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Clinical Studies

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

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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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ing from vertebral endplate changes as a clinically distinct subgroup of CLBP. Vertebral endplates are innervated by the basivertebral nerve (BVN), a branch of the sinuvertebral nerve, which becomes thinly or non-myelinated after entering the bone marrow through the posterior basivertebral foramen (BVF) [4,5]. Biomechanically, the endplates are subjected to significant loads during activities of daily living and are susceptible to damage. With physiological aging, endplates gradually thin and calcification occurs. High tensile strains associated with disc degeneration further increase the endplate vulnerability [6]. Endplate damage has been shown to result in cellular communication between the inflammatogenic disc nucleus and vertebral bone marrow triggering chronic inflammation and densification of endplate nociceptors [7], a process that is visible as Modic changes on magnetic resonance imaging (MRI) [8]. An association has been reported between the presence of Type 1 or Type 2 Modic changes and CLBP [9,10].

Two randomized controlled trials (RCTs) have evaluated the BVN as a target for radiofrequency ablation in treating this subgroup of vertebrogenic CLBP patients. In the pivotal SMART trial, a significant difference between arms for reduction in mean Oswestry Disability Index (ODI) was demonstrated for BVNA over a sham-control at the 3-month primary endpoint and clinically relevant improvements in visual analog pain scores (VAS) and function were sustained through 2 and 5 years [11–13]. A second RCT was conducted to compare BVNA to non-surgical standard care (SC). A pre-specified intent-to-treat interim analysis conducted when $N = 104$ patients ($n = 51$ BVN ablation, $n = 53$ SC) completed their 3-month primary endpoint visit, demonstrated clear statistical superiority ($p < 0.001$) of BVNA over SC for all primary and secondary endpoints (change in ODI, VAS, SF-36, EQ-5D-5L) and resulted in a recommendation by the independent Data Management Committee (DMC) to halt study enrollment and offer the SC arm an early cross to active treatment [14].

At the point of crossover (median of 5.8 months), the between arm results for the full randomized cohort ($N = 140$) showed a significant difference in mean ODI reduction (26.1 points for BVNA vs 1.6 points for SC; $p < 0.001$) and in mean VAS reduction (3.6 cm for BVNA vs 0.3 cm for SC; $p < 0.001$). Likewise, in the 91% of SC arm patients that opted to cross to BVNA, similar results were observed, with reductions of 25.9 points in mean ODI and 3.8 cm in mean VAS from re-baseline at 6 months post ablation. Treatment outcomes for the BVNA remained durable through 12 months [15]. We report 24-month outcomes of the treatment arm for this second RCT and explore the applicability of these results in practice today.

## Methods

### *Design*

The INTRACEPT trial is a prospective, parallel, open-label RCT of 140 patients randomized in 20 U.S. sites from September 2017 to January 2019. The trial was registered on ClinicalTrials.gov as NCT03246061 (https://clinicaltrials.gov/ct2/show/NCT03246061) and sponsored by Relievant Medsystems, Inc. (Minneapolis, MN). The study was conducted under Institutional Review Board approval and participant informed consent. Data was source-verified by independent study monitors (M Squared Associates Inc., New York, NY). Independent statisticians (Abond CRO Inc., Grand Rapids, MI) prepared the computer-generated randomization schemes and conducted the statistical analyses. Full design details were previously published [14].

### *Participants*

Study participants were recruited from current pain populations at study sites and through web-based self-referral. Consecutively consented patients were screened for further eligibility prior to MRI review for endplate changes and radiographic exclusion criteria. The primary requirements for inclusion were CLBP of vertebrogenic origin with a duration of greater than 6-months with conservative treatment and associated Modic Type 1 or Type 2 changes in vertebral levels L3 to S1. See Table 1 for a full listing of the inclusion and exclusion criteria. Eligibility for randomization was confirmed by an independent orthopedic surgeon medical monitor and included a review of pain characteristics and radiographic presentation to rule out other primary sources of CLBP. Consecutive eligible patients were randomized 1:1 to either BVNA or SC using permuted blocks of four or six stratified by study site.

### *Interventions*

Patients randomized to BVNA received treatment at all levels (L3-S1) that exhibited qualifying Modic changes using the Intracept ® System (Relievant Medsystems, Minneapolis, MN USA) which was performed under image guidance, under moderate conscious sedation or general anesthesia, and in an outpatient setting, using a unilateral transpedicular approach to access the BVN. Targeted location for electrode placement was approximately 30–50% across vertebral body width from the posterior wall, and in the same horizontal plane as the BVF (channel that houses the BVN) on sagittal imaging. After confirmation of placement, thermal ablation was delivered for 15 min at 85°C to create an approximately 1-cm spherical lesion within each vertebral body [14]. All patients continued nonsurgical therapies as per the investigator's medical judgment and patient symptoms.

Standard care for both arms was determined by the investigator based on patient treatment history and clinical need. Standard care treatments included (but was not limited to) the following: physical therapy, exercise, chiropractic treatment, acupuncture, oral pain medications and spinal injections.

### *Follow-up*

Per the original protocol design, BVNA arm patients were followed at 6 weeks, and 3, 6, 9, 12, and 24-months. SC patients were to be followed at 3, 6, 9, and 12-months, and then offered active treatment with BVN ablation. A pre-specified interim analysis was performed when approximately 60% of randomized patients completed their 3-month primary endpoint visit. Statistical superiority was demonstrated in the primary and all secondary endpoints. Per informed consent regulations that require disclosure of new information during a clinical trial that may affect a participant's decision to continue participation, the reviewing DMC recommended stopping randomization and offering the SC arm early cross to active treatment after collecting a re-baseline at their next scheduled study visit. Re-baseline occurred at a median of 175 (range 24 to 372) days post randomization. SC arm patients who elected to cross to active treatment with BVN ablation were followed at 6-weeks, 3-months, and 6-months post BVNA treatment per the original protocol. SC patients that declined BVN ablation were exited from the study. The BVNA treatment arm continued systematic, prospective follow-up per the protocol through 24 months and are reported here.

### *Target success*

MR imaging (T1, T2, and STIR time constants) was performed at 6-weeks post BVN ablation for all treated patients. Target success was confirmed by an independent neuroradiologist based on a pre-defined threshold of overlap between the terminus of the BVN and the ablation lesion. All levels with either Type 1 or Type 2 Modic changes between L3 and S1 were required to be treated. Untreated levels with Modic changes were deemed a target failure.

