Title:	**INTRACEPT: A Prospective, Randomized, Multi-Center Study of Intraosseous Basivertebral Nerve Ablation for the Treatment of Chronic Low Back Pain**
Protocol Number:	**CIP 0006, REV E**
Device:	**INTRACEPT® INTRAOSSEOUS NERVE ABLATION SYSTEM**
Regulatory Status:	The device has FDA 510(k) clearance in the US and is CE marked in the EU for its intended purpose as defined in the Instructions for Use
Sponsor:	Relievant Medsystems 385 Moffett Park Drive, Suite 105 Sunnyvale, CA 94089
Date:	**OCTOBER 17, 2018**

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1.0 SYNOPSIS

Protocol Title:	A Prospective, Randomized, Multi-center Study of Intraosseous Basivertebral Nerve Ablation for the Treatment of Chronic Low Back Pain
Protocol Number:	CIP 0006, Rev E
Sponsor:	Relievant Medsystems, Inc.
Objectives	The primary efficacy endpoint is the mean change from baseline to 3 months post-treatment in the Oswestry Disability Index (ODI). The primary endpoint will be evaluated in both the treatment and control groups with between-group comparisons used to assess the success of the Intracept System in reducing chronic axial low back pain.
Indication/ Population	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 6 months' duration that has not responded to at least 6 months of conservative care, and is also accompanied by either Type 1 or Type 2 Modic changes on magnetic resonance imaging (MRI).
Study Design	This is a prospective, randomized, multi-center, controlled study with an optional crossover component. Subjects will be randomized 1:1 RF ablation arm vs Control arm; this is an open-label trial. Subjects in the RF ablation arm will receive the Intracept System procedure to treat one or two motion segments at L3/L4, L4/L5, or L5/S1 as identified by Modic type 1 or 2 changes. Subjects in the Control arm will continue non-surgical management therapies to treat their CLBP and will be offered optional crossover after 12 months of follow-up.
Number of Subjects	150 randomized and treated subjects. Approximately 600 subjects will be screened to achieve 150 enrolled (randomized) subjects [based on assumption of 75% screen failure rate].
Number of Sites	Between 10 and 25 US sites.
Duration of Participation	Subjects in the RF Ablation arm will be followed for 24 Months following treatment. Control arm subjects will be offered optional crossover treatment after the 12-month follow-up visit and will then be followed for an additional 6 months following crossover. It is estimated that this study may take up to 2 years to enroll, therefore from first subject consented through last subject 12-month visit, this study will take approximately 42 months for completion of all 12-month follow-up. The subjects in the RF Ablation arm will take an additional 6 months to complete the 24-month follow-up.
Primary Efficacy Endpoint	The primary efficacy variable is the Oswestry Disability Index (ODI) and the primary efficacy endpoint is the mean change from baseline to 3 months post-treatment in the ODI. The primary efficacy endpoint will be evaluated in both the treatment and control groups with between-group comparisons used to assess the success of the Intracept System in reducing chronic axial low back pain.

Secondary Efficacy Endpoints	• ODI
	  ○ The mean change in disability from Baseline to 6, 9 and 12 months, as measured by the ODI.
	  ○ The percentage of subjects who have ≥ 10-point reduction in ODI from Baseline to 3 months post-treatment
	• Visual Analog Scale (VAS)
	  ○ The mean change in pain from Baseline to 3, 6, 9 and 12 months, as measured by VAS
	  ○ The percentage of subjects who have ≥ 1.5 cm reduction in VAS from Baseline to 3 months post-treatment
	• The mean change in the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MC) scores from Baseline to 3, 6, 9 and 12 months
	• The mean change in quality of life from Baseline to 3, 6, 9 and 12 months, as measured by the EQ-5D-5L index.
	• Mean satisfaction ratings at 3, 6, 9 and 12 months, as measured on satisfaction rating scales.
	• The percentage of subjects who have radiographic evidence of targeting success based on lesion location on MRI.

Long-term Surveillance Endpoints	Subjects in the RF Ablation arm only will return for additional long-term surveillance follow-up at 24 months post-treatment. Evaluations to be performed will include the mean change from Baseline to 24 months post-treatment, as measured by the ODI, VAS, SF-36, and EQ-5D-5L, as well as the Patient Satisfaction rating. At the 24-month visit, RF Ablation subjects will be approached to participate in a sub-study entailing five years of post-procedure (additional study visits at 36, 48, and 60 months).
Additional Outcomes of Interest	• Additional analyses of health-related quality of life and disability associated with back pain at baseline, 3, 6, 9, and 12 months as estimated via the EQ-5D-5L, SF-36, and ODI questionnaires. • Resource utilization and related costs associated with back pain at baseline, 3, 6, 9 and 12 months, as estimated via treatment procedures, back pain medication usage, and national database statistics. • Quality of Life Years (QALY) gain for RF ablation arm and control arm, determined based on EQ-5D-5L data and mortality, and difference between the two strategies at various follow-up time points. • Incremental cost-effectiveness based on costs and QALYs for RF ablation vs. control arm.
Safety Endpoints	• The cumulative incidence and severity of device, procedure, neurological and spine related adverse events from the treatment procedure through the final follow-up visit. Deterioration of neurological status will be recorded as an AE (defined as a 1-grade or more deficit in any motor or dermatomal sensory group). • The cumulative incidence of device, procedure, or spine-related SAEs and Significant neurological events (defined as a 2-grade or more deficit in any motor or dermatomal sensory group) from the treatment procedure through the final follow-up visit.

Inclusion/ Exclusion Criteria	Inclusion Criteria: 1) Skeletally mature subjects age 25 – 70 years, inclusive 2) Chronic lower back pain for at least six (6) months 3) Failure to respond to at least six (6) months of non-operative conservative management. 4) Oswestry Disability Index (ODI) at time of evaluation of at least 30 points 5) Baseline Visual Analog Scale (VAS) of at least 4 cm on a 10 cm scale 6) Modic changes (Type 1 or 2) in at least one vertebral endplate, at one or more levels from L3 to S1 7) Fluent in reading, writing, speaking, and understanding the English language, and is willing and able to follow the requirements of the protocol, including the post-operative management program and follow-up schedule 8) Understands the informed consent and signs the institutional review board (IRB) approved informed consent form Exclusion Criteria: 1) Radicular pain by history or evidence of pain or neurological deficit within the past one year. Radicular pain is defined as nerve pain following a dermatomal distribution and that correlates with nerve compression on imaging. Somatic referred pain is allowed. 2) Previous surgery performed on the lumbar spine i) Note: previous lumbar decompression not affecting spinal stability or mechanics is allowed (unilateral or bilateral laminotomy or laminoforaminotomy) if procedure was more than six-months prior to screening date and all radicular pain has resolved 3) Current or history of symptomatic spinal stenosis 4) Current or history of osteoporotic or tumor-related vertebral body compression fracture 5) Current or history of vertebral cancer or spinal metastasis 6) Current or history of spinal infection 7) Metabolic bone disease (e.g. osteogenesis imperfecta) 8) BMI ≥40 (without rounding) unless there is documentation that obesity is not a primary contributing factor for the potential subject's CLBP (i.e. muscularly dense subject with vertebrogenic pain). 9) History of a fragility fracture (fracture following a low energy injury-vertebral compression, hip, wrist, pelvis, etc.) or current treatment with prescription medications for osteopenia. 10) Any radiographic evidence of other important back pathology, such as: a) Nerve root compression, neurogenic claudication, or severe effacement of the thecal sac that correlates with radicular pain or muscle weakness b) Disc extrusion or disc protrusion >5mm c) Facet arthrosis or facet effusion at any lumbar level that correlates with clinical evidence of facet mediated low back pain d) Spondylolisthesis 2 mm or greater at any level e) Spondylolysis at any level 11) MRI evidence of Modic changes, Type I or Type II at vertebral bodies other than L3 to S1. 12) Any back pathology related to trauma, evidence of vertebral compression fracture or other spinal pathology that could affect assessment of response to back pain 13) Subjects who are bed bound 14) Demonstrates 3 or more Waddell's signs of Inorganic Behavior 15) Any evidence of current systemic infection 16) Uncorrected bleeding diathesis 17) Any neurologic problem that prevents early mobilization after surgery or interferes with assessment of ODI

	18) Contraindication to MRI or subjects who have allergies to the components of the Intracept device specifically nitinol, PEEK (Poly Ether Ether Ketone), stainless steel, or PEBAX (Poly Ether Block Amide) 19) Pregnant, lactating or plan to become pregnant in next year 20) Evidence of mental instability or uncontrolled depression; subjects requiring new or any change in anti-depressants or anti-psychotic medications within 3 months of enrollment; subjects with a Beck Depression Score of greater than 24 21) Compensated injuries or ongoing litigation regarding back pain/injury, or financial or other incentive to remain impaired 22) Any medical condition that impairs follow-up (i.e. fibromyalgia, rheumatoid arthritis, chronic regional pain syndrome, reflex sympathetic dystrophy) 23) Contraindications to the proposed anesthetic protocol. 24) Evidence of substance abuse; subjects using prescribed extended release narcotics (e.g. fentanyl patch, MS contin, oxycontin) within the 3 months prior to screening and who are motivated to remain impaired for continued prescribing of extended release narcotics. 25) Known, at the time of screening and/or randomization, to require additional surgery to the lumbar spinal region within six months 26) History of SI joint fusion within the past two years 27) Being treated with radiation, chemotherapy, immunosuppression, or chronic steroid therapy (prednisone, or its equivalent, use of up to 5 mg/qd is allowed, as well as inhalation steroids for asthma) 28) Has a life expectancy of less than 2 years 29) Has active implantable devices, such as cardiac pacemakers, spinal cord stimulators, etc.
Treatment and Follow-up Schedule	• Screening Visit (may be completed over more than one study visit): Written informed consent. Collection of demographic information. Pregnancy test. Completion of BDI questionnaire. Review of medical history. Physical and neurological examination. MR imaging and standing lateral x-ray. Review of densitometry if available. Review of inclusion/exclusion criteria. Completion of questionnaires (ODI, VAS). LBP concomitant medications and therapies • Baseline Visit: Physical and neurological examination. Pregnancy test. Completion of questionnaires (ODI, VAS, SF-36, EQ-5D-5L). LBP concomitant medications and therapies. • Randomization and Treatment with Intracept System or assignment to Control arm • 6 Weeks Post-Treatment: MR imaging. (RF Ablation arm and crossover subjects only) • 3 Month Follow-up: Physical and neurological exam, completion of questionnaires, assessment of adverse events, LBP concomitant medications and therapies. • 6 Month Follow-up: Physical and neurological exam, completion of questionnaires, assessment of adverse events, LBP concomitant medications and therapies. • 9 Month Follow-up: Physical and neurological exam, completion of questionnaires, assessment of adverse events, LBP concomitant medications and therapies. • 12 Month Follow-up: Physical and neurological exam, completion of questionnaires, assessment of adverse events, LBP concomitant medications and therapies. • 24 Month Long-term Surveillance: To be performed in RF Ablation arm subjects only. Physical and neurological exam, completion of questionnaires, and assessment of adverse events. • Crossover: Intracept procedure will be offered to Control arm subjects following the 12-month follow-up visit. The study clock will reset for Control arm subjects who

	elect crossover; they will undergo a 6-week post-crossover MRI and be followed at 3 and 6 months post-crossover as described above. • RF Ablation arm subjects that consent to participate in the five-year sub study will have an additional 36, 48, and 60 month follow-up with physical and neurological exam and questionnaire collected.

2.0 LIST OF ABBREVIATIONS

510(k)	Premarket Notification, per FDA
ADE	Adverse device effects
AE	Adverse events
ASADE	Anticipated serious adverse device effect
BDI	Beck Depression Inventory
BMI	Body mass index
BVN	Basivertebral nerve
BVF	Basivertebral foramen
C	Cervical (vertebral level)
CFR	Code of Federal Regulations
CRA	Clinical research associate
CRF	Case report form
CT	Computed tomography
DDD	Degenerative disc disease
eCRF	Electronic case report form
EQ-5D-5L	EuroQOL quality of life instrument
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ID	Identification
IDET	Intradiscal electrothermal therapy
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
L	Lumbar (vertebral level)
LBP	Lower back pain
MRI	Magnetic resonance imaging
NSAID	Non-steroidal anti-inflammatory drug
ODI	Oswestry Disability Index
PEBAX	Polyether block amide
PEEK	Polyether ether ketone
PP	Per Protocol
QALY	Quality Adjusted Life Years
RF	Radiofrequency
S	Sacral (vertebral level)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SF-36	Short Form-36 instrument
SMT	Spinal manipulative therapy
TENS	Transcutaneous electrical nerve stimulation
USADE	Unanticipated serious adverse device event
US	United States of America
VAS	Visual analogue scale
VB	Vertebral body

3.0 BACKGROUND

3.1 Causes of Low Back Pain

The causes of low back pain (LBP) are varied and complex. Traumatic or degenerative conditions of the spine are the most common causes of LBP and there are known pathologic changes that occur in the intervertebral disc, which lead to the subsequent abnormal loading of the adjacent vertebral bodies. In addition, it is known that afferent nerve fibers carry pain signals associated with spinal degeneration from the low back to the spinal cord and ultimately to the brain. Tissue sources of LBP are generally believed to include the paraspinal musculature, facet joints, and the intervertebral disc. Acute muscle strains typically heal within days to weeks with activity modifications, analgesics, and rehabilitation. Radiculopathy can include leg pain, numbness, and weakness, often due to spinal nerve root compression from either disc herniation or other sources of nerve compression. Alternatively, chronic mechanical LBP (back pain localized to the lumbar spine exacerbated by loading) typically does not include symptoms of nerve root compression and is thought to be caused most frequently by degenerative disc disease (DDD). Approximately 10% of acute LBP patients go on to have chronic pain, which is defined as pain lasting longer than 3 months (Bogduk and McGuirk 2002; Merskey and Bogduk 1994).

The classical degenerative cascade, as first described by Kirkaldy-Willis, consists of the widely accepted pathophysiologic model that describes the degenerative process as it affects the lumbar spine and individual motion segments (Kirkaldy et al 1978). The degenerative process is generally believed to occur in 3 phases, dysfunction, instability and restabilization, that comprise a continuum, with gradual transitions to each subsequent phase.

The typical initiating event in the cascade involves the loss of internal disc integrity. Circumferential tears or fissures in the outer disc annulus characterize this loss histologically. In particular, tears, which may result from repetitive microtrauma, may be accompanied by vertebral endplate separation or failure that subsequently interrupts blood supply to the disc and impairs nutritional supply and waste removal. Since the outer third of the annulus fibrosis is innervated, tears or fissures in this area may be painful. Experimental evidence suggests that most episodes of chronic LBP are a consequence of disc injury, rather than musculotendinous or ligamentous strain. Magnetic resonance images (MRIs) obtained at this stage may reveal desiccation, disc bulging without herniation, or a high-intensity zone in the annulus. Changes associated with facet joints during the dysfunctional phase may include synovitis and hypomobility, which implicate the facet joint as a possible pain source.

The next phase of the cascade consists of disc-related changes including multiple annular tears (e.g., radial, circumferential), internal disc disruption and resorption, and loss of disc-space height. Concurrent changes in the facet joints include cartilage degeneration, capsular laxity, and subluxation. The biomechanical result of these alterations may include segmental instability.

The last phase of the degeneration cascade involves further disc resorption, disc-space narrowing, vertebral endplate destruction, disc fibrosis, and osteophyte formation; this phase is generally referred to as stabilization. Pain at this phase of joint degeneration may have a higher incidence than in phases 1 and 2; however, there can be substantial variation in different motion segments for any given individual and in reported pain responses for patients of similar ages.

While the classical model represents the standard reference for lumbar degeneration, an increasing body of evidence suggests the fundamental basis of disc degeneration may be associated with structural changes associated with microdamage at the vertebral endplate; it is this damage that

may initiate the sequence of events precipitating DDD (Rajasekaran et al 2008). It should be noted that vertebral endplate changes can be identified on an MRI using the classification system described by Modic (Modic et al 1988).

In summary, the degenerative cascade occurs due to the body's response to repetitive trauma and loading through the spinal column. The associated pathologic changes at the motion segment (such as loss of disc-space height) can be visualized radiographically and confirmed histologically.

3.2 Epidemiology of Chronic Low Back Pain

Low back pain (LBP) is the most expensive, benign condition treated in industrialized countries and is the most common cause of activity limitation in individuals younger than 45 years of age (Kelsey and White 1980). LBP is second only to the common cold as a cause of lost productivity; it is the fifth most frequent cause for hospitalization and the third most frequent cause for surgery (Anderssen and Frymoyer 1997; National Center for Health Statistics, 1978; National Center for Health Statistics 1973a; National Center for Health Statistics 1973b). Although acute LBP has a favorable prognosis, chronic low back pain (CLBP) - and its associated disability - have profound societal impacts. Specifically, CLBP is the leading cause of work-related disabilities. In the United States, an estimated 149 million work days are lost every year because of low back pain, with total costs estimated to be 100 to 200 billion dollars a year (of which two-thirds is due to lost wages and lower productivity) (Guo et al 1999; Katz 2006; Rubin 2007). The lifetime prevalence of non-specific (common) low back pain is estimated at 60% to 70% in industrialized countries (one-year prevalence 15% to 45%, adult incidence 5% per year) (Elders and Burdorf 2004). For these reasons, the availability of cost-effective, safe, and efficacious treatments for acute and CLBP are of substantial importance to individual patients, physicians, and the health-care system as a whole.

3.3 The Differential Diagnosis of Chronic Lower Back Pain

A definitive and confident identification of the primary source of clinically severe chronic LBP remains a challenge to clinicians. As with many spine disorders, the diagnosis of LBP and the attribution of its cause generally result from the confluence of clinical and radiographic findings. Specifically, the current standard used to diagnosis LBP involves conducting a combined review of clinical imaging study results (e.g., MRI and X-ray), patient histories, and physical examinations.

Most episodes of acute LBP resolve spontaneously within 6 weeks of onset. For patients who have continued pain and disability beyond this 6-week period, LBP can result in long-term chronic disability. The diagnosis of chronic LBP is characterized by patient complaints of tightness or stiffness in the low back and paraspinal region; patients generally report worsening pain associated with prolonged standing, activity, or upon rising in the morning. The pain may radiate toward the buttocks, or to the posterior or anterior thighs. (Note that thigh pain arising from LBP is usually distinguished easily from leg pain of neurogenic origin [i.e., sciatica], since neurogenic pain is typically described as a burning, shooting, or stabbing pain that travels down the back of the leg towards the foot, is usually accompanied by numbness or tingling, and may present with a neurologic deficit.)

In addition to patient complaints, lumbar degeneration is also characterized by pathologic changes in the disc and the subsequent abnormal loading of the adjacent vertebral bodies as seen on patient

imaging. Specifically, DDD is characterized radiographically by loss of disc-space height, osteophyte formation, and endplate sclerosis. Additionally, the alteration in the lumbar motion segment can frequently lead to changes in the adjacent vertebral bodies. The identification of these changes, known as Modic changes, is possible with MRI (and occasionally plain radiographs).

In 1988, Modic (Modic et al 1988) described and validated vertebral anomalies that were detected by MRI. The anomalies were defined as signal changes in the vertebral bone extending from the vertebral endplate and included 3 specific types:

- **Type 1:** Changes are characterized by fibrovascular replacement and demonstrate decreased signal intensity on T1-weighted MRIs and increased signal intensity on T2-weighted MRIs. Histopathology of Type 1 changes demonstrates disruption and fissuring of the vertebral endplate and vascularized granulation tissue within the adjacent marrow, producing prolongation of T1 and T2 relaxation times. Osteoblasts and osteoclasts are present with thickened trabeculae.
- **Type 2:** Changes are represented by increased signal intensity on T1-weighted MRIs and an iso- or slightly hyper-intense signal on T2-weighted MRIs. Type 2 changes show evidence of vertebral endplate disruption with yellow marrow replacement in the adjacent vertebral body (VB), resulting in a shorter T1. Vertebral endplate damage appears more chronic with reactive trabeculae thickening. Type 1 changes appear to convert to Type 2 changes over time.
- **Type 3:** Changes are represented by decreased signal intensity on both T1- and T2-weighted MRIs. These correlate with sclerosis on plain radiographs, which is a reflection of dense woven bone within the VB rather than marrow elements.

Modic changes are uncommon in asymptomatic individuals who do not present with DDD. For example, in the series by Toyone et al., (Toyone et al 1994) only 9.6% of patients without DDD had Modic changes. In this same series, 73% of patients with Type 1 Modic changes had LBP as opposed to 11% of patients with Type 2 Modic changes. Further, in a study of 60 asymptomatic volunteers who were 20 to 50 years of age, the prevalence of Modic changes was 3% to 10% (Weishaupt et al 1998). In particular, the radiologist saw Type 1 changes in just 1 of 300 lumbar motion segments.

In a population-based sample of 412 patients who were 40 years of age, Modic changes were observed in the lumbar spines of 9.6% of the patients without DDD and 34.1% of the patients with DDD (Kjaer et al 2006). In addition, this study indicated that DDD in the absence of Modic changes is a relatively quiet disorder (i.e., generally asymptomatic), whereas DDD in association with Modic changes is frequently observed with clinical symptoms. In this same population-based sample, three subgroups of patients were described: those with both DDD and Modic changes, those with only DDD, and those without DDD or Modic changes. An investigation of the clinical patterns across the three subgroups revealed that individuals with both DDD and Modic changes have a more pronounced clinical profile of LBP than those with neither finding. Overall, the study concluded that Modic changes constitute a crucial element in the evaluation of the degenerative process.

In order to investigate associations between Modic changes and the frequency and intensity of LBP and sciatic pain, a cross-sectional study of 228 middle-aged male workers was conducted (Kuisma et al 2007). Sagittal T1- and T2-weighted MRIs from these patients were reviewed and both vertebral endplates of 1,140 lumbar bodies were graded for the type and extent of Modic

changes. Logistic regression was used to analyze associations of pain variables with Modic changes. Overall, 178 Modic changes were recorded in 128 subjects. Of the recorded changes, 30% were Type I, 66% were Type 2, and 4% were both Type 1 and 2; 80% of the observed changes occurred at L4-L5 or L5-S1. Modic changes at L5-S1 showed significant association with pain symptoms and increased frequency of LBP. Type 1 Modic changes and extensive Modic changes, in particular, were closely associated with pain.

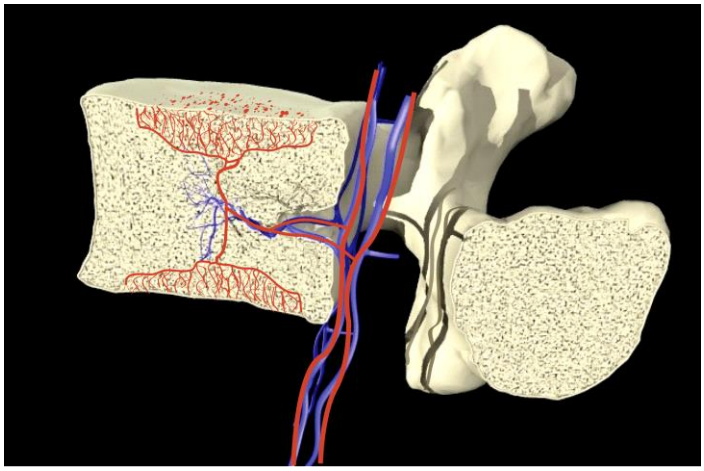
Other studies reported in the literature have also supported the correlation between Modic changes and LBP. For example, one report showed a positive correlation between the evolution of Type 1 to Type 2 changes and a subsequent improvement in symptoms (Mitra et al 2004). In a different clinical study, 60% of patients with Modic changes had LBP compared to 20% of patients without Modic changes. Additionally, in this same study, Type 1 Modic changes were observed to be more strongly associated with LBP than Type 2 Modic changes (Albert and Manniche 2007).

Overall, research published over the last 2 decades, including natural history investigations, pathogenesis studies, differential diagnosis of Modic change evaluations, and examinations of Modic change-LBP associations, demonstrate that Modic changes constitute dynamic markers of normal age-related degeneration affecting the lumbar spine. Additionally, recognizing Modic changes is critical to the differential diagnosis of chronic LBP as these changes are strongly associated with active lower back symptoms (Rahme and Moussa 2008).

3.4 Pathophysiology of Vertebrogenic Back Pain

During spinal compressive loading, the VB is responsible for supporting 80% of the load. If the load is applied quickly, the VB may fail before either the disc or the cartilaginous endplates, resulting in fracture (White and Panjabi 1990). If the excessive load is applied slowly or repetitively, the principal mode of spinal segment injury is degeneration of the vertebral endplate (the vertebra/disc interface), which is suspected as being the most common mechanism for the initiation of intervertebral disc degeneration (Adams et al 2000). In contrast to the intervertebral disc, the VB and endplate are highly innervated, and therefore, are important sources of spinal pain (van Dieen et al 1993). The basivertebral nerve (BVN) is an intraosseous nerve (figure 1), which has been shown to be a branch of the sinuvertebral nerve (Edgar and Ghadially 1976). The BVN enters the vertebra *via* the posterior neurovascular foramen and has been observed and characterized as a major source of afferent vertebral and endplate innervation (Antonacci et al 1998). The density of vertebral endplate innervation is comparable to that of the peripheral annulus, suggesting that the endplate is an equally important source of pain; this may have traditionally been reported as discogenic in origin (Fagan et al 2003). Indeed, vertebral endplate nerves are prototypical pain fibers that demonstrate nociceptor markers such as the neurotransmitter Substance P and high affinity nerve growth factor receptor trk-A (Freemont et al 2002). The clinical significance of afferent vertebral innervation *via* the BVN in patients with back pain is reinforced by reports of immediate pain amelioration after BVN disruption during vertebroplasty. This immediate relief is far more characteristic of a deafferentation mechanism—in this case probable serendipitous ablation (by the exothermic reaction) or transection of the BVN—as opposed to the more commonly conjectured mechanism of restoration of biomechanical stability (Freemont et al 2002). Pain provocation studies on human subjects also support the primacy of the BVN as an afferent pathway for nociception (Niv et al 2003).

Figure 1: Illustration of the BVN (red)



Further evidence for the clinical importance of vertebral innervation is derived from the association between vertebral marrow abnormalities on MRIs and presumed "discogenic" pain. It is known that VB endplates deflect in response to the intradiscal pressure produced during provocative discography (Kuslich et al 1991). Vertebral endplates in patients with discogenic pain are innervated by nociceptors (versus otherwise normal, non-painful discs) (Heggeness and Doherty 1993) and can elicit a pain response upon direct mechanical stimulation (Niv et al 2003). Consistent with these observations, nerve signaling associated with the innervated vertebral endplates appears to play a significant role in concordant pain reported by patients during provocative discography at the associated disc level. The BVN, which traverses the VB and arborizes to the endplates, is likely a significant conduit for this pain signaling (Brown et al 1997).

During the degenerative process, damage to the VB and endplate adjacent to the degenerating intervertebral discs triggers a fibrovascular repair response. This reparative process is observed as Modic changes on MRIs. Further, given that the endplates are richly innervated vertebral regions, the established correlation between the degenerative cascade, Modic changes, and chronic LBP, and based on both the painful response to vertebral endplate deflection during discography and the immediate pain relief noted during ablation from vertebroplasty procedures, the endplates are considered to be an important source of mechanical LBP. Consequently, vertebral denervation *via* ablation of the BVN is hypothesized to have significant therapeutic benefit.

3.4.1 Discogenic versus Vertebrogenic Back Pain

As noted previously, the specific source of LBP is often difficult to determine. Therefore, after excluding other sources or causes of pain (e.g., compressed nerve root, compression fracture, facet joints, and muscular etiology), the VB and endplates should be considered potential pain generators. It is now well established that pressurization of the disc during discography causes significant mechanical deflection of the bony vertebral endplate (Braithwaite et al 1998). Additionally, as shown in a study of awake patients who underwent lumbar surgery using only local anesthesia, direct mechanical stimulation of the vertebral endplate is correlated directly with severe pain (Sandhu et al 2000).

A clear association has been established between the presence of Modic changes, disabling LBP, and positive lumbar discography. Modic changes (in particular, Types 1 and 2) are positively associated with pain as defined by concordant pain reported by patients during provocative discography. Data from multiple independent studies have suggested that Type 1 or 2 Modic vertebral endplate abnormalities are among the most specific of all typical MRI observations in the prediction of adjacent concordant discography pain at the associated disc level (Toyone et al 1994; Kjaer et al 2006; Braithwaite et al 1998; Kjaer et al 2005). Modic changes have been reported as having a very high specificity (96.0%-96.8%) and positive predictive value (88.0%-91.3%) for pain reproduction during discography in patients with chronic LBP (Kuslich et al 1991). Further, it has been shown that moderate and severe Modic changes (i.e., changes extending up to 25% or more of vertebral height) correlate 100% with positive concordant pain at the disc-level associated with the culprit vertebral endplate (Weishaupt et al 2001). Finally, denervation of discs or disc excision have shown only modest success, perhaps indicating that a primary component of axial LBP is not the disc, but rather vertebral pain (Ohtori et al 2006).

Overall, the relevant data suggest that damage accumulation in the VB adjacent to degenerating intervertebral discs triggers a fibrovascular repair response that underlies Modic changes observed on MRIs. These innervated vertebral regions are considered to be an important source of mechanical LBP. To date, pain relief following disc denervation and/or disc excision (with accompanying fusion) has been poor. Consequently, vertebral denervation *via* disruption of the BVN is a reasonable and potentially viable treatment option for patients with chronic LBP.

3.5 Treatments for Chronic Lower Back Pain

The management of chronic LBP often involves numerous specialists and may include the use of medications, active exercise programs, alternative medical treatments, and manual, educational, and behavioral therapies. More invasive treatments may include injection and surgical therapies. Non-surgical, conservative care for LBP varies widely as there are no true standards associated with the types and durations of physical therapy, medication usage, or interventional treatments. Thus, before recommending surgical intervention for chronic LBP, the current standard of care is to recommend a patient-appropriate course of non-surgical treatment.

Standard practice for the treatment of LBP in the US involves a prescription of rest, medication, and physical therapy. Patients who do not respond to this conservative treatment may seek alternative approaches, such as chiropractic manipulation, massage, or acupuncture. Interventional therapies, including nerve blocks, facet blocks, or epidural steroid injections, are also commonly prescribed. In cases that are unresponsive to conservative care, surgery may be recommended (e.g., fusion or arthroplasty). It should be noted that the rate of lumbar fusion surgery is increasing in the US. In 1992, the US average rate of lumbar fusion was 0.3 per 1000 Medicare enrollees. The rate increased over the following decade, doubling to 0.6 per 1000 enrollees in 1998, and reaching 1.1 per 1000 in 2003 (Weinstein et al 2006). From 2000 to 2009, the rate of lumbar fusion for the treatment of DDD continued to steadily increase by 2.8-3.0 fold (depending on the type of fusion procedure performed) (Yoshihara and Yoneoka 2015). Overall, motion segment degeneration is the primary indication leading to fusion surgery in patients under 60 years of age, while spinal stenosis is the primary indication leading to surgery in patients over 60 years of age; for this older patient population, fusion surgery is adjunctive to a primary decompressive procedure (Deyo et al 2005).

3.6 Non-surgical Treatments for Lower Back Pain

Non-surgical treatments for LBP include patient education, the use of analgesics, exercise, physical treatments, spinal manipulative therapy (SMT), needle acupuncture, multidisciplinary rehabilitation, and injections and nerve treatments. From a joint practice guideline from the American College of Physicians and the American Pain Society, a discussion of each of these treatments follows (Chou et al 2007).

3.6.1 Education

The purpose of educating patients about LBP is to provide reassurance regarding the diagnosis, information associated with the prognosis, encouragement toward self-care, and advice to remain physically active despite discomfort or pain (Brox et al 2008). Education may include short interactions with a health provider, lay group discussions, educational booklets, electronic materials, or web-based discussion groups (Airaksinen et al 2006).

3.6.2 Analgesics

There are numerous types of analgesics available for chronic LBP, including acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). Acetaminophen generally is recommended as the first-line medication for chronic LBP, with NSAIDs as a second-line medication in cases where acetaminophen is ineffective or contraindicated. Should neither class of medication prove effective, weak opioid analgesics such as codeine or tramadol may be used on a short-term basis. If severe pain persists, stronger opioid analgesics such as morphine, oxycodone, or fentanyl may be prescribed, with caution.

Adjunctive analgesics include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and antiepileptic drugs. Commonly prescribed TCAs include amitriptyline, desipramine, and nortriptyline (Chang et al 2008).

3.6.3 Exercise

Back strengthening exercises are defined as supervised, dynamic, progressive resistance exercises that include isolation of the lumbar extensor muscles (Mayer et al 2008). Modes of administration for this form of exercise include machines, benches, Roman chairs, free weights, floor exercises, and stability ball exercises. Trained personnel in rehabilitation clinics or fitness centers typically supervise strengthening exercises, which are based on the principles of muscular strength development and generally require 1 to 3 training sessions each week (Medicine ACoS 2010). Strengthening exercises are performed throughout the full, pain-free range of motion of back extension, while exercise load gradually and progressively is increased via weight stacks, metal plates, machine angle, or back position. Back strengthening exercises usually are performed at a higher intensity than other forms of exercises that have been advocated for chronic LBP.

3.6.4 Physical Treatments

Interferential current, shortwave diathermy, and therapeutic ultrasound are physical treatments generally applied by physiotherapists. Specifically, interferential current involves the application

of a medium frequency, alternating current that is modulated to produce low frequencies of up to 150 Hz (Hurley et al 2001); shortwave diathermy, which is often used to treat soft tissue disorders and arthritis, involves the application of shortwave electromagnetic radiation (continuous or pulsed) within a frequency range of 10 to 100 MHz (Kitchen and Partridge 1992); and therapeutic ultrasound involves the combination of a generator, which produces electromagnetic energy with a frequency of 0.5 to 3.5 MHz, and a transducer, which converts the electromagnetic energy to mechanical energy with a similar frequency and an intensity of up to 3 W/cm (Van Der Windt et al 2002).

Separate from these methods, application of heat is often used due to its beneficial effects on blood circulation and muscle stiffness. Through these effects, it may result in relaxation, pain relief, and improvements in functional disability.

Lumbar traction is another physical treatment that is applied by putting a single harness around the lower rib cage and a second harness around the iliac crest; a force, equivalent to at least 25% of the patient's body weight, is then applied to separate both harnesses. The duration and level of exerted traction is varied in a continuous or intermittent mode. Different types of traction include manual traction (i.e., traction exerted by the therapist, using the patient's head, arms, or legs), motorized traction (i.e., traction exerted by a motorized pulley), suspension (i.e., traction exerted by gravitational forces, through the body weight of the patient), and bed-rest traction (i.e., traction exerted by a pulley and weights) (van den Hoogen et al 1995).

Transcutaneous electrical nerve stimulation (TENS) represents a non-invasive therapeutic modality for pain relief. This technique consists of electrical stimulation of the peripheral nerves via skin surface electrodes. In clinical practice, various types of TENS applications are used, which generally differ from one another with regard to intensity and electrical characteristics.

Finally, massage therapy is defined as soft tissue manipulation using the hands or a mechanical device. Different massage techniques are used, such as effleurage, petrissage, friction, kneading, or hacking, either in a classical manner or in a manner through which the rules of massage from physical medicine are combined with those of acupuncture. In clinical practice, massage is often either applied as a sole treatment or is used in combination with other therapies such as exercise.

3.6.5 Spinal Manipulative Therapy

High-velocity, low-amplitude SMT involves applying a manual thrust to spinal joints slightly beyond their passive ranges of motion, whereas mobilization involves application of manual force without thrusting (Halderman and Phillips 1991). SMT can be administered by several groups of trained practitioners, including chiropractors, osteopathic physicians, and physical therapists. The dose of SMT required for clinical improvement of chronic LBP is unclear, although the United Kingdom Clinical Practice Guideline (UKCPG) recommends a maximum of 9 SMT sessions over a period of up to 12 weeks (Low back pain 2009).

3.6.6 Needle Acupuncture

Needle acupuncture involves stimulation of anatomical points by penetrating the skin with solid metallic needles that are either manually or electrically stimulated (Ammendolia et al 2008); the treatment is administered by licensed acupuncturists and other credentialed providers (e.g., traditional Chinese medicine practitioners, physicians, chiropractors, or physiotherapists). In a

typical treatment for chronic LBP, approximately 20 to 30 needles are applied to the skin along meridians (vital energy pathways in the body) and associated acupuncture points and left in place for 20 to 30 minutes. The United Kingdom Clinical Practice Guideline (UKCPG) recommends a maximum of 9 acupuncture sessions over a period of up to 12 weeks (Low back pain 2009).

3.6.7 Multidisciplinary Rehabilitation

Multidisciplinary rehabilitation programs vary widely, but usually consist of 4 components: physical; behavioral; vocational; and pharmacologic management. Multidisciplinary rehabilitation is usually delivered by at least 3 healthcare providers with different clinical backgrounds, combining intensive supervised exercise therapy with behavioral approaches to decrease pain, improve function, reduce the impact of psychological co-morbidities, and foster a return to normal activities for patients with chronic LBP (Guzman et al 2001).

3.6.8 Injections and Nerve Treatments

Epidural injections are possible by the caudal, sacral, sacral transforaminal, lumbar midline, paralumbar (lateral), and lumbar transforaminal approaches. They are given "blindly" or with X-ray guidance (by either fluoroscopy or computed tomography [CT]); various glucocorticoids are also used either alone or in combination with a local anesthetic or saline. Spinal nerve root blocks are normally carried out under fluoroscopy or CT guidance and are given "periradicularly" (i.e., in the vicinity of the nerve root). Corticosteroids that are most often injected include methylprednisolone, triamcinolone, and dexamethasone (Mayer et al 2010; Chou et al 2009).

Facet block injections involve the instillation of local anesthetic and/or corticosteroid into a facet joint or around its nerve supply (ramus medialis of the ramus dorsalis). Fluoroscopic monitoring is necessary to check the position of the needle. When a joint is anesthetized through its nerve supply, typically at least 2 nerves (rami dorsalis) are blocked for each joint.

Myofascial trigger points are hyperirritable loci within a taut band of skeletal muscle. Trigger points are located in the muscle or its associated fascia. They are painful on compression and can evoke a reliable, characteristic referred pain, with or without autonomic response. Injection in the trigger points results in the selective destruction of mature myocytes by local anesthetic, saline infiltration, dry needling, or the "breaking of the reflex mechanism" of the pain.

3.7 Surgical Treatments for Chronic Lower Back Pain

Surgical approaches to LBP treatment include intradiscal procedures, fusion surgeries, and total disc arthroplasty. Descriptions of these treatments follow.

3.7.1 Intradiscal Procedures

A variety of intradiscal procedures have been developed because the disc is frequently the presumed source of many painful spinal and radicular syndromes. A prospective, randomized, double-blind study of intradiscal injections, however, demonstrated that painful discs show no statistically significant benefit from intradiscal administration of corticosteroids relative to local anesthesia (Simmons et al 1992). Despite this, other therapies have been evaluated for the

treatment of "discogenic" pain and include chymopapain injections to achieve nucleolysis, percutaneous manual nucleotomy with various mechanical devices, thermal vaporization using a laser, and percutaneous decompression with nucleotomy using ablative technology (nucleoplasty).

The use of diagnostic discography has been combined with therapeutic percutaneous intradiscal procedures in patients who demonstrate a concordant pain response. These include intradiscal electrothermal therapy (IDET), percutaneous laser disc decompression, percutaneous radiofrequency annular neurolysis, and nucleoplasty (Pinzon 2001). These procedures are postulated to shrink collagen fibers and coagulate neural tissues, thereby alleviating nociception produced by the mechanical loading of a painful, degenerated disc.

As a treatment for chronic LBP due to "discogenic" pain, IDET is performed using radiographic placement of a 17-gauge introducer needle through a posterolateral annular wall into the nucleus. Symptomatic discs are determined by discography. A navigable catheter with a temperature controlled, thermal-resistant coil is passed through the needle so that it curls along the posterior inner annulus. Catheter temperatures are slowly raised to 90°C, causing thermocoagulation of intradiscal and inner annular collagen, as well as associated nociceptors. Reduction in pain symptoms may result from denervation or shrinking and remodeling of the disc structure, or both (Pauza et al 2004).

The outcomes of IDET, however, are generally poor. Specifically, there have been 2 randomized, controlled studies designed to evaluate the safety and efficacy of IDET. In the first study, moderate pain reduction in an IDET-treated group was observed relative to a sham group (Freedman et al 2003); it was noted, though, that the data in this study did not exclude placebo effects. In the second study, although the IDET procedure was shown to be generally safe, there was no significant reduction in pain (i.e., no benefit) observed in patients who received treatment with IDET (Fritzell et al 2001).

3.7.2 Fusion Surgery

Spinal fusion is the most common surgical procedure performed for LBP. Spinal fusion surgery attempts to eliminate pain by preventing motion across a painful spinal segment and stabilizing the spine. Spinal instrumentation is often used with spinal fusion to improve the fusion rate. Lumbar fusion for LBP is controversial due to relatively low efficacy rates, high costs, co-morbidities, and the transfer of stress to adjacent spinal segments, which may lead to degeneration at adjacent levels.

The fusion approach may be posterior, anterior, or both. Radiographically, successful fusion is usually obtained in 60% to 90% of patients who undergo a posterior fusion procedure. Anterior interbody fusions typically have a successful fusion rate above 90%. Unfortunately, clinical outcomes following lumbar spinal fusions for LBP are satisfactory in only 40% to 70% of the patients and clinical success does not always correlate with the presence or absence of a successful fusion (Shealy 1975). Even with rigid posterior instrumentation, there is still micromotion across the disc space, which may account for persistent symptoms in some patients. Residual symptoms in other patients may be related to approach related muscle denervation or disruption of the adjacent facet joints.

Circumferential fusions are performed to fuse both the anterior interbody space and posterolateral spine. Historically, this was accomplished through both an anterior and posterior procedure. Although successful fusion rates are in excess of 95% with this combined approach, most studies

still only report clinical success in approximately 70% of the patients. Additionally, the morbidity of 2 procedures can lead to prolonged recovery and rehabilitation.

Posterior lumbar interbody fusion or transforaminal lumbar interbody fusion can allow posterior decompression and concurrent anterior column stabilization, while avoiding the morbidity of a separate anterior operation. The drawbacks include limitations on the size of the anterior graft or implant, nerve root injury, epidural fibrosis and chronic radiculitis, and potential instability from resection of the facet joints needed for exposure.

3.7.3 Total Disc Arthroplasty

Total disc arthroplasty (i.e., artificial disc replacement) is an alternative to spinal fusion surgery for patients who have painful lumbar motion segments due to DDD. The artificial disc is designed to preserve range of motion, which (theoretically) should diminish the incidence of adjacent level degeneration. Unfortunately, the overall efficacy in relieving pain is comparable to that of lumbar fusion surgery. This has caused a lack of uniform acceptance of total disc arthroplasty as a common treatment for LBP.

3.8 RF Ablation of the BVN for Treatment of Vertebrogenic Back Pain

The clinical utility of radiofrequency (RF) energy to treat diseases and conditions in general by heating and/or destroying tissue has been established over many decades of use in the medical profession. RF energy is used to heat tissue for the purposes of remodeling, shaping, or ablating (van Dieen et al 1993), for controlled treatment of tumors (Lord et al 1996), and for nerve destruction (Dupuy et al 2000).

In particular, the use of RF ablation for the treatment of nerve pain in other parts of the body has been extensively reported in the literature (Lord et al 1996). In particular, RF ablation of lumbar facet joints is commonly performed (van Dieen et al 1993; Shealy 1975). RF ablation has also been utilized in the VB for palliative treatment of pain due to metastatic bone lesions (Mayer et al 2008). Finally, RF ablation has been used as a definitive treatment for osteoid osteomas of the extremities and spinal column (Lindner et al 2001; Mahnken et al 2006).

As stated previously, the BVN is an intraosseous nerve within the VB that plays a role in afferent pain transmission. Given that RF ablation of nerves has been shown to be safe and to improve pain in other settings, RF ablation of the BVN appears to be a reasonable clinical target for the treatment of chronic back pain (Lord and Bogduk 2001).

The Intracept® System is a novel therapy intended to relieve CLBP in the presence of Modic type 1 or 2 abnormalities by denervating the BVN within the VB. The device is a percutaneous, minimally invasive system that ablates nerve tissue via a transpedicular or extrapedicular approach. The technique is based on the principle of bipolar tissue ablation using RF energy as a heat source. Ablation of the BVN occurs in a controlled manner by limiting the ablation zone to approximately 1.0 to 1.2 centimeters in diameter. This percutaneous procedure is intended to provide an alternative to patients who have failed conservative therapy and are considering more invasive surgical interventions. To this end, patients eligible for participation in the Intracept studies will be selected based on current clinical examinations and previous medical histories that are indicative of chronic LBP of vertebrogenic origin. The diagnosis will be further correlated by

confirmation of Modic changes. Finally, extensive exclusion criteria will be applied to ensure that patients with confounding conditions or other sources of back pain will not be entered into the study.

3.9 Clinical Experience to Date

Two prior clinical studies have been performed to evaluate the Intracept System: A feasibility study and a pivotal clinical trial to support 510(k) clearance by the FDA for the specific indication of RF ablation of the BVN for the treatment of CLBP. The design and results of these studies are briefly described below.

3.9.1 Feasibility Study

Study Design: The feasibility study was a prospective, single arm, international study performed to demonstrate preliminary effectiveness and safety of the Intracept System for treatment of chronic low back pain of at least 6 months duration that had not responded to at least three months of conservative care, and was also accompanied by either Type 1 or Type 2 Modic changes on an MRI (Magnetic Resonance Imaging), or positive provocative discography.

Methods: 17 patients were enrolled, and 16 successfully received treatment with the Intracept System. One patient was not treated due to spinal anatomy that was not amenable to treatment. Patients were evaluated at discharge, 6 weeks, 3 months, 6 months and 12 months. Each visit consisted of directed physical and neurological exam, assessment of adverse events and medications as well as patient reported outcomes; a visual analog scale (VAS) and ODI. Additionally, MRI images were collected at baseline and during each follow up visit for analysis by a core lab.

Results: The mean reported ODI (disability) and VAS (pain) scores showed significant statistical improvement in patient reported pain and low-back-pain-specific disability when compared to baseline at all study follow-up time points. Mean baseline ODI scores decreased from 52 ± 13 at baseline to 23 ± 21 at three months follow-up ($p < 0.001$) and this result was maintained through 12 months. VAS scores decreased from 61 ± 22 at baseline to 45 ± 35 at three months follow-up ($p < 0.05$). The overall patient treatment success using the pre-defined criteria at twelve months was 13 out of 16 patients or 81%. There were no device- or procedure-related serious adverse events in the study (Becker et al 2016).

Conclusions: this feasibility study demonstrated that the Intracept System was effective for treatment of chronic low back pain with successful outcomes for all primary and secondary efficacy measures. Further, the required treatment procedure had a high degree of procedural success and safety, with no adverse procedure or treatment-related effects as confirmed by independent core lab review of post-treatment MRI exams. Investigators and patients reported good success and satisfaction with the treatment procedure and results. Based on the results of this study, a pivotal clinical trial was undertaken (the SMART study).

3.9.2 Pivotal Clinical Trial – the SMART Study

Study Design: The SMART Study was a randomized, double-blinded, sham-controlled, multicenter, international, investigational device exemption (IDE) trial performed too evaluate the

safety and efficacy of RF ablation of the BVN, for the relief of chronic axial low back pain in the presence of Modic Type 1 and 2 changes.

Methods: 225 patients were randomized 2:1 into either the investigational group (147 patients) receiving BVN ablation via the Intracept® System, or the control group (78 patients), receiving the sham procedure by anchoring the introducer within the pedicle. Patients were evaluated preoperatively as well as postoperatively at 2 and 6 weeks and 3, 6, and 12 months. The primary study endpoint was the mean improvement from baseline to 3 months in the ODI, compared between the treatment arms.

Results: Results of the primary end point analysis for the per protocol (PP) population at 3 months showed that the ODI improvement observed in the investigational arm (LS Mean = 20.5 points) was statistically superior (p=0.019) to the sham arm (LS Mean = 15.2 points). This result was sustained through one year of follow-up. Furthermore, an analysis of ODI responder rates found that 75.6% of patients treated with BVN ablation demonstrated a greater than 10-point, clinically meaningful improvement in their low back pain and associated disability at 3 months. There were no unanticipated adverse device effects. There were no device related serious adverse events (SAE) and only one procedure related SAE. The rates of transpedicular and neurological events reported were minimal and comparable between treatment arms. MRI evaluations at the 6-week and 6-month follow-up time points found no evidence of any spinal canal abnormalities, vertebral body collapse, or accelerated disc degeneration.

Conclusions: Ablation of the BVN using a bipolar RF System is safe and effective for the treatment of CLBP, since the analysis of the primary study end point showed a significantly greater improvement in ODI for the investigational arm over the sham arm in the PP population. BVN ablation provides a new, minimally invasive, treatment option for a subset of patients with chronic low back pain.

Based on the review of the results of the SMART study, FDA granted 510(k) clearance of the Intracept System on July 9, 2016 for RF ablation of the BVN for treatment of CLBP in the presence of Modic type 1 and 2 changes.

4.0 DEVICE DESCRIPTION

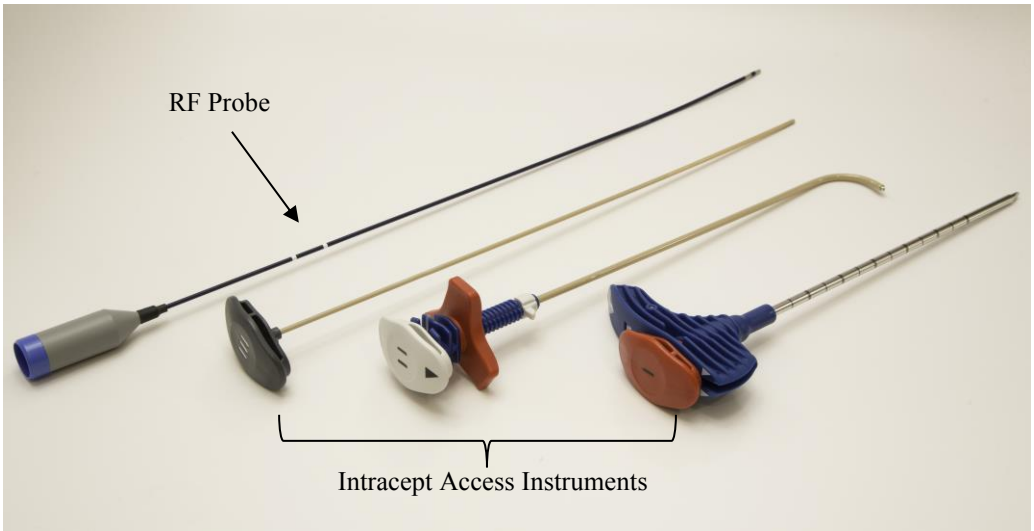
4.1 The Intracept® Intraosseous Nerve Ablation System (Intracept System)

The Intracept System is comprised of two basic, sterile, single use components:

- The Intracept Access Instruments (Instrument Set) is an instrument kit containing a trocar, cannulas and guides that provide access to the intended site of RF ablation.
- The Intracept Flexible Bi-Polar RF Probe (RF Probe) conducts RF energy to the target location.

The Intracept System is shown in Figure 2.

Figure 2: The Intracept System



The Intracept Access Instruments are described briefly in Table 1 and in more detail in the Instructions for Use. It should be emphasized that the Instrument Set is designed specifically for RF ablation of the BVN in the VB. However, it shares many design aspects with several systems currently on the market for ablation in other parts of the body.

Table 1: Brief Description of Intracept System

Tool	Purpose
Introducer Assembly	Create the initial straight channel through soft tissue and bone; delivers the subsequent J-Stylet and Curved Cannula.
Curved Cannula	Used in conjunction with the J-Stylet to create a curved delivery channel in bone
J-Stylet	Used in conjunction with the Curved Cannula to create a curved delivery channel in bone
Straight Stylet	Create a straight channel in bone beyond the end of the Curved Cannula
Flexible Bi-polar RF Probe	RF Probe which can be delivered through a curved channel

Additionally, a commercially available, legally marketed RF Generator provides RF energy to the RF Probe. An Interconnect Cable is provided to connect the RF Probe to the RF Generator.

5.0 STUDY PROTOCOL

5.1 Study Objectives

The objective of this study is to evaluate the procedural success rate, clinical effectiveness, and health-economic profile of using the Intracept® Intraosseous Nerve Ablation System in adult subjects with chronic low back pain in the post-market setting.

5.1.1 Primary Objectives

The primary efficacy endpoint is the mean change from baseline to 3 months post-treatment in the Oswestry Disability Index (ODI). The primary endpoint will be evaluated in both the treatment and control groups with between-group comparisons used to assess the success of the Intracept System in reducing chronic axial low back pain.

Safety will also be evaluated as determined by the incidence of severe or serious adverse events reported either by the subject or observed by the investigator, relating to the procedure, the device, or the spine, either perioperatively or during the follow-up period.

5.1.2 Secondary Objectives

The secondary objectives of this study will include evaluation of the improvement in LBP associated disability and pain; improvement in quality of life measures; assessment of health economic measures; and evaluation of targeting success with the Intracept System.

- Changes in ODI compared to baseline at 6, 9 and 12 month timepoints; and the percentage of subjects who have ≥ 10-point reduction in ODI from Baseline to 3 months post-treatment
- Changes in the Visual Analog Scale (VAS) compared to baseline at all follow-up time points; and the percentage of subjects who have ≥ 1.5 cm reduction in VAS from Baseline to 3 months post-treatment
- Changes in quality of life measures (SF-36, EQ-5D-5L, patient satisfaction rating)
- Intracept procedure targeting success based on lesion location on MRI.
- Resource utilization, including procedures and medications, and consequent costs for RF ablation and Control arms.
- Incremental differences in costs and quality of life measures between baseline and follow-up time points for RF ablation and Control arms, and incremental differences between the study arms.

5.2 Study Design

This is a prospective, randomized multi-center, controlled study with an optional crossover component.

Subjects will be randomized 1:1 RF Ablation arm vs Control arm; this is an open-label trial. Subjects in the RF Ablation arm will receive the Intracept System procedure to treat one or all of the functional spine units bounded by L3 and L4, L4 and L5, or L5 and S1 as identified by Modic type 1 or 2 changes. Subjects in the Control arm will continue non-surgical management therapies to treat their CLBP and will be offered optional crossover at after 12 months of follow-up.

5.3 Number of Sites

Between 10 and 25 US sites may participate in the study.

5.4 Number of Subjects

Up to 150 enrolled (randomized) subjects. Based on the results of the SMART study, it is anticipated that there will be approximately a 75% screen failure rate. Thus, approximately 600 subjects will be screened to achieve 150 enrolled and treated subjects.

An assessment of the overall (ignoring treatment groups) standard deviation will be performed at approximately 50% of subjects being randomized to confirm sample size and statistical power.

5.5 Study Duration

Subjects in the RF Ablation arm will be followed for 24 Months following treatment. At the 24-month visit, RF Ablation subjects will be approached to participate in a sub-study entailing five years of follow-up post procedure (additional study visits at 36, 48, and 60 months). Control arm subjects will be offered optional crossover treatment after the 12-month follow-up visit and will be followed for 6 months following crossover.

It is estimated that this study may take up to 2 years to enroll, therefore from first subject consented through last subject 12-month visit, this study will take approximately 42 months for completion of all 12-month follow-up. The subjects in the RF Ablation arm will take an additional 6 months to complete the 24-month follow-up. RF Ablation arm subjects that agree to participate in the sub-study will have an additional 36 months of follow-up.

5.6 Study Population

The study will enroll subjects who are candidates for treatment with the Intracept System; that is, skeletally mature patients with chronic (≥ 6 months), isolated low back (lumbar) pain, who have not responded to at least six months of non-operative management (conservative care). The treatment is limited to L3, L4, L5, and/or S1 vertebrae. The disease state must be accompanied with Modic type 1 or 2 changes as seen on MRI.

5.7 Subject Selection Criteria

The following section outlines the specific inclusion and exclusion criteria. Each subject must meet all of the inclusion criteria and have none of the exclusion criteria to proceed past the Baseline Visit.

5.7.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria in order to be considered eligible for participation in this trial:

1) Skeletally mature subjects age 25 – 70 years, inclusive
2) Chronic lower back pain for at least six (6) months

3) Failure to respond to at least six (6) months of non-operative conservative management.
4) Oswestry Disability Index (ODI) at time of evaluation of at least 30 points
5) Baseline Visual Analog Scale (VAS) of at least 4 cm a 10 cm scale
6) Modic changes (Type 1 or 2) in at least one vertebral endplate, at one or more levels from L3 to S1, per MRI
7) Fluent in reading, writing, speaking, and understanding the English language, and is willing and able to follow the requirements of the protocol, including the post-operative management program and follow-up schedule
8) Understands the informed consent and signs the institutional review board (IRB) approved informed consent form

5.7.2 Exclusion Criteria

Subjects will be excluded from participating in this trial if they meet any of the following exclusion criteria:

1) Radicular pain by history or evidence of pain or neurological deficit within the past one year. Radicular pain is defined as nerve pain following a dermatomal distribution and that correlates with nerve compression on imaging. Somatic referred pain is allowed.
2) Previous surgery performed on the lumbar spine
    i. Note: previous lumbar decompression not affecting spinal stability or mechanics is allowed (unilateral or bilateral laminotomy or laminoforaminotomy) if procedure was more than six-months prior to screening date and all radicular pain has resolved
3) Current or history of symptomatic spinal stenosis
4) Current or history of osteoporotic or tumor-related vertebral body compression fracture
5) Current or history of vertebral cancer or spinal metastasis
6) Current or history of spinal infection
7) Metabolic bone disease (e.g. osteogenesis imperfecta)
8) BMI ≥40 (without rounding) unless there is documentation that obesity is not a primary contributing factor for the potential subject's CLBP (i.e. muscularly dense subject with vertebrogenic pain).
9) History of a fragility fracture (fracture following a low energy injury-vertebral compression, hip, wrist, pelvis, etc.) or current treatment with prescription medications for osteopenia.
10) Any radiographic evidence of other important back pathology, such as:
    a. Nerve root compression, neurogenic claudication, or severe effacement of the thecal sac that correlates with radicular pain or muscle weakness
    b. Disc extrusion or disc protrusion >5mm
    c. Facet arthrosis or facet effusion at any lumbar level that correlates with clinical evidence of facet mediated low back pain

d. Spondylolisthesis 2 mm or greater at any level

e. Spondylolysis at any level

11) MRI evidence of Modic changes, Type I or Type II at vertebral bodies other than L3 to S1, per MRI

12) Any back pathology related to trauma, evidence of vertebral compression fracture or other spinal pathology that could affect assessment of response to back pain

13) Subjects who are bed bound

14) Demonstrates 3 or more Waddell's signs of Inorganic Behavior

15) Any evidence of current systemic infection

16) Uncorrected bleeding diathesis

17) Any neurologic problem that prevents early mobilization after surgery or interferes with assessment of ODI

18) Contraindication to MRI or subjects who have allergies to the components of the Intracept device specifically nitinol, PEEK (Poly Ether Ether Ketone), stainless steel, or PEBAX (Poly Ether Block Amide)

19) Pregnant, lactating or plan to become pregnant in next year

20) Evidence of mental instability or uncontrolled depression; subjects requiring new or any change in anti-depressants or anti-psychotic medications within 3 months; subjects with a Beck Depression Score of greater than 24

21) Compensated injuries or ongoing litigation regarding back pain/injury, or financial or other incentive to remain impaired

22) Any medical condition that impairs follow-up (i.e. fibromyalgia, rheumatoid arthritis, chronic regional pain syndrome, reflex sympathetic dystrophy)

23) Contraindications to the proposed anesthetic protocol.

24) Evidence of substance abuse; subjects using prescribed extended release narcotics (e.g. fentanyl patch, MS contin, oxycontin) within the 3 months prior to screening and who are motivated to remain impaired for continued prescribing of extended release narcotics.

25) Known, at the time of screening and/or randomization, to require additional surgery to the lumbar spinal region within six months

26) History of SI joint fusion within the past two years

27) Being treated with radiation, chemotherapy, immunosuppression, or chronic steroid therapy (prednisone ,or its equivalent, use of up to 5 mg/qd is allowed, as well as inhalation steroids for asthma)

28) Has a life expectancy of less than 2 years

29) Has active implantable devices, such as cardiac pacemakers, spinal cord stimulators, etc.

5.8 Treatment Plan

5.8.1 Screening

A patient is considered a study subject and may begin the required screening procedures after he/she has signed the informed consent document. Once a patient has provided informed consent, the site will assign unique subject ID numbers.

Subjects who are evaluated for participation but do NOT meet eligibility criteria will be considered screen failures, and the reason(s) for screen failure will be documented.

5.8.2 Enrollment Monitor

This study will use an **Enrollment Monitor** to verify subject eligibility to continue to the Baseline Visit. The Enrollment Monitor will be an independent reviewer who is not involved with subject treatment nor affiliated with an investigational site. The Enrollment Monitor must have appropriate expertise in radiology, neurology, orthopedic surgery and pain management. The Enrollment Monitor will not be a Sponsor employee, but will be compensated for his or her time.

Investigators will submit complete information regarding each potential study participant to the Enrollment Monitor. The Enrollment Monitor will review all subject screening information collected prior to the Baseline Visit. To be deemed eligible to proceed to Baseline, the Enrollment Monitor must agree with the site investigator that the subject meets all study eligibility criteria up to that point. In cases of disagreement between the Enrollment Monitor and the site investigator, a consulting investigator will make the final determination. The purpose of the Enrollment Monitor is to ensure that all subjects meet all eligibility criteria prior to proceeding to Baseline.

5.8.3 Baseline Assessments

Once the Enrollment Monitor has confirmed subject eligibility to proceed to the Baseline Visit, the subject may be scheduled for the Baseline Visit. This visit should be scheduled in coordination with a potential procedure date such that the patient can undergo the Intracept procedure within three weeks of the Baseline Visit, should the subject be randomized to the RF Ablation arm. The following Baseline Assessments will be performed in the office:

- Physical and Neurological examinations (including documentation of baseline symptoms)
- Oswestry Disability Index (ODI)
- Visual Analog Scale (VAS) assessment of pain
- Short Form Health Survey (SF-36)
- EQ-5D-5L
- Documentation of current CLBP concomitant medications and therapies

Following Baseline Assessments, the subject's continued eligibility must be confirmed prior to randomization (e.g: no neurological deficits, ODI remains ≥ 30, and VAS remains ≥ 4). Once the study subject has completed the Baseline Assessments and continued eligibility has been confirmed per the inclusion and exclusion criteria, the subject may proceed to randomization (enrollment).

5.8.4 Randomization

A subject is considered enrolled in the trial once they have been randomized. Subjects will be assigned in a 1:1 fashion to RF ablation using the Intracept System or to non-surgical management (NSM).

Randomization will be stratified by site only and will use randomly chosen blocks. The purpose of blocking the randomization by site is to ensure a good balance of treatment assignment within each study site while maintaining the unpredictability of the assignment. Treatment will be provided in a single procedure as described below in Section 5.8.6.

5.8.5 Choosing the Target Vertebral Bodies

A single motion level segment in the lumbar spine involves the structures that allow the motion to occur: two vertebral bodies and the intervening disc. For the purposes of this study, the focus is on the motion due to the cushioning and elasticity of the intervertebral disc. Although motion does also occur at the facet joint, the predominant load (80%) passes through the anterior column of the spine (VB and intervertebral disc).

The degenerative cascade, which can lead to chronic low back pain, is believed to be due to pathologic changes in the disc and the subsequent abnormal loading of the adjacent vertebral bodies. Alteration in the motion segment can frequently lead to changes in the adjacent vertebral bodies. Identification of the changes, known as Modic changes is possible on MRI studies. Although these Modic changes are frequently seen on both sides of the disc (L4-5 changes would be seen in the inferior portion of L4 VB and the superior portion of the L5 VB), they are occasionally seen in only one VB. As noted in Section 3.4, vertebrae are also a likely source of pain provoked by discography. Evidence suggests VB endplates deflect in response to disc pressure produced during provocative discography and may be a source of pain.

The Intracept System therapy is based on the hypothesis that ablation of the BVN in one or more VBs may prevent the transmission of pain centrally, thus resulting in an immediate and sustained reduction in back pain. This nerve is thought to be a common pathway for pain transmission from spinal pathology; the data from the SMART trial indicate that this hypothesis is clinically supported.

The BVN transmits pain signals from the nociceptors on the endplates caudal and cephalad to a given disc. For this reason, even if Modic changes are only observed in one bounding vertebral body, both that body and the other vertebral body bounding the affected disc level are treated. In this manner, single level DDD necessitates treatment of two adjacent vertebrae, and two level DDD requires treatment of three adjacent vertebrae.

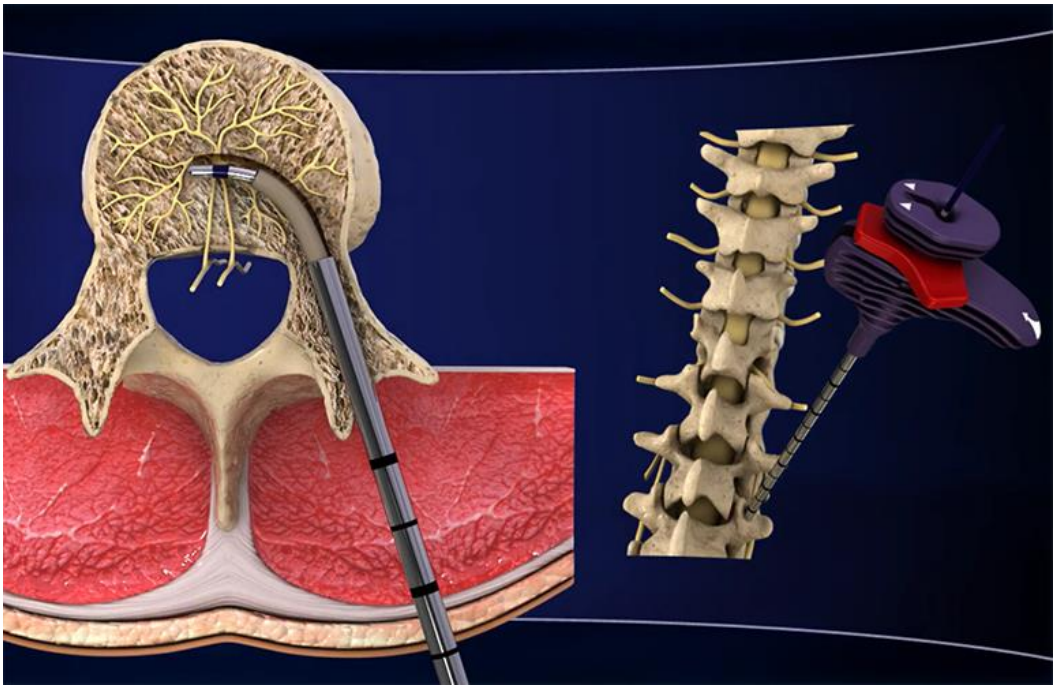
5.8.6 Procedure for RF Ablation of the BVN using the Intracept System

The Intracept procedure can be performed under general anesthesia or a moderate conscious sedation protocol per the operator's preference. The Intracept study procedure involves a two-step process. First, the Intracept Access Instruments are used via a minimally invasive, transpedicular or extrapedicular approach to create a channel to the terminus of the basivertebral foramen. Fluoroscopic or CT imaging must be utilized frequently throughout the procedure to ensure proper entry and placement of the devices. A small incision is made in the skin. The Introducer Assembly

is inserted through the incision and docked at the entry point of the VB pedicle. Using standard techniques, the cancellous bone of the VB is cannulated via the pedicle. Specific procedure instructions, including targeting the basivertebral foramen are provided in the Intracept Intraosseous Nerve Ablation System Instructions for Use (IFU) document.

Once VB access is gained, an RF Probe is inserted through the cannula into the central part of the target vertebral body and positioned at the terminus of the basivertebral foramen (see Figure 3).

Figure 3: VB access and Positioning at the Basivertebral Foramen



The Introducer Cannula is shown engaging with the VB through an incision (right side of image) and with the RF probe deployed at the BVN target (left side of image).

Controlled RF energy is delivered at 85°C for 15 minutes to destroy the basivertebral nerve. The pre-specified RF ablation parameters are shown in (Table 2). Once ablation is complete, the RF Probe and Access Instruments are removed and the skin incision repaired.

Table 2: RF Ablation Parameters.

Target Temperature	85°C
Treatment Time	900 seconds, 15 minutes
Temperature Ramp Rate	1°C/second
Impedance Limit Set to	Off

5.8.6.1 IMPORTANT NOTES

1) Due to the nature of this Clinical Protocol, it is not possible to "retreat" a motion segment once ablation energy has been delivered to the vertebral body due to a failure to complete the ablation procedure. Re-treatment post RF ablation would interfere with the planned statistical analyses as such, no repeat RF ablation is permitted. In the situation that there is an inability to access the BVN target (i.e. hardened bone or inadequate anesthesia); a re-treatment may be performed and the subject will be included in the statistical analyses as no RF ablation therapy was delivered in the first attempt.

2)

3) Setting and verification of the treatment parameters are a critical safety step. Only the treatment parameters defined in Table 2 above are allowed. Under no circumstances should treatment parameters be altered, nor should additional or longer thermal treatments be provided.

5.9 Schedule of Assessments

In the RF Ablation arm, follow-up visits will occur at 3, 6, 9 and 12 months post-treatment. An additional long-term surveillance follow-up visit will also be performed in the RF Ablation arm subjects only at 24 months. RF Ablation arm subjects will be approached at their 24-month visit for participation in a sub-study entailing a five-year follow-up post procedure (additional follow-up visits at 36, 48, and 60 months).

The Control arm subjects will be followed at 3, 6, 9 and 12 months following the Baseline visit. After completion of the 12-month visit, the Control arm subjects will be given the option to crossover to receive the Intracept treatment. Subjects who receive the crossover procedure will have their study clock reset, and will have additional post-treatment follow-up visits at 3 and 6 months. Subjects from the Control arm who elect not to crossover will cease participation in the study following the 12-month visit. The study coordinator will schedule these visits and be responsible for making sure that CRFs are complete.

At each visit, the subject will be interviewed and examined by the investigator. The investigator will assess medical history, perform a physical and neurological examination and the subject will complete the patient assessment questionnaires. The subject will complete the ODI and VAS assessments at all visits, as well as the SF-36 and EQ-5D-5L and patient satisfaction questionnaires. Assessments of additional LBP-related therapies, interventions, or medications will be documented as well as any procedure, device or spine related adverse events. The data will be entered by the site into the relevant CRFs.

In addition, at 6 weeks following the procedure, subjects in the RF ablation arm, as well as crossover subjects, will have an MRI of the spine with sequences described in Section 6.4. These are research-oriented MRIs and will not be interpreted clinically by site radiologists. The study coordinator will submit the MRI in anonymous DICOM format to the study Sponsor as directed.

A brief summary of the study schedule of assessments is as follows:

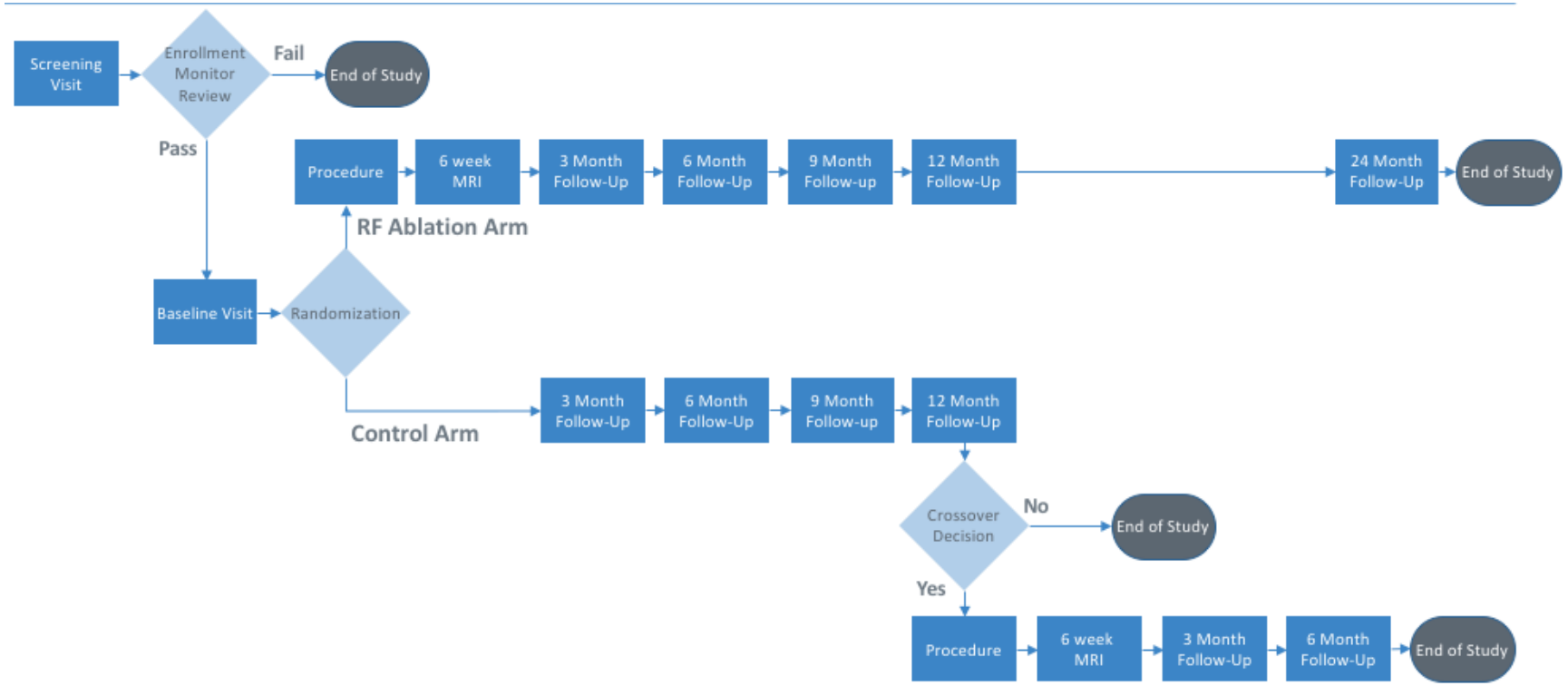
- Screening Visit (may be completed over more than one study visit): Written informed consent. Collection of demographic information. Pregnancy test, if indicated. Completion of BDI questionnaire. Review of medical history. Physical and neurological examination. MR imaging. A standing lateral x-ray may be requested, but is not required. Review of

densitometry if available. Review of inclusion/exclusion criteria. Completion of questionnaires (ODI, VAS). LBP concomitant medications and therapies

- Baseline Visit: Physical and neurological examination. Pregnancy test, if indicated. Completion of all questionnaires (ODI, VAS, SF-36, EQ-5D-5L). LBP concomitant medications and therapies.
- Randomization to either Treatment with Intracept System or assignment to Control arm will be performed at the baseline visit.
- Procedure Visit for treatment with Intracept System.
- 6 Weeks Post-Treatment: MR imaging (in subjects treated with RF Ablation)
- 3 Month Follow-up: Physical and neurological exam, completion of all questionnaires, assessment of adverse events, LBP concomitant medications and therapies.
- 6 Month Follow-up: Physical and neurological exam, completion of all questionnaires, assessment of adverse events, LBP concomitant medications and therapies.
- 9 Month Follow-up: Physical and neurological exam, completion of all questionnaires, assessment of adverse events, LBP concomitant medications and therapies.
- 12 Month Follow-up: Physical and neurological exam, completion of all questionnaires, assessment of adverse events, LBP concomitant medications and therapies.
- 24 Month Long-term Surveillance: To be performed in RF Ablation arm subjects only. Physical and neurological exam, completion of all questionnaires, and assessment of adverse events.
- Crossover: Intracept procedure will be offered to Control arm subjects following the 12-month follow-up visit. The study clock will reset for Control arm subjects who elect crossover; they will undergo a 6-week post-crossover MRI and be followed at 3 and 6 months post-crossover as described above.
- RF Ablation arm subjects that consent to participate in the five-year sub study will have an additional 36, 48, and 60 month follow-up with physical and neurological exam and questionnaire collected.

A schematic of the study follow-up schedule for both treatment arms in the Main Study is provided in Figure 4. The full schedule of assessments is shown in Appendix 2. Most assessments in this study are routine for back pain studies. Characteristics of individual assessments are described in Section 6.0.

Figure 4: Main Study Schematic



5.10 Crossover

This trial has a crossover component. At 12 months after the Baseline visit, subjects in the Control arm may elect to crossover to receive the Intracept treatment. **The subject may cross over only after the 12-month visit is complete.** Control subjects may cross for any reason and must be allowed to cross unless the investigator believes the Intracept procedure is medically contraindicated, or the subject would no longer benefit from the Intracept treatment. A subject who crosses over must decide whether they are going to proceed with the Intracept procedure and schedule the procedure within 30 days of the 12-month visit.

Site personnel must not, in any way, influence the subject's decision as to whether to crossover.

When a subject crosses over, the **study visit clock is reset**. Therefore, a crossed subject who is treated with the Intracept System will have a 6 week MRI performed, and will have second 3 and 6 month visits.

5.11 Study Exit

Subjects in the RF Ablation arm who are followed to the 24-month visit are considered to have completed the main study. Crossover subjects will be considered to have completed the study after the 6-month post-Intracept procedure visit. Subjects in the Control arm who do not crossover will be considered to have completed the study after the 12-month visit. The Investigator or designee will complete a study exit form. RF Ablation subjects that consent to participate in the sub-study, will be exited from the study at the completion of the sub-study.

5.12 Study Withdrawal/Termination

A subject may withdraw from the study at any time if he/she no longer wishes to participate. If subjects elect to withdraw from the study post-randomization, the study coordinator should inquire if the subject is withdrawing due to treatment failure (i.e. lack of improvement in low back pain) or for other reasons, and document the reason accordingly on the study completion CRF.

Importantly, any subject who undergoes a non-study-related invasive surgical therapy for back pain at any level during follow-up (e.g. lumbar spine fusion) will be considered a treatment failure (if in the RF ablation arm), or ineligible for a study RF ablation treatment (if in the Control arm), and the subject must be withdrawn from the study.

If a subject does not respond to at least 3 documented contact attempts and/or misses scheduled appointments such that the follow-up visit does not occur, the visit will be documented as a "missed visit". Subjects who miss a follow-up visit should still be contacted again for their next scheduled follow-up visit. It is important that continued attempts be made to re-establish contact at subsequent follow-up visits. **A subject should not be deemed lost to follow up and withdrawn from the study until the site has documented efforts at achieving subject contact.**

If a subject withdraws from the study or is terminated from the study, the reason must be carefully documented on the study completion CRF. The investigator and study coordinator should carefully screen subjects for their ability and desire to participate in the study. Continued participation should be encouraged at every study visit and using telephone calls as necessary. Sites should carefully maintain current subject contact information.

6.0 STUDY ASSESSMENTS AND OUTCOME MEASURES

The clinical condition of each subject will be evaluated using an assessment of a combination of the following parameters:

6.1 Medical History

The investigator will verify the health of the subject based on medical history, including surgeries/medical procedures, significant illnesses, and neurological and/or psychiatric conditions. Specific attention will be given to:

- Waddell's signs of non-organic behavior;
- Back and leg pain assessment;
- Previous back or neck surgery;
- Previous spinal neurological procedures;
- Back pathology, including VB compression fracture, spinal stenosis or compression of the thecal sac, spondylolisthesis, spondylolysis, disc extrusion or protrusion, nerve root compression, facet joint degeneration, trauma, and/or spinal cancer, infection, or disease.

The investigator will also assess the likelihood of osteoporosis and review densitometry findings, if available.

6.2 Laboratory Tests

A urine test for pregnancy (female subjects of childbearing potential only) will be performed in-office at the Screening and Baseline Visits. Women of childbearing potential are defined as any female who has experienced menarche and who is NOT permanently sterile or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

6.3 Beck Depression Inventory (BDI-II)

The BDI is a psychometric test of the severity of depression. It consists of 21 questions, each scored from 0-3. Higher scores indicate worse depression. It is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished as well as physical symptoms such as fatigue, weight loss and lack of interest in sex. This questionnaire has been used to assess depression in patients with chronic pain. Total scores range from 0-63, within the following categories: 0-13: minimal; 14-19: mild; 20-28: moderate; 29-63: severe depression (Beck et al 1988). The BDI is used at the Screening Visit as a screening tool for depression; potential participants with BDI scores greater than 24 will not be enrolled in the study. Participating study sites must have a plan in place in the event of positive results of suicidality based on the T score if it is greater than 24, or if the answer to question #9 in the Beck Depression Index is "yes."

6.4 Imaging

During the screening process, MR images of the lumbar spine will be evaluated to confirm eligibility. A standing lateral x-ray may also be evaluated to confirm eligibility. The standing lateral x-ray should be within 6 months and the MRI within 3 months of the screening date. If available images are beyond those timeframes, they may be requested to be repeated and evaluated as part of the screening.

If the MRI is within the time window, **but the study does not clearly show the basivertebral foramen at the target level(s) or provide all of the sequences as listed below, a repeat MRI may be required** for determining the ablation target using the instructions provided as follows:

It is preferred that all MR studies performed for this clinical trial should be performed with MR equipment that has at least a 1.5 Tesla magnet and submitted in DICOM format. The following imaging sequences are required:

MR Imaging Sequences:

1. Sequence 1: Scout images using department/machine protocol
2. Sequence 2: Sagittal T1-weighted images, 3 mm slice thickness with 1mm gap. Matrix 256 x 256 or greater. Cover full lateral dimensions of vertebral body. TR/TE, NEX, bandwidth per institution standard
3. Sequence 3: Sagittal T2-weighted images, 3 mm slice thickness with 1mm gap. Matrix 256 x 256 or greater. Cover full lateral dimensions of vertebral body. TR/TE, NEX, bandwidth per institution standard
4. Sequence 4: Sagittal STIR images, 3 mm slice thickness with 1mm gap. Matrix 256 x 256 or greater. Cover full lateral dimensions of vertebral body. TR/TI/TE, NEX, bandwidth per institution standard
5. Sequence 5: Axial T1 from superior L3 endplate to L4-5 disc, 3/1mm, contiguous stack, angle to upper L4 endplate Matrix 256 x 192 or greater. TR/TE, NEX, bandwidth per institution standard
6. Sequence 6: Axial T1 from superior L4 endplate through S1-2 junction, 3/1mm, contiguous stack, angle to upper S1 endplate Matrix 256 x 192 or greater. TR/TE, NEX, bandwidth per institution standard
7. Sequence 7: Axial T2 from superior L3 endplate to L4-5 disc, 3/1mm, contiguous stack, angle to upper L4 endplate Matrix 256 x 192 or greater. TR/TE, NEX, bandwidth per institution standard
8. Sequence 8: Axial T2 from superior L4 endplate through S1-2 junction, 3/1mm, contiguous stack angle, to upper S1 endplate Matrix 256 x 192 or greater. TR/TE, NEX, bandwidth per institution standard

Modic changes (Type 1 and/or 2) must be present for study eligibility, and will facilitate identification of the target vertebrae for treatment.

For assessment after treatment, the MR imaging must be performed with the same equipment that was utilized for the screening MRI and the study must consist of all sequences as listed above. Follow-up MR images of the lumbar spine will be scheduled to be taken at 6 weeks following the Intracept procedure and will be evaluated for targeting success by an independent radiologist (see Section 9.5.6 Targeting Success for imaging review protocol).

6.5 Neurologic and Physical (Orthopedic) Exam

A detailed and focused neurologic and orthopedic examination will be performed at Screening and all follow-up time points during the study. The examinations will focus on lumbosacral spine and nerve root function as well as pain presentation, function and range of motion. Investigators will complete a uniform neurologic examination case report form (CRF) at screening, and report any subsequent neurological deviations from baseline at each follow-up time point.

6.6 Oswestry Disability Index (ODI)

The ODI is a 10-item measure of back-pain related disability. It assesses the impact of back pain on activities of daily living and participation. It is scored on a scale of 0 (no disability) to 100 (complete disability), with categories of 0-20 (minimal disability), 21-40 (moderate disability), 41-60 (severe disability), 61-80 (crippling back pain), and 81-100 (bed-bound or exaggerating). Several validity studies have been done to determine the minimally clinically important difference, which is considered to be approximately 10 points (Fairbank and Pynsent 2000; Copay et al 2008).

6.7 Visual Analogue Scale (VAS)

A visual analog scale (VAS) is a commonly used technique to assess subjective, patient-oriented outcomes. The VAS is a 10-cm scale marked at its ends "0 (no pain)" and "10 (worst imaginable pain)". Respondents will indicate the point on the scale that corresponds to their perceived pain intensity of their low back pain. The distance between the 0 cm origin and the respondent's mark is measured as the pain rating. **Subjects will be specifically instructed to report their <u>average low back pain for the last seven days</u>.** Studies have shown that a minimally clinically important difference in VAS is considered to be approximately 1.5cm (Ostelo et al 2008).

6.8 Short Form-36 Instrument (SF-36)

The SF-36 was developed by the Rand Corporation as part of the Medical Outcomes Study. It consists of 36 scaled questions across the categories of vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Total scores range from 0-100, where lower scores indicate more disability. It can be used as an indicator of health-related quality of life and also for health economics (Ware and Sherbourne 1992; McHorney et al 1993). Specifically, a subset of the SF-36, the SF-6D, provides a means for using the SF-36 in economic evaluation by estimating a preference-based single index measure for health from these data using general population values. The SF-6D allows the analyst to obtain QALYs from the SF-36 for use in cost utility analysis.

6.9 EuroQOL Quality of Life Instrument (EQ-5D-5L)

The EQ-5D-5L measures health status. It consists of five multiple-choice items and a VAS scale of health (worst vs. best). EQ-5D-5L responses can be converted to a single index value ranging from 0.0 – 1.0, where higher scores indicate better health. The EQ-5D-5L has been translated to over 50 languages, and country-, region-, and condition-specific population norms have been

published. EQ-5D-5L scores are typically presented as a health-related quality of life measure and can be applied to cost-utility analyses (Copay et al 2008; Ostelo et al 2008; Ware and Sherbourne 1992).

6.10 Patient Satisfaction

Satisfaction will be assessed with a short, non-validated questionnaire employing rating-scale questions about satisfaction with treatment, willingness to repeat the treatment for the same outcome, and willingness to recommend the treatment to a loved one with the same condition. Only subjects in the RF Ablation arm and Crossover subjects will be asked to complete this questionnaire at the post-treatment follow-up time points.

6.11 Concomitant Back Pain Medications

Current and historical concomitant medications for treatment of LBP will be documented at the time of screening and will be monitored throughout the study. Failure to respond to at least six (6) months of non-operative conservative management is required for a subject to be eligible for participation. The look-back period for concomitant medications may be 6 months or up to many years. Documentation of at least six (6) months of non-operative conservative management in the designated CRFs is required.

The name, dosage, and frequency of all medications used for treating back pain since the last study visit will be captured. The average daily dosage for each back pain medication will be record for the two weeks (14 days) prior to the visit or for the two-weeks prior to discontinued use of the medication.

6.12 Concomitant Therapy

Current and historical concomitant therapy for treatment of LBP will be documented at the time of screening and will be monitored throughout the study. Failure to respond to at least six (6) months of non-operative conservative management is required for a subject to be eligible for participation. The look-back period for therapies, surgeries, and procedures may be 6 months or up to many years. Documentation of at least six (6) months of non-operative conservative management in the designated CRFs is required.

All low back pain therapies or interventions will be documented on a designated CRF (i.e., physical therapy, acupuncture, chiropractic care, epidural steroids, etc.).

6.13 Adverse Events

An AE is defined as any untoward medical occurrence in a subject. Only such events that are procedure, device, neurological, or spine-related will be documented for this study. The investigator will make an assessment of procedure or device relatedness of adverse events. All reported adverse events will be adjudicated by a third-party Clinical Event Committee (CEC) for a final determination of procedure or device relatedness.

AEs related to the use of an investigational medical device are considered Adverse Device Effects (ADEs). This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

AEs will be assessed continuously in the study and the types of events noted above will be reported as they occur using a specific CRF. . All reported adverse events will be reviewed by the CEC.

A summary of AE types, which are further explained in this section, are presented in Table 3:

Table 3: Categories of AEs

<table>
<tr><th>AEs</th><th>Non-device Related</th><th colspan="2">Device- or Procedure-Related</th></tr>
<tr><td>Non-serious</td><td>Adverse Event (AE)[a]</td><td colspan="2">Adverse Device Effect (ADE)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse Event (SAE)[b]</td><td colspan="2">Serious Adverse Device Effect (SADE)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated Serious Adverse Device Effect (ASADE)</td><td>Unanticipated Serious Adverse Device Effect (USADE)</td></tr>
<tr><td colspan="4">[a] Includes all categories.
[b] Includes all categories that are serious.</td></tr>
</table>

A preexisting condition is one that was present at the start of the study. A preexisting condition will only be recorded as an AE if the frequency, intensity, or the character of the condition worsened during the study period. Note: a planned procedure or hospitalization for a preexisting condition, without serious deterioration in health, will not be considered an AE.

An increase in LBP will be reported as a new AE if one of the following criteria is met:

- 10 point increase in ODI over baseline (if a subject has not reported this degree of functional impact from LBP previously).
- 2 point increase in VAS over baseline (if a subject has not reported this degree of pain that is similar in location, severity, or nature previously).
- Increase in narcotic medication or a new prescription for narcotic medication that is outside of standing post-operative orders or is used beyond the post-operative healing period of 7 days.
- Invasive medical intervention for treatment of new or exacerbated LBP (i.e., epidural injection)

Note that an abnormal radiographic finding without symptoms does not constitute an AE.

Examples of events to be reported as being procedure, device, neurological, or spine-related are as follows:

Procedure-Related AE

An adverse event that is deemed a proximate procedure related adverse event is defined as an event that is related to the treatment procedure, but not specifically related to the Intracept device. Examples of these types of events include: anesthesia related complications, fluid overload,

retroperitoneal hemorrhage due to failed transpedicular cannulization, wound infection or transpedicular cannulization that leads to motor deficit, etc.

Device-Related AEs

An adverse event that is deemed a proximate device related event or Intracept therapy related event may be defined as follows:

- Breakage of the device or any of the components that lead to an adverse or serious adverse event
- Over or under heating during the RF ablation that leads to an adverse or serious adverse event
- Infection as a result of compromised sterility of the device prior to use (resulting from a manufacturing failure)
- Allergic reaction to the device components
- Operative, peri-operative, or post-operative pain associated with or resulting from the procedure (including new sensation of pain or increase in original pain)
- Thermal injury to neural, disc or paraspinal tissues (not due to overheating during RF ablation)
- Injury to anatomical structures adjacent to the target treatment location
- Vertebral body fracture (with no other traumatic cause) within 6 months of the Intracept procedure
- Permanent nerve damage resulting in loss of function or paralysis
- Any new motor deficit, dermatomal sensory loss or radiculopathy with no compression seen on MRI, at the nerve root corresponding to the treated level within 6 weeks of the treatment procedure
- Herniation/Protrusion at treated level with MRI evidence of thermal zone encroachment into the disc space and/or evidence biomechanic instability secondary to the RF lesion. In addition, the neurologic compression is worsened, compared to the pre-procedure MRI.
- Foraminal stenosis at treated level with MRI evidence of thermal zone encroachment into the disc space and/or evidence biomechanic instability secondary to the RF lesion. In addition, the neurologic compression is worsened, compared to the pre-procedure MRI

Neurological AEs

A neurological examination will be performed at screening, baseline, and at each follow-up visit. A neurological deficit will be recorded as an AE when there is a decrease in motor strength of 1 grade (or more) in a muscle group or 1 grade (or more) dermatomal sensory loss from baseline. All reports of significant neurological deficit; defined as a grade 2 or greater motor or dermatomal sensory deficit will be reviewed by the CEC. The final determination of procedure- or device-related, and permanent or transient, neurological deficit will be adjudicated by the CEC.

Spine-Related AEs

A conservative approach was taken when considering events that could potentially be considered as related to the spine, and thus, the following categories are examples of events that should be reported as potentially being "spine-related": aching in limb, arthropathy, back muscle spasms, back strain, buttock pain, compression fracture, leg cramps, leg pain, low back pain, lower extremities weakness, lumbar intervertebral discitis, lumbar disc herniation, lumbar radiculopathy, lumbar spondylosis, lumbar strain, lumbar vertebral fracture, motor dysfunction, muscle spasm, neck pain, nerve root injury, numbness in leg, pain in hip, pain of lower extremities, paraesthesia, sacroiliac pain, sciatica, sensory deficit, spondylolysis, tightness of back muscles, and upper back pain. The final determination of spine-related will be adjudicated by the CEC.

Event Severity

Adverse events will also be rated by severity as mild, moderate, or severe as defined in Table 4. The investigator at each study site is responsible for rating the severity of each adverse event. All adverse events will be adjudicated for severity by the CEC.

Table 4: Severity of Adverse Events

Severity of Adverse Event	Definition
Mild	The subject has awareness of signs or symptoms, but they are easily tolerated and are of minor irritant type causing little to no loss of time from normal activities. Symptoms do not require therapy beyond simple interventions and do not require a medical evaluation; signs and symptoms are transient and improve with simple therapeutic measures, if used.
Moderate	Events introduce a low level of inconvenience or concern to the subject and interfere with daily activities, but are usually improved by simple therapeutic measures or medication; moderate experiences may cause some interference with functioning.
Severe	Events cause marked interruption to the subject's normal daily activities. Subject requires therapeutic measures (including medication, hospitalization, or prolongation of hospitalization, or other treatments).

Serious Adverse Event (SAE)

An SAE is defined per ISO 14155 as any event that:

- Leads to death.
- Leads to serious deterioration in the health of a subject that
    - Results in a life-threatening illness or injury,
    - Results in a permanent impairment of a body structure or a body function,
    - Requires in-patient hospitalization or prolongation of existing hospitalization,

  - Results in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.

- Leads to fetal distress, fetal death, or a congenital abnormality or birth defect.

Note: Severity is not synonymous with Seriousness. A severe rash is not likely to be an SAE. However, mild chest pain may result in hospitalization and is therefore an SAE.

Procedure, device or spine-related SAEs are to be reported to the study Sponsor immediately upon occurrence (within 24 hours of discovery). The investigator will report SAEs to the local IRB as required by local policies.

Serious Adverse Events, Significant Neurological Events, and/or other important clinically significant adverse events, including those that are proximate events related to the device or procedure, will be recorded on the CRF and reviewed by the Clinical Event Committee. The final determination of procedure- or device-related, and permanent or transient neurological deficit, will be adjudicated by the Clinical Event Committee.

Unanticipated and Anticipated Serious Adverse Device Effect

An unanticipated and serious adverse device effect (USADE) is defined as an event that meets the definition of an SAE, is definitely or probably device or procedure-related, and was not identified in nature, severity or degree of incidence in the study protocol or IFU. USADEs are to be reported to the study Sponsor immediately upon occurrence (within 24 hours of discovery). The Sponsor will be responsible for evaluating the occurrence of any USADE as it relates to study continuation consistent with the appropriate regulations and reporting requirements.

Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the protocol or IFU. ASADEs are to be reported to the study Sponsor immediately upon occurrence (within 24 hours of discovery). The Sponsor will be responsible for evaluating the occurrence of any ASADE as it relates to study continuation consistent with the appropriate regulations and reporting requirements.

7.0 ASSESSMENT OF EFFICACY

7.1 Primary Efficacy Endpoint

The primary efficacy variable is the Oswestry Disability Index (ODI) and the primary efficacy endpoint is the mean change from baseline to 3 months post-treatment in the ODI. The primary efficacy endpoint will be evaluated in both the treatment and control groups with between-group comparisons used to assess the success of the Intracept System in reducing chronic axial low back pain.

7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- ODI

  - The mean change in disability from Baseline to 6, 9 and 12 months as measured by the ODI.
  - The percentage of subjects who have ≥ 10-point reduction in ODI from Baseline to 3 months post-treatment
- Visual Analog Scale (VAS)
  - The mean change in pain from Baseline to 3, 6, 9 and 12 months as measured by VAS
  - The percentage of subjects who have ≥ 1.5 cm reduction in VAS from Baseline to 3 months post-treatment
- The mean change in SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores from Baseline to 3, 6, 9 and 12 months.
- The mean change in quality of life from Baseline to 3, 6, 9 and 12 months as measured by the EQ-5D-5L index.
- Mean satisfaction ratings at 3, 6, 9 and 12 months post-treatment in the RF Ablation arm, as measured on satisfaction rating scales.
- The percentage of subjects who have radiographic evidence of targeting success based on lesion location on MRI.

7.3 Long-term Surveillance Endpoints

Subjects in the RF Ablation arm only will return for additional long-term surveillance follow-up at 24 months post-treatment. Evaluations to be performed will include the mean change from Baseline to 24 months post-treatment, as measured by the ODI, VAS, SF-36, EQ-5D-5L, as well as the Patient Satisfaction rating. RF Ablation arm subjects that consent to the five-year post procedure follow-up sub-study will be evaluated for the mean change from Baseline to 36, 48, and 60 months as measured by the ODI, VAS, SF-36, EQ-5D-5L, as well as the Patient Satisfaction rating.

7.4 Additional Outcomes of Interest

Additional outcomes of interest are:

- Additional analyses of health-related quality of life and disability associated with back pain at baseline, 3, 6, 9, and 12 months as estimated via the EQ-5D-5L, SF-36, and ODI questionnaires.
- Resource utilization and related costs associated with back pain at baseline, 3, 6, 9 and 12 months, as estimated via treatment procedures, back pain medication usage, and national database statistics.
- QALY gain for RF ablation arm and control arm, determined based on EQ-5D-5L data and mortality, and difference between the two strategies at various follow-up time points.
- Incremental cost-effectiveness based on costs and QALYs for RF ablation vs. control arm.

8.0 ASSESSMENT OF SAFETY

8.1 Safety Endpoints

- The cumulative incidence and severity of device, procedure, neurological and spine-related adverse events from the treatment procedure through the final follow-up visit. Deterioration of neurological status will be recorded as an AE (defined as a 1-grade or more deficit in any motor or dermatomal sensory group).
- The cumulative incidence of device, procedure, or spine-related SAEs and significant neurological events (defined as a 2-grade or more deficit in any motor or dermatomal sensory group) from the treatment procedure through the final follow-up visit.

9.0 DATA ANALYSIS AND STATISTICAL METHODS

This section provides the key details of the statistical analyses to be performed. All statistical processing will be performed using SAS® software Version 9.2 or later unless otherwise stated. Multiple imputation will be used as the default method of estimating missing data for the primary variable.

9.1 Determination of Sample Size

Sample size calculations for the study have been performed for the proposed primary endpoint assuming certain responses in each study group. Estimated responses were based on a survey of literature for other treatments as well as the SMART Study results. The "Two group t-test of equal means (unequal n's)" option of the program nQuery Advisor Version 7.0 was used to perform the power computations.

Assuming a standard deviation of 15 and a mean difference of 10 in the change from baseline for the ODI score, a total sample size of 75 RF Ablation and 75 Control subjects would give approximately 90% power for a two-sided test with an alpha level of 0.05. A randomization ratio of 1:1 (treated: control) was chosen to allow for an appropriate determination of the profile of the Control subjects.

An assessment of the overall (ignoring treatment groups) standard deviation will be conducted at approximately 50% of subjects being randomized to confirm sample size and statistical power. A revised sample-size may then be calculated using suitably modified assumptions.

9.2 Analysis Populations

The primary analysis will be based upon a Modified Intent to Treat (mITT) population per the Food and Drug Administration E9 Statistical Principals for Clinical Trials outlined intent to treat principles. Subjects will be included in the mITT population, or as otherwise defined in the Statistical Analysis Plan (SAP), if they meet the following criteria:

- Met the primary inclusion criteria and none of the primary exclusion criteria

- Were a procedural success (for subjects in the RF ablation arm). Procedural success is defined as successfully treated at the initial study procedure, as well as being a targeting success (appropriate ablation of the BVN) as determined by an Independent Adjudicator using the 6-week post-treatment MRI based on the measurements described in section 9.6.6.

A Per Protocol (PP) analysis will also be conducted and considered supportive. The PP population is defined as all patients who were enrolled into the study and were randomly assigned to a treatment group and the following criteria were met:

- Met the inclusion criteria and none of the exclusion criteria
- Were a procedural success (for subjects in the RF ablation arm). Procedural success is defined as successfully treated at the initial study procedure, as well as being a targeting success (appropriate ablation of the BVN) as determined by an Independent Adjudicator using the 6-week post-treatment MRI based on the measurements described in section 9.6.6.
- Have been compliant with the requirements of the protocol (i.e., no significant protocol deviations or surgical spine-related interventions)
- Have completed the 6week MRI, for RF Ablation arm subjects, and 3-month follow-up visit for all randomized subjects.

Have not undergone a non-study-related needle-based injection (epidural steroids, facet block, intradiscal procedures, etc.) for back pain prior to their 3-month follow-up visit.

An Intent-to-Treat (ITT) analysis will also be conducted and considered supportive. The ITT safety population is defined as all patients who were enrolled into the study. The ITT for efficacy population is defined as all patients who were enrolled into the study, and were randomly assigned to a treatment group and the treatment was completed.

The Safety population will be comprised of all randomized subjects.

9.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics responses will be summarized with descriptive statistics by treatment group and for the ITT population. Past and current medical conditions and medical history will not be compared statistically.

9.4 Primary Efficacy Analysis

The primary efficacy endpoint of the study is the mean improvement from baseline to 3 months in the ODI which will be evaluated with an analysis of covariance (ANCOVA) with factors of treatment group and analysis center (see Section 9.6 for the definition of analysis center) and a covariate of baseline ODI score. The mITT analysis will be primary while the PP analysis and ITT analysis will be supportive.

A conclusion of success for the primary end point will be reached (i.e., confirmation that the Intracept System is effective in reducing CLBP) if the mean improvement from baseline to 3 months in the ODI is significantly greater in the RF Ablation arm than in the Control arm.

Multiple imputation will be the primary imputation method used to account for missing ODI values.

Using a parametric regression model assuming multivariate normality and a monotone missing data pattern, ODI values at baseline and 3 months will be imputed. The missing values will be filled in 50 times to generate 50 complete data sets.

9.5 Interim Analysis

9.5.1 Interim Analysis 1

Interim Analysis 1 will take place when approximately 50% of subjects have been randomized and have completed the 3-month follow-up. The purpose will be to conduct an inspection of the overall standard deviation (SD); treatment groups will not be used. If the SD is deemed too large to expect that the study is adequately powered, a revised sample size may be considered. Otherwise, Interim Analysis 2 will proceed.

9.5.2 Interim Analysis 2

Interim Analysis 2 may be performed when approximately 60% of subjects have been randomized and have completed the 3-month follow-up. This will consist of an unblinded assessment of the primary analysis using the mITT population. Depending on the results of this analysis, the trial may stop early in case of futility, continue to full enrollment based on the results of Interim Analysis 1, or stop for efficacy if superiority of the treatment under study is clearly established.

The interim analysis will be performed by an independent statistician who will report to the independent Data Management Committee (DMC). The DMC will have unblinded access to all data and will discuss the results with the Medical Advisors and make recommendations for the study based on the defined stopping criteria.

Full details will be provided in the Statistical Analysis Plan.

9.6 Secondary Efficacy Analyses

Secondary efficacy analyses will be completed for the PP population as follows. Results will be reported for observed data only; missing values will not be imputed.

9.6.1 ODI

The mean change from baseline to 3, 6, 9 and 12 months in the ODI, will be summarized by treatment group using descriptive statistics.

Responder rates for ODI will be determined by the proportion of subjects who achieve ≥ 10-point reduction in ODI from Baseline to 3 months post-treatment. Results will be presented for both treatment groups.

9.6.2 VAS

The mean change from baseline to 3, 6, 9 and 12 months in the VAS score will be summarized by treatment group using descriptive statistics.

Responder rates for VAS will be determined by the proportion of subjects who achieve ≥ 1.5cm reduction in VAS from Baseline to 3 months post-treatment. Results will be presented for both treatment groups.

9.6.3 SF-36

The mean change from baseline to 3, 6, 9 and 12 months in the SF-36 physical component summary (PCS) and the mental component summary (MCS) will be summarized by treatment group using descriptive statistics.

9.6.4 EQ-5D-5L

The mean change from baseline to 3, 6, 9 and 12 months in the EQ-5D-5L will be summarized by treatment group using descriptive statistics.

Crossover Subjects

The above secondary end point measures will also be evaluated in the Crossover subjects post-treatment at 3 and 6 months compared to baseline for informational purposes only. The 12-month Control arm visit will be considered the baseline visit for these analyses in the Crossover subjects. Results will be summarized using descriptive statistics.

9.6.5 Patient Satisfaction

The Patient Satisfaction survey responses at 3, 6, 9 and 12 months post-treatment for the RF Ablation arm will be summarized using descriptive statistics.

9.6.6 Targeting Success

All treated vertebral body levels will be evaluated for targeting success by an independent radiologist. Targeting parameters will be evaluated based on MRI data collected at six weeks post-treatment for each of the treated subjects (RF Ablation arm and crossover subjects).

Analysis of targeting success will consist of evaluation of the RF ablation zone location for each treated vertebral body as described below:

- Targeting Success (hit) - Sufficient overlap of the ablation zone with the basivertebral foramen (BVF) in the mid-sagittal view/plane for each treated vertebral body (VB), as defined below, to ensure BVN ablation.
- Targeting Failure (miss) - The ablation zone does not provide sufficient overlap of the BVF in the mid-sagittal view/plane (both the central zone and the outer ring) for attempted treatment of a VB.

Images will be analyzed using suitable hardware and software in a step-wise manner as described below.

1. Each VB shall be evaluated for targeting success as follows:
    i. Perform review of all 6-week post-treatment MR sequences
    ii. Measure the following:

i. "A" - the length of the vertebral body from the posterior wall to the anterior wall along the mid-sagittal plane of the BVF and parallel to the superior endplate.

ii. "B" - the distance from the posterior wall to the furthest point of the ablation zone which intersects with the mid-sagittal plane of the BVF.

iii. "C" – the distance from the posterior wall to the closest point of the ablation zone which intersects with the mid-sagittal plane of the BVF.

iii. In the event that the BVF is not visible, either due to ablation overlap or MRI slