practice setting, with similar 12 month improvements in patient reported outcomes as seen in previously published randomized control trials.

Background

Chronic low back pain (CLBP) is a common and debilitating condition, affecting 5–10% of the adult US population and impacting the lives of more than 30 million Americans [1-3]. The source of CLBP is challenging to identify and treat, resulting in long term disability and a disproportional consumption of healthcare resources at a significant rate [3]. Recent studies have highlighted the potential contribution of vertebrogenic sources of CLBP [4-6]. Altered force transfer and endplate loading occur through disc derangements secondary to degenerative disc disease, resulting in changes to endplate morphology and composition with additional impairment in permeability and transport; further accelerating disc degeneration [7]. Proinflammatory material in the disc triggers an inflammatory response in the bone marrow that sensitizes local nociceptors, and results in Modic changes visible on MRI [4, 8-11]. Although low back pain is a complex and multifactorial pathology, multiple studies have suggested the presence of Modic changes to positively correlate with chronic low back pain [12, 13].

The basivertebral nerve (BVN), enters the vertebrae through the posterior basivertebral foramen and then arborizes to innervate the superior and inferior endplates. Pain signals from the BVN are transmitted via the sinuvertebral nerve to the central nervous system [14]. Immunohistochemical studies of the BVN demonstrate the presence of PGP 9.5 and substance-P, supporting its role in nociceptive innervation [14-17]. Two level 1 trials have reported successful outcomes of radiofrequency (RF) ablation of the BVN compared to sham-control and standard care-control arms in patients with chronic vertebrogenic low back pain [18, 19].

Randomized control trials designed to test efficacy of a therapy are often more restrictive in inclusion and exclusion criteria to isolate treatment effects, and may not fully reflect the broader low back pain population encountered in typical spine clinics. A prospective single arm effectiveness study of BVN ablation, employing more permissive criteria, including use of extended release narcotics and prior lumbar discectomies, was initiated. An interim analysis was conducted and reported when the first 28 patients treated reached their 3-month post procedure visit [20]. Superiority of the primary endpoint was demonstrated with a change in ODI of -30.07 ± 14.52 points ($p < 0.0001$) and with 75% of patients reporting a ≥ 20-point improvement in ODI. Pain scores were decreased by 3.5 points on a 0–10 scale at 3-months. Enrollments were stopped in the study with 50 study participants enrolled and 47 of these successfully treated. This manuscript reports the 12-month follow-up results for all patients enrolled and treated with BVN ablation at these two typical spine practices.

https://doi.org/10.1016/j.xnsj.2020.100030

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Prospective, Single-Arm Study: 12-Month Results

A prospective, open-label, single-arm, multi-center study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 12-month results		
Enrollment Criteria	**Effectiveness Endpoints**	**Study Population**
• Skeletally mature patients • Chronic (≥ 6 months) isolated lumbar back pain • Not responsive to at least 6 months of nonoperative management • Type 1 or Type 2 Modic changes at one or more vertebral body for levels L3-S1	**Primary:** Patient reported change in Oswestry Disability Index (ODI) from baseline to 3 months posttreatment. **Secondary:** Patient reported change in ODI at 6, 9 and 12 months and improvement in VAS, SF-36 and EQ-5D-5L and responder rates at 3, 6, 9 and 12-months posttreatment **Statistics:** 90% powered to detect 15-point change in ODI at N=50; Interim analysis at 60% completing 3-month primary endpoint visit	• 47 patients successfully treated (45 with 12-month follow-up) • Baseline ODI of 47.13 • Baseline VAS of 6.82 • Mean age of 44.5 years • Symptom duration: 72.3% > 5 years • Working full-time: 75% • Opioid use at baseline: 21.3% • Previously treated with injections: 48.9%

Truumees, E., Macadaeg, K., Pena, E. et al., A prospective, open-label, single-arm, multi-center study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain Eur Spine J (2019). doi.org/10.1007/s00586-019-05995-2

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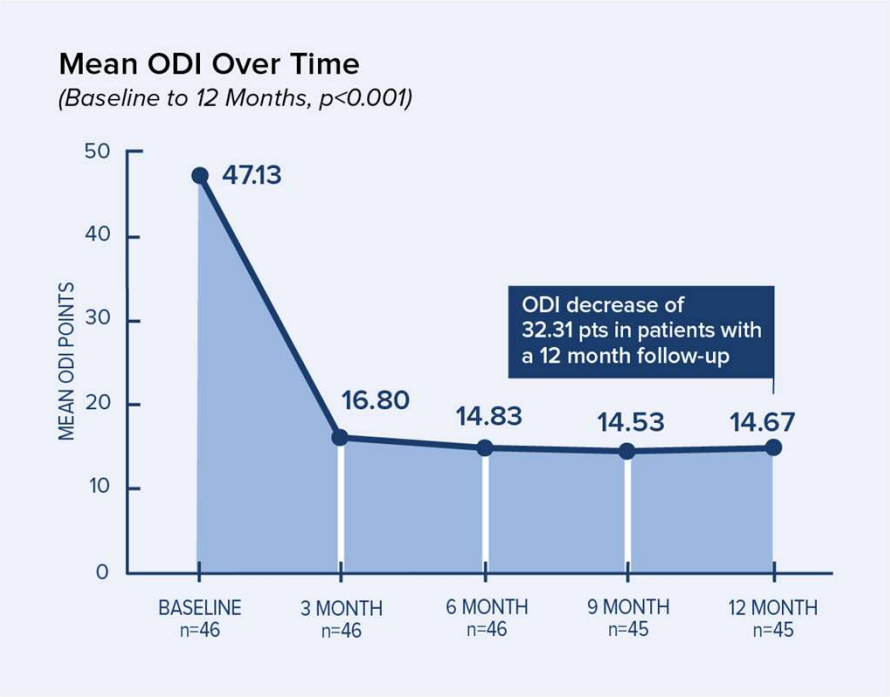
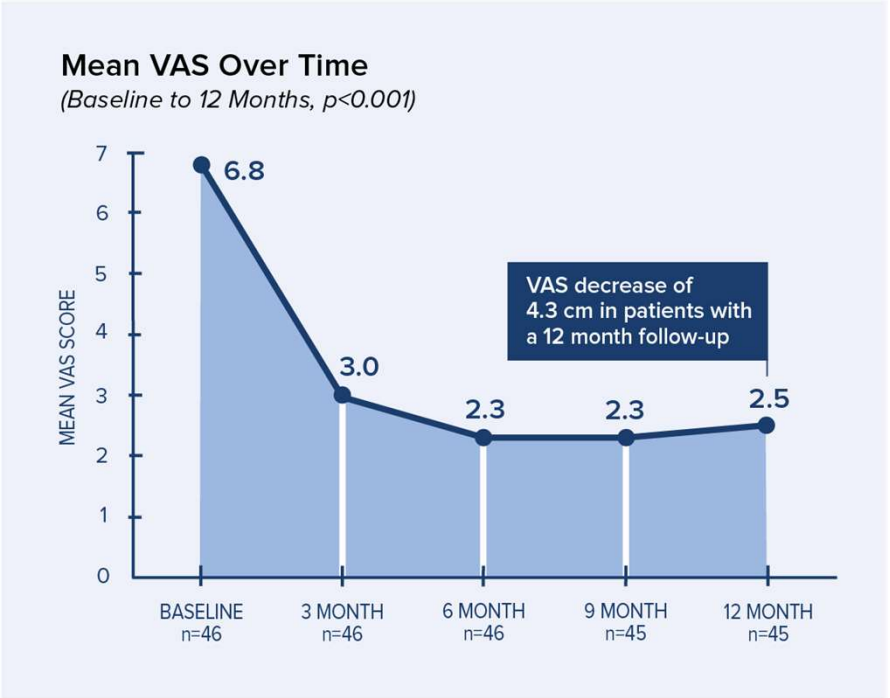
Mean ODI and VAS from Baseline to 12 Months





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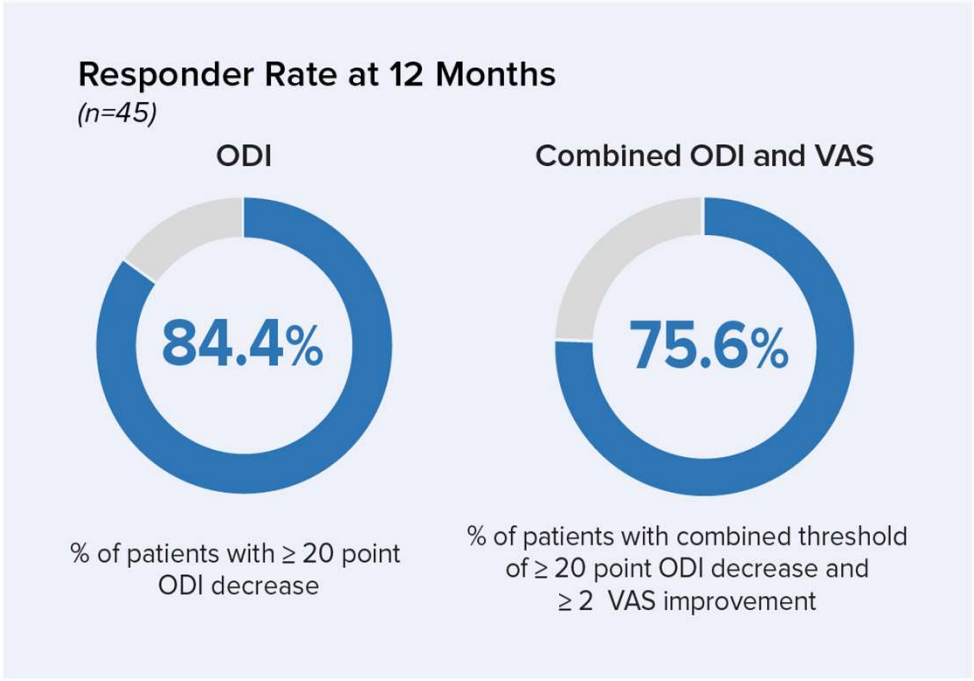
Responder Rates from Baseline to 12 Months; Majority Report Improvements Above Typical MCID*



*Minimal Clinically Important Difference is ≥15 point reduction in ODI and ≥2cm reduction in VAS.

Truumees, E., Macadaeg, K., Pena, E. et al., A prospective, open-label, single-arm, multi-center study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain Eur Spine J (2019). doi.org/10.1007/s00586-019-05995-2

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