### *Outcome measures*

The validated patient-reported outcomes completed by subjects at each study visit included: functional impact using the Oswestry Disability Index (ODI) [16] with a minimal clinically important difference (MCID) of 15-points [17], low back pain using a Visual Analog

**Table 1**
**Inclusion and exclusion criteria.** A listing of the inclusion and exclusion criteria for the study is noted.

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Skeletally mature patients with chronic (≥6 months) isolated lumbar back pain, who had not responded to at least 6 months of non-operative management<br>• Type 1 or Type 2 Modic changes at one or more vertebral body for levels L3-S1<br>• Minimum Oswestry Disability Index (ODI) of 30 points (100-point scale)<br>• Minimum Visual Analog Scale (VAS) of 4 centimeters (cm) on a 10 cm scale<br>• Ability to provide informed consent, read and complete questionnaires | • Magnetic Resonance Imaging (MRI) evidence of Modic at levels other than lumbar level 3 to sacral level 1 (L3-S1)<br>• Radicular pain (defined as nerve pain following a dermatomal distribution and that correlates with nerve compression in imaging)<br>• Previous lumbar spine surgery (discectomy / laminectomy allowed if > 6 months prior to baseline and radicular pain resolved)<br>• Symptomatic spinal stenosis (defined as the presence of neurogenic claudication and confirmed by imaging)<br>• Metabolic bone disease, spine fragility fracture history, or trauma / compression fracture, or spinal cancer<br>• Spine infection, active systemic infection, bleeding diathesis<br>• Radiographic evidence of other pain etiology<br>• Disc extrusion or protrusion > 5 millimeters (mm)<br>• Spondylolisthesis > 2 mm at any level<br>• Spondylolysis at any level<br>• Facet arthrosis / effusion correlated with clinically suspected facet-mediated low back pain<br>• Beck Depression Inventory (BDI) > 24 or 3 or > Waddell's signs<br>• Compensated injury or litigation<br>• Currently taking extended-release narcotics with addiction behaviors<br>• Body Mass Index (BMI) > 40<br>• Bedbound or neurological condition that prevents early mobility or any medical condition that impairs follow up<br>• Contraindication to MRI, allergies to components of the device, or active implantable devices, pregnant or lactating |

Abbreviations: MRI, magnetic resonance imaging; ODI, Oswestry Disability Index; VAS, visual analogue scale; cm, centimeters; mm, millimeters; Beck Depression Index, BDI; BMI, body mass index.

Scale (VAS) [18] from 0 (no pain) to 10 (worst pain imaginable) with a MCID of 2.0 cm [17], and health status and quality of life (QOL) using the Short Form (SF-36) [19] with a physical component MCID of 4.9 [17] and EuroQual Group 5 Dimension 5-Level Quality of Life (EQ-5D-5L) [20] with a MCID of 0.03 points [17]. Data entries by research coordinators for patient-completed questionnaires were verified by the independent study monitors. Spinal and neurological adverse events (AEs) were collected at each study visit and were adjudicated by an independent clinical event committee (CEC) that determined relatedness to the device therapy. All pain interventions and surgeries that were performed in patients post randomization were adjudicated by the CEC for a determination of BVNA treatment failure based on location and reason for treatment from submitted medical records and images.

*Sample calculations*

The primary endpoint for this study was the difference between arms in the change in mean ODI at 3-months. The study had one planned interim analysis for primary end-point superiority testing. Statistical significance of the primary endpoint was defined as $p < 0.025$ for the group sequential design for an overall alpha of $p < 0.05$. Initial sample size was 150 patients (75 in each group) with an estimated 15% attrition rate to detect a 10-point difference in mean ODI reduction between arms.

*Statistical analysis*

Statistical analysis was performed with SAS version 9.3 software (SAS Institute Inc, Cary, NC), using an analysis of covariance (ANCOVA) with a factor of treatment group and a covariate of baseline scores for statistical comparisons between arms for the primary endpoint ODI and secondary endpoints of VAS, SF-36 and EQ-5D-5L. The 3-month ODI was analyzed as intent to treat with multiple imputations for missing data for both arms. Six-month between arm results are reported using last observation prior to the blinded re-baseline in the standard care control arm. Comparisons between post BVNA and the baseline values at 12 and 24 months are performed using a paired t-test without imputation for missing values. Responder rates, using MCID thresholds described above, were analyzed using Fischer's Exact test.

*Study revisions*

Protocol revisions allowed for treatment of up to four vertebrae and non-consecutive levels from L3-S1 with FDA clearance, as described previously [14], and the addition of an optional five-year follow-up sub study for BVNA arm patients. An evaluation of the impact of protocol revisions to the 3-month primary endpoint detected no significant differences, and therefore no adjustment was required. A final study revision stopped randomization and allowed for re-baseline and the early option of active treatment to the SC control arm patients per the DMC recommendation.

## Results

*Patient disposition, baseline characteristics, and treatment success*

At the time of the DMC recommendation to stop enrollment, 140 patients were randomized (66 BVNA, 74 SC) at 20 study sites. In the BVNA treatment arm 58 of the 66 randomized patients had a 24-month follow-up visit (a retention rate of 88%). See Fig. 1 for a detailed participant disposition at each follow-up timepoint. In this population of BVNA randomized patients with a 24-month visit, the percentage of patients with LBP symptoms ≥ 5 years was 67% and patients reported moderate to severe pain and disability levels at baseline with mean VAS of 6.6

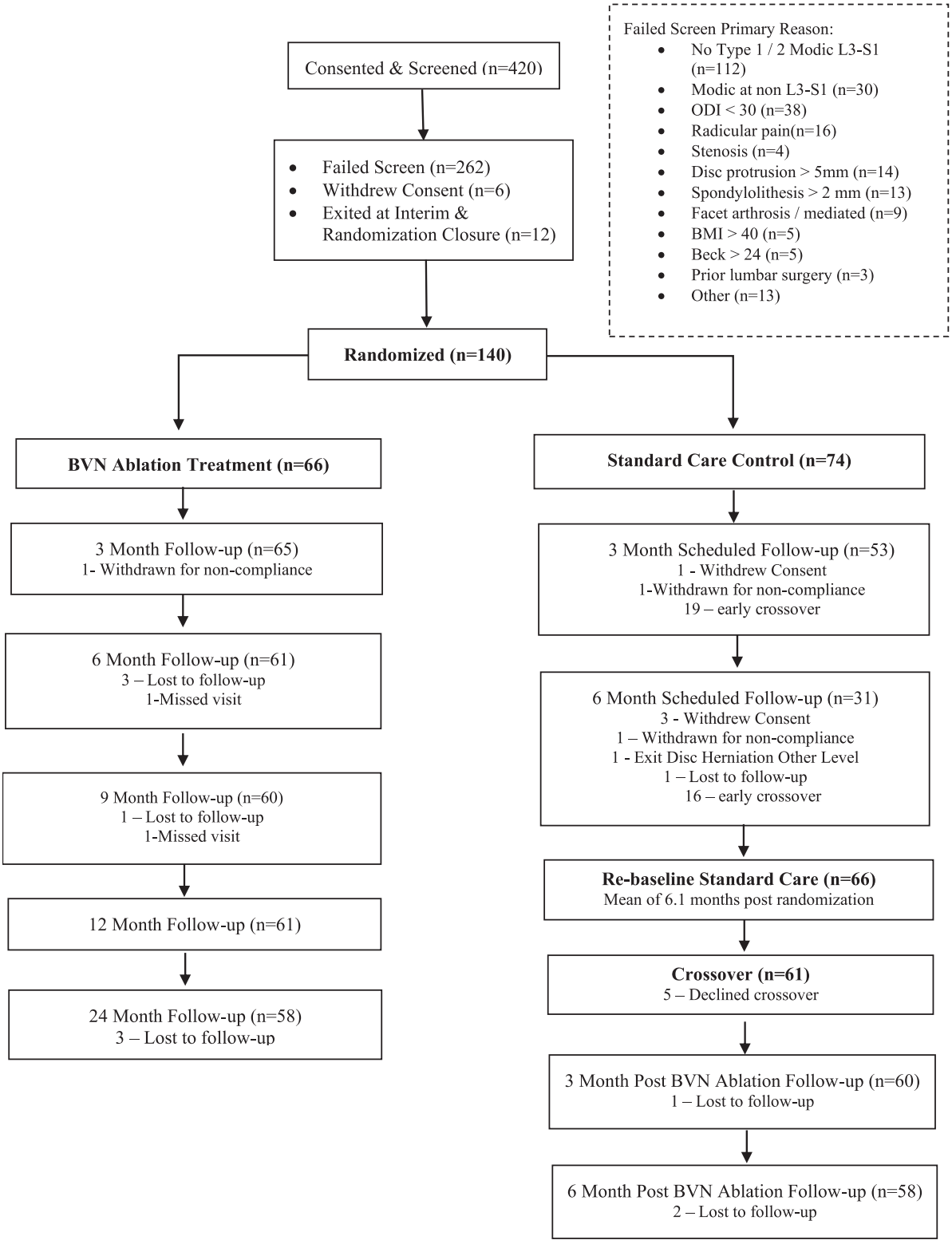


**Fig. 1. Patient disposition flow diagram**. At the point of enrollment halt due to statistical superiority at an interim analysis, 140 participants were randomized (66-BVN Ablation, 74-SC) in the study. After a blinded re-baseline, the remaining SC arm patients ($n$ = 66) were offered BVN ablation, with 61(92%) electing to cross to active treatment ($N$ = 61); of whom 3 were lost to follow-up. In the BVN ablation treatment arm 58 of the 66 randomized had a 24-month follow-up visit (a retention rate of 88%). Details on reasons for study exit are reported for each follow-up time point. Abbreviations: ODI, Oswestry Disability Index; VAS, visual analogue scale; BMI, body mass index; BVN, basivertebral nerve.

**Table 2**
**Baseline characteristics.** Demographic and baseline characteristics for BVN ablation randomized patients showed no statistically significant differences between those with a 24-month follow-up and the full treatment arm.

| | Basivertebral nerve ablation arm full cohort($N$ = 66) | Basivertebral nerve ablation arm with 24 month visit($N$ = 58) |
|---|---|---|
| Mean Age in years (range) | 49.4 (30 to 68) | 50.4 (30 to 68) |
| Male, *n* (%) | 34 (51.5%) | 30 (51.7%) |
| Duration LBP symptoms ≥ 5 years *n*(%) | 42 (63.6%) | 39 (67.2%) |
| Mean Days per week with LBP | 6.8 (4 to 7) | 6.8 (4 to 7) |
| Pain Location (per patient-completed body diagram) | | |
| Midline only *n* (%) | 17 (25.8%) | 17 (29.3%) |
| Paraspinal only *n* (%) | 8 (12.1%) | 7 (12.1%) |
| Midline and Paraspinal *n* (%) | 25 (37.9%) | 20 (34.5%) |
| Lateral only *n* (%) | 12 (18.2) | 10 (17.2%) |
| Below mid-gluteal line *n* (%) | 4 (6.1%) | 4 (6.9%) |
| Mean ODI (Range) | 44.7 (30 to 76) | 44.2 (30 to 76) |
| Mean VAS (Range) | 6.7 (4.0 to 10.0) | 6.6 (4.0 to 9.0) |
| Mean SF-36 PCS[2] (Range) | 32.06 (18.43 to 46.93) | 32.33 (18.43 to 46.07) |
| Mean SF-36 MCS[3] (Range) | 53.42 (22.24 to 69.80) | 53.85 (33.18 to 69.80) |
| Mean EQ-5D-5L[4] (Range) | .613 (.270 to .832) | 0.624 (0.378 to 0.832) |
| Mean BDI[5] (Range) | 6.2 (0 to 20) | 6.2 (0 to 20) |
| Grade 1 Spondylolisthesis *n* (%) | 9 (13.6%) | 7 (12.1%) |
| Disc Protrusion (< 4 mm) *n* (%) | 37 (56.1%) | 33 (56.9%) |
| Pfirrmann Grades in Patients *n* (%) | Patients ($N$ = 66) | Patients ($N$ = 58) |
| Grade I *n* (%) | 0 (0.0%) | 0 (0.0%) |
| Grade II *n* (%) | 1 (1.5%) | 1 (1.7%) |
| Grade III *n* (%) | 15 (22.7%) | 12 (20.7%) |
| Grade IV *n* (%) | 32 (48.5%) | 29 (50.0%) |
| Grade V *n* (%) | 25 (37.9%) | 23 (39.7%) |
| Pfirrmann Grades for Treated Motion Segment *n* (%) | Motion Segments($n$ = 82) | Motion Segments($n$ = 73) |
| Grade I *n* (%) | 0 (0.0%) | 0 (0.0%) |
| Grade II *n* (%) | 1 (01.2%) | 1 (01.4%) |
| Grade III *n* (%) | 18 (22.0%) | 14 (19.2%) |
| Grade IV *n* (%) | 37 (45.1%) | 34 (46.6%) |
| Grade V *n* (%) | 26 (31.7%) | 24 (32.8%) |
| Treatment History *n* (%) | | |
| Opioid Use at Baseline *n* (%) | 22 (33.3%) | 21 (36.2%) |
| Epidural Steroid Injections *n* (%) | 36 (54.5%) | 29 (50.0%) |
| Past Lower Pack Surgeries *n* (%) | 7 (10.6%) | 7 (12.1%) |
| Type of Modic by Subject, *n* (%) | | |
| Type 1 | 23 (34.8%) | 19 (32.8%) |
| Type 2 | 34 (51.5%) | 32 (55.2%) |
| Mixed (Type 1 & Type 2) | 9 (13.6%) | 7 (12.1%) |

Abbreviations: LBP, low back pain; ODI, Oswestry Disability Index; VAS, Visual Analog Scale; SF-36, Short Form 36, PCS, physical component summary; MCS, mental component summary; EQ-5D-5L, EuroQual Group 5 Dimension 5-Level Quality of Life; BDI, Beck Depression Index; BVN, basivertebral nerve; BVNA, basivertebral nerve ablation.

and mean ODI of 44.2. The majority (81%) of patients in this BVNA 24-month population presented with midline and /or paraspinal axial back pain that was exacerbated with sitting, standing, and flexion. Twenty-two percent of the patients in this follow-up had one or more BVNA treated motion segments with associated Modic changes that were categorized as Pfirrmann grade III (on the 5-point Pfirrmann grading scale) per independent radiologic review.

Fifty percent of the patients had epidural steroid injections in the 24-months prior to baseline, 36% were actively taking opioids, and 12% had previous low back surgery (microdiscectomy or laminectomy) of the same level as planned treatment (with a minimum of 6-months healing period prior to enrollment). Baseline characteristics of the full cohort of BVN ablation treatment arm patients ($N$ = 66) and patients with a 24-month visit ($N$ = 58) are similar. See Table 2. Targeting success in this group of patients with a 24-month visit was 98% (130/132) of vertebral bodies treated per independent radiologic review.

*BVN ablation arm: 24-month results*

In the BVNA treatment arm patients with a 24-month visit, statistically significant improvements in pain and function compared to baseline were observed for all timepoints through 24 months. BVN ablation arm patients with a 24-month follow-up visit reported a mean improvement in ODI of 28.5 ± 16.2 points (from a paired baseline of 44.5 to 16.0; $p < 0.001$) and mean improvement in VAS of 4.1 ± 2.7 cm (from 6.6 to 2.5; $p < 0.001$) at 2 years post ablation. See Table 3 and Figs. 2 and 3.

Seventy-two percent (72%) of the BVN ablation arm patients reported a ≥ 50% reduction in VAS, 47% achieved a >75% reduction, and 31% reported 100% pain relief at their 24-month visit. See Fig. 4. An ODI improvement of ≥ 15-points was reported in 77.2% ($p < 0.001$), and ≥ 20-points in 68.4% of these patients ($p < 0.005$). Seventy-nine percent reported a reduction in VAS pain score by ≥ 2 cm at 24-months. The combined MCID function and pain responder rate (ODI ≥ 15 and VAS ≥ 2 reduction) for BVN ablation arm patients with a 24-month visit was 73.7% ($p < 0.001$). See Table 4. Quality of life outcomes measured via SF-36 (physical component) and EQ-5D-5L were also significant for all timepoints through 24 months. See Table 3.

*Healthcare utilization and treatment success rate*

In the 24 months prior to enrollment 29/58 (50%) of BVN ablation arm patients with a 24-month follow-up visit received an epidural steroid injection (ESI). In the 24-months following BVNA 7/58 (12%) of BVN ablation arm patients received an ESI (a 76% reduction); with only three of the post ablation ESIs involving the same treatment level as BVNA. In BVNA arm patients 11/58(19%) were taking opioid medications at 24 months compared to 21/58 (36%) at baseline with 10/21(48%) stopping opioid medications entirely. In the BVNA arm patients who continued opioid medications, only 8 (14%) were actively

**Table 3**
**BVNA arm patients with a 24 month visit outcomes**. Paired comparisons to baseline demonstrated significant reductions for both pain and function at all follow-up timepoints through 24-months for the BVNA arm patients who had a 24-month follow-up. Quality of life outcomes (SF-36 PCS and EQ-5D-5L) were also significant compared to baseline at all timepoints of follow-up through 24-months while SF-36 MCS did not achieve significance.

| Visit | Baseline | Month 3 | Month 6 | Month 9 | Month 12 | Month 24 |
|---|---|---|---|---|---|---|
| **Oswestry Disability Index (ODI)** | | | | | | |
| N | 66 | 66[a] | 61 | 60 | 61 | 57 |
| Baseline Mean ODI± SD | 44.7 ± 11.3 | 44.6 ± 11.3 | 44.3 ± 11.1 | 44.4 ± 11.2 | 44.3 ± 11.1 | 44.5 ± 11.2 |
| Follow-up Mean ODI±SD | | 21.0 ± 16.0 | 19.1 ± 15.4 | 18.8 ± 16.4 | 18.6 ± 15.7 | 16.0 ± 15.6 |
| Δ from Baseline ± SD | | -23.6[b] ± 18.0 | -25.1 ± 17.4 | -25.6 ± 17.1 | -25.7 ± 18.5 | -28.5 ± 16.2 |
| *p*-value[b] | | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| **Visual Analog Scale (VAS)** | | | | | | |
| N | 66 | 66 | 60 | 60 | 61 | 58 |
| Baseline Mean VAS± SD | 6.7 ± 1.3 | 6.7 ± 1.3 | 6.7 ± 1.2 | 6.7 ± 1.3 | 6.7 ± 1.3 | 6.6 ± 1.2 |
| Follow-up Mean VAS±SD | | 3.2 ± 2.7 | 3.1 ± 2.4 | 2.6 ± 2.5 | 2.9 ± 2.6 | 2.5 ± 2.5 |
| Δ from Baseline ± SD | | -3.5 ± 2.6 | -3.5 ± 2.5 | -4.0 ± 2.6 | -3.8 ± 2.6 | -4.1 ± 2.7 |
| *p-value*[b] | | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| **SF-36 Physical Component Score (PCS)** | | | | | | |
| N | 66 | 64 | 61 | 60 | 61 | 57 |
| Baseline Mean SF-36 PCS | 32.06 ± 6.76 | 32.12 ± 6.84 | 32.48 ± 6.75 | 32.21 ± 6.55 | 32.11 ± 6.53 | 32.26 ± 6.66 |
| Follow-up Mean SF-36 PCS ± SD | | 45.63 ± 9.67 | 45.80 ± 9.67 | 46.75 ± 9.52 | 47.03 ± 9.87 | 48.56 ± 9.76 |
| Δ from Baseline ± SD | | 13.51 ± 9.05 | 13.32 ± 9.82 | 14.55 ± 9.54 | 14.92 ± 10.16 | 16.30 ± 10.32 |
| *p-value*[b] | | <0.001 | <0.001 | <0.0001 | <0.0001 | <0.0001 |
| **SF-36 Mental Component Score (MCS)** | | | | | | |
| N | 66 | 64 | 61 | 60 | 61 | 57 |
| Baseline Mean SF-36 MCS | 53.42 ± 9.49 | 53.84 ± 8.77 | 53.77 ± 8.47 | 53.38 ± 8.80 | 53.53 ± 8.81 | 53.95 ± 8.59 |
| Follow-up Mean SF-36 MCS ± SD | | 56.17 ± 7.33 | 55.12 ± 8.42 | 54.06 ± 8.58 | 54.36 ± 7.60 | 53.62 ± 9.97 |
| Δ from Baseline ± SD | | 2.32 ± 6.80 | 1.36 ± 9.47 | 0.685 ± 7.54 | 0.830 ± 8.01 | -0.328 ± 9.38 |
| *p-value*[b] | | 0.0081 | 0.2678 | 0.4846 | 0.4212 | 0.7931 |
| **EQ-5D-5L** | | | | | | |
| N | 66 | 65 | 61 | 60 | 61 | 57 |
| Baseline Mean EQ-5D-5L | 0.613 ± 0.132 | 0.614 ± 0.133 | 0.623 ± 0.126 | 0.616 ± 0.130 | 0.616 ± 0.129 | 0.622 ± 0.124 |
| Follow-up Mean EQ-5D-5L ± SD | | 0.793 ± 0.130 | 0.809 ± 0.138 | 0.805 ± 0.157 | 0.806 ± 0.159 | 0.822 ± 0.144 |
| Δ from Baseline ± SD | | 0.179 ± 0.150 | 0.186 ± 0.157 | 0.189 ± 0.181 | 0.189 ± 0.187 | 0.200 ± 0.164 |
| *p-value*[b] | | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

[a] Multiple imputation for missing values for 3 Month ODI primary endpoint, all other measurements as observed.
[bPbp] -value from a paired t-test.

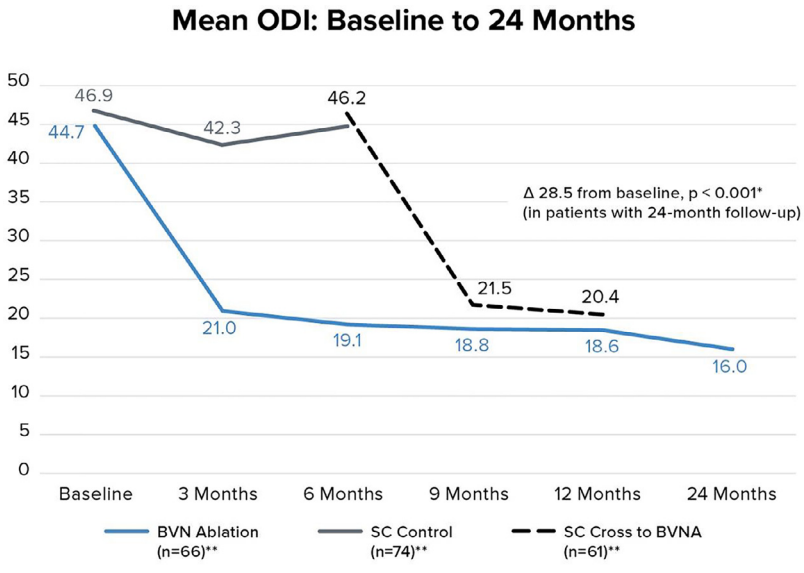


**Fig. 2.** Mean oswestry disability index (ODI) over time. This graph depicts the mean ODI at each study follow-up for each arm of the RCT through the longer-term follow-up of the BVNA arm. A statistically significant and clinically meaningful difference in mean ODI was observed from baseline/re-baseline for each timepoint in patients treated with BVN ablation, including in control patients that crossed to active treatment. Abbreviations: ODI, Oswestry Disability Index; BVNA, basivertebral nerve ablation.

taking opioids greater than one time per week, for an overall 62% reduction in active opioid use from baseline at 24 months.

Five of the 66 BVNA arm patients (8%) had an additional pain procedure or surgery performed at the same treatment level through 24-months (1- fusion at 24 months for disc collapse and radiating pain, 1- fusion at 24 months reason unknown, 1- disc replacement at 6 months reason unknown, 2 - radiofrequency neurotomy for ongoing low back pain). Seventy-two percent of BVNA patients met the composite treatment success definition that included the following criteria: 1.) an ODI improvement of ≥15-points from paired baseline, 2.) a VAS

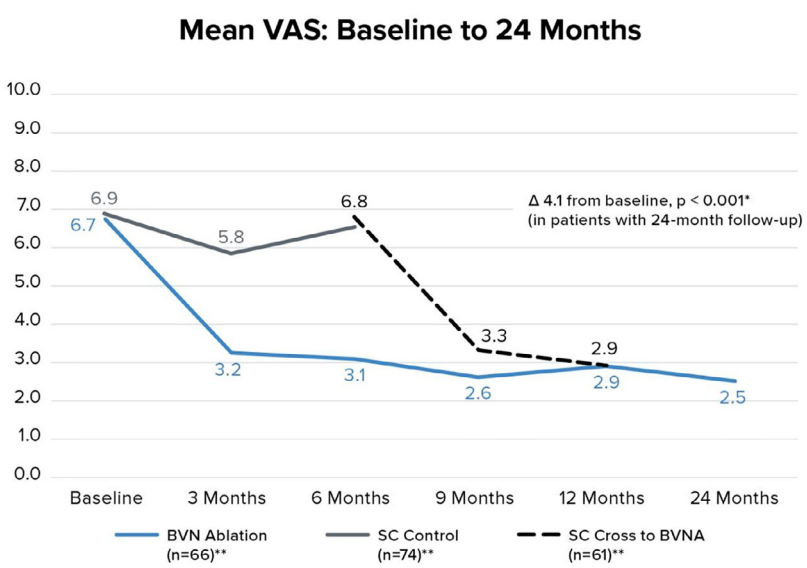


**Fig. 3.** Mean visual analog scale (VAS) over time. This graph depicts the mean VAS at each study follow-up for each arm of the RCT through the longer-term follow-up of the BVNA arm. A statistically significant and clinically meaningful difference in mean VAS was observed from baseline/re-baseline for each timepoint in patients treated with BVN ablation, including in control patients that crossed to active treatment. Abbreviations: VAS, visual analogue scale; BVNA, basivertebral nerve ablation.

**Table 4**
**Responder rates**. Responder rates were defined as ≥15-point reduction in Oswestry Disability Index (ODI) and ≥2 cm reduction in Visual Analog Scale (VAS). Individual measurement responder rates and combined responder rates were significant at all timepoints for BVNA arm patients.

| Responder rates (≥ 15-point ODI and ≥ 2 cm VAS reduction) | Basivertebral nerve ablation arm ($N = 66$) | $p$-Value |
|---|---|---|
| **3 Month** | $N = 65$[a] | <0.001[b] |
| **ODI ≥ 15-point reduction** – *n* (%) | 45 (69.2%) | |
| **VAS ≥ 2 cm reduction** – *n* (%) | 48 (72.7%) | |
| **Combined (reductions in ODI ≥ 15 and VAS ≥ 2)** – *n* (%) | 41 (63.1%) | |
| **6 Month** | $N = 60$[a] | <0.001[b] |
| **ODI ≥ 15-point reduction** – *n* (%) | 41 (67.2%) | |
| **VAS ≥ 2 cm reduction** – *n* (%) | 45 (75.0%) | |
| **Combined (reductions in ODI ≥ 15 and VAS ≥ 2)** – *n* (%) | 35 (58.3%) | |
| **9 Month** | $N = 60$[a] | <0.001[b] |
| **ODI ≥ 15-point reduction** – *n* (%) | 40 (66.7%) | |
| **VAS ≥ 2 cm reduction** – *n* (%) | 45 (75.0%) | |
| **Combined (reductions in ODI ≥ 15 and VAS ≥ 2)** – *n* (%) | 37 (61.7%) | |
| **12 Month** | $N = 61$[a] | <0.001[b] |
| **ODI ≥ 15-point reduction** – *n* (%) | 42 (68.9%) | |
| **VAS ≥ 2 cm reduction** – *n* (%) | 48 (78.7%) | |
| **Combined (reductions in ODI ≥ 15 and VAS ≥ 2)** – *n* (%) | 40 (65.6%) | |
| **24 Month** | $N = 57$[a,c] | <0.001[b] |
| **ODI ≥ 15-point reduction** – *n* (%) | 44 (77.2%) | |
| **VAS ≥ 2 cm reduction** – *n* (%) | 46 (79.3%) | |
| **Combined (reductions in ODI ≥ 15 and VAS ≥ 2)** – *n* (%) | 42 (73.7%) | |

Abbreviations: ODI, Oswestry Disability Index; VAS, visual analogue scale; cm, centimeters
[a] As observed, with no imputation for missing data.
[b]Pbp -value from a Binomial test.
[c] 57 patients with ODI and 58 patients with VAS at 24 months.

improvement of ≥2 cm from paired baseline, 3.) no spinal injections post ablation, and 4.)no additional low back pain procedures/surgeries of the same etiology and treatment level as BVNA at 24 months of follow-up.

*Patient satisfaction*

Seventy-nine percent (79%) of BVN ablation arm patients reported improvement of their condition (with 50% of those indicating "vastly improved") and 21% reported no change in their condition at 24-months post procedure. Seventy-one percent (71%) of the patients reported they had returned to the level of activity that they enjoyed prior to having low back pain and 84% indicated they would have the procedure again.

*Adverse events*

No serious device-related adverse events were reported through 24 months. Eleven percent (14/127) of the patients with BVN ablation treatments (66 BVNA and 61 patients SC crossing to BVNA) in this study reported non-serious device-procedure related leg pain events. All except one event (which was unable to be evaluated due to technical limitations of the MRI) were deemed a pedicle breach (with access being too medial per independent evaluation of the tract using the 6-week MRI). Thirteen of the breaches were at levels L5 or S1. Reported leg pain events were transient, with resolution in a median of 48.5 days, and mild in severity (primarily treated with a single course of oral medications). The events occurred at nine different study sites with no ob-

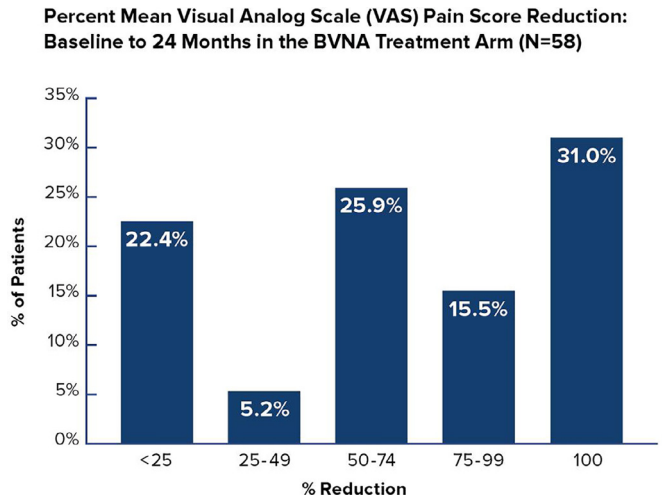


**Fig. 4. Visual analog scale (VAS) pain reduction by quadrant of improvement.** At 2 years post BVN ablation, 72.4% of patients in the BVNA treatment arm with a 24 month visit, reported a greater than 50% reduction in pain from baseline and 31.0% had complete pain relief. Abbreviations: VAS, visual analogue scale; BVNA, basivertebral nerve ablation.

served correlations to specialty or procedure experience of the treating physician.

## Discussion

This report outlines the 24-month results of the treatment arm of the INTRACEPT RCT. Significant differences between BVNA and SC in pain reduction and functional improvement that were reported at 3 and 6 months were sustained through 12-months for BVNA patients [14,15]. We report statistically significant and clinically meaningful improvements in paired analyses from baseline values for all timepoints post ablation through 24 months for the BVNA arm in this trial.

Improvements in pain and function in this single arm follow-up of BVNA arm patients compared favorably to the SMART RCT treatment arm results at 24 months with a mean ODI reduction of 28.5 points compared to 23.4 and a mean VAS reduction of 4.1 cm compared to 3.6 cm) [12]. Outcomes are also similar to treatment arm outcomes at 5 years in the SMART trial where patients reported mean reductions from baseline in ODI of 25.9 points and VAS of 4.4 cm at a mean of 6.4 years, supporting the durability of treatment effect.

Improvements noted in this study for BVNA treated patients were consistent with a single arm multi-center study conducted in typical spine practices where significant reductions from baseline in mean ODI and VAS were reported to be 32.31 and 4.31, respectively, at 12 months post ablation [21]. Lastly, pain and functional improvements in the BVNA patients in this study are similar to an independent single arm cohort study of 56 intraosseous BVN ablated patients, were a mean ODI reduction of 32.1 and a mean VAS reduction of 4.3 at 12 months post ablation was reported; further demonstrating the reproducibility of outcomes for BVNA [22].

In the three studies conducted on this therapy to date, 297 BVNA procedures have been performed at 41 different global study sites, by proceduralists from multiple specialties who were previously trained in transpedicular access [12,14,21]. Similar response rates and a low event rates have been demonstrated across these studies, supporting the generalizability of these outcomes with standard procedure training and transpedicular access experience.

Conservative treatments for axial CLBP are often limited by low effect sizes [1], with low patient satisfaction [23]. In comparing these longer term BVNA treatment results to non-surgical pain interventions, patients in this study demonstrated nearly twice the degree of functional improvement compared to lumbar interlaminar steroid injections for CLBP (reduction of 28.5 in mean ODI compared to 14.6) with an average of 6 injections over a 24-month period required to maintain results [24].

In comparing to other pain procedures, improvements in function for the BVNA arm of this study at 24 months are nearly 4 times those reported for biacuplasty (use of cooled radiofrequency to lesion the nociceptive fibers of the annulus fibrosus for discogenic low back pain) with reported mean ODI reduction of 7.43 at 6 months [25]. Likewise, the mean low back pain VAS reduction of 4.1 from a baseline of 6.6 observed in this study at 24 months is similar to lumbar radiofrequency neurotomy where an average VAS reduction of 4.1 from a baseline of 5.1 is reported at 12 months in a well-selected study population [26]. Finally, while long term data are not available for cooled radiofrequency ablation of the medial branch nerves, responder rates at 24 months in this trial were much higher at 72.4% of patients reporting ≥50% reduction in VAS than a response rate of 52% at 6 months in a recently reported RCT [27].

In comparing BVNA results to surgical treatment, functional improvements found in this study are approximately twice those of lumbar fusion for degenerative low back pain where a systematic review of RCTs reported 12-month ODI reductions of 11 to 15 points compared to 28.5 points at 24 months in this study [28,29].

While this RCT had a rigorous review process of medical history, clinical assessment, and imaging confirming a primary diagnosis of vertebrogenic pain (damaged vertebral endplates as the source of low back pain), the patients included in this study are reflective of typical axial low back pain patients seen in clinical practice with patients having low grade spondylolisthesis (12%), prior low back surgeries (12%), and disc protrusions (57%). A clinical picture of the vertebrogenic pain patient is emerging with analysis of clinical presentation and pain location body diagrams and associated response rates from aggregated characteristics from the three published studies on intraosseous BVN ablation. Responders to BVNA present with midline and /or paraspinal anterior column low back pain that infrequently radiates below the mid gluteal line. Pain is often exacerbated upon sitting and standing, and with flexion.

Surprising to the authors is the proportion of the patients in this study of vertebrogenic pain that had one or more vertebral bodies that displayed Modic changes where the associated motion segments were classified as Pfirrmann grades IIII or below per independent radiologic evaluation (22% of patients in this 24-month BVNA population). This suggests that endplate changes may occur alongside less degenerated discs yet contribute to disabling chronic vertebrogenic pain (study required a minimum VAS level of 4 and minimum ODI of 30). Responder rates did not significantly differ based on Pfirrmann grade of the treated motion segments in this study, further suggesting that treatment with BVNA is appropriate when clinical assessment and imaging findings are consistent with vertebrogenic pain.

Patients treated with BVN ablation in this study utilized fewer healthcare resources post procedure. A substantial decrease in opioid use was observed in this study with 62% of the patients who were taking opioids at baseline either stopping or reducing their use of opioids to less than one time per week by 24 months: a meaningful reduction in a population at increased risk for developing opioid use disorder.

In patients who had received epidural steroid injections in the 24 months prior to treatment, only 3(5%) had an injection performed at the same level as the BVN ablation in the 24 months post ablation. Decreasing the reliance on short-term steroid injections is clinically important as it has been reported that patients who have > 3 epidural steroid injections within a two-year period have a statistically greater likelihood of undergoing subsequent lumbar surgery [29].

Consistent with long-term data from the previous RCT on BVN ablation [12], in 24-months of follow-up in this study only 2/66 (3.0%) of BVNA treatment arm patients had additional pain interventions and 3/66 (4.5%) had surgery for unresolved low back pain or increasing radiculopathy. The composite treatment success rate of 72% observed

in this study at 24 months post ablation is impressive in a patient population where 2/3 of the patients had been experiencing CLBP for ≥ 5 years despite active treatment including injections and prior low back surgeries.

Patients in this study indicate a high degree of satisfaction with 79% reporting improvement in their low back pain and 71% of patients reporting they had returned to a level of activity that they enjoyed prior to experiencing low back pain. This degree of patients' enhanced quality of life and satisfaction along with the clinical treatment success rates and reductions in healthcare utilization following BVN ablation in this study further supports the value of this therapy.

Safety data in this study is consistent with the 5-year safety data reported in the SMART trial which reported one serious device-procedure related event [13]. In this study there were no serious device or procedure related adverse events reported in BVNA randomized patients through 24 months in this study. The risk of this minimally invasive procedure remains low, with only one serious device-procedure related event reported in the literature for the 493 clinical study cases (including sham and crossover procedures) for an overall serious device-procedure related event rate of 0.2% [12,14,15,21].

The primary non-serious device-procedure related event reported in this study were transient leg and back pain events. Leg pain events were mild in nature, primarily treated with oral medications, and had a median resolution of 48.5 days. It is noteworthy that the days to resolution may be inflated as the date of resolution was often clustered around a study visit. The possibility that the actual resolution timeframe is shorter is further supported by treatment with a single dose pack in most instances of leg pain.

Leg pain events were all considered to be related to a pedicle breach in independent MRI evaluation and the majority were at the L5/S1 levels where a more medialized approach for targeting the BVN is needed. While most of the investigators in the clinical studies did have transpedicular access experience, all but four of the treating physicians were new to the BVNA procedure. There were no observed learning curve patterns for anesthesia type, proceduralist specialty, or experience with the procedure for the leg pain events. Pedicle breaches were not isolated to initial cases and were spread across nine different study sites.

A review of the 473 clinical studies procedures performed to date (involving the unilateral transpedicular access of 868 vertebral bodies) showed 24 non-serious reports of post-ablation radiculitis and radiculopathy for an overall leg pain rate of 5%. Therefore, it is reasonable to counsel patients (particularly those with L5/S1 anatomy that requires a more medialized approach), that they may have approximately a 5% risk of experiencing temporary leg pain after the procedure which typically resolves with a single course of oral medication in an average of 4 to 6 weeks.

### *Strengths and limitations*

Strengths of this study are the robust design, the independent oversight of the study and results, the low attrition rate, and the consistency of outcomes for patients with active treatment to other RCT results. While enrollment was halted in this study at the interim analysis, limiting the between arm results to 6 months, the treatment arm patients continued with systematic, prospective follow-up per protocol through 24 months with a high retention rate. Pain and functional outcomes observed in this study are consistent with long-term results of other RCTs on vertebrogenic pain patients treated with BVN ablation including one non-sponsored single arm study [22]. The generalizability of treatment outcomes for a well-defined subgroup of vertebrogenic CLBP patients was further demonstrated by this study with similar results reported by the 20 different study sites performing BVNA in this study compared to previously published RCTs and single arm studies involving 21 different study sites and multiple specialties.

Limitations of this study include potential sources of bias, such as an open-label design, industry-funding, and a non-structured standard care control. Multiple processes were implemented in this RCT to limit any potential selection or results bias in this industry-funded study including an independent medical monitor confirming inclusion of a primary vertebrogenic population, third-party monitoring of source data, the independent adjudication of events and interventions by the CEC, and data analysis by a third-party statistical firm and reporting overseen the independent DMC. Results of this study are consistent with 12-month results for a non-industry funded single arm study of intraosseous BVN ablation compared to standard care [22].

Although this study population was derived from a randomized control trial, there may have been a nocebo effect in this study where it was impossible to blind patients to their treatment, and closer observation and management of patients when participating in a research study may have led to an enhanced treatment effect. However, an open-label study design is acceptable in a post-market environment where the treatment effect has previously been demonstrated in comparison to a sham procedure, and treatment outcomes have remained consistent across studies and through long-term follow-up; further suggesting that improvements are largely due to the intervention. Additionally, the standard care performance in this study was in line with non-surgical care control arm results in a meta-analysis of RCTs for lumbar fusion [30].

While regression to the mean is a possibility given the non-controlled nature of the study follow-up, in a population where 67% of patients experienced LBP for > 5 years, such regression to the mean phenomenon would likely already have occurred. Additionally, prior analyses of ODI reduction from baseline to 12 months estimated as a function of the baseline ODI using a regression analysis, demonstrated that improvements were due to the intervention rather than a regression to the mean [21].

These results demonstrate the benefits of BVN ablation relative to currently available alternatives. Standard care treatments in this study were based on the clinical assessment by the treating investigator and are reflective of the variability in conservative treatment that exists in actual practice today with multiple specialties involved in the care of low back pain, a lack of clarity on the effectiveness of therapies, and limited treatment consensus. This study design provides a more clinically meaningful understanding of real-world outcomes than comparing to a prescribed control.

## Conclusions

This study further demonstrates the long-term clinical effectiveness and safety of BVN ablation in a well-defined primary vertebrogenic CLBP population. Patients treated with BVN ablation exhibited statistically significant and clinically meaningful improvements from baseline in measurements of pain, function, and quality of life at all follow-up timepoints through 24 months. Responder rates remained high at 24 months while opioid use and injections were significantly reduced, further demonstrating the utility and clinical impact of BVN ablation for patients with vertebrogenic CLBP over existing treatments with published poor effect sizes.

## Informed Patient Consent

The authors declare that informed patient consent was taken from all the patients.

## Declarations of Competing Interests

The following authors declare conflicts of interest related to consulting, teaching/proctoring roles, and/or scientific board roles for Relievant Medsystems – Dr. J. Khalil and Dr. S. Garfin.

The following authors declare conflicts of interest for research funding paid to their institution from Relievant Medsystems during the con-

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Study Type: Clinical Study

## Summary sentence

INTRACEPT RCT 24-month treatment arm results demonstrate the safety, durability, reproducibility, and effectiveness of basivertebral nerve ablation for the treatment of vertebrogenic CLBP.

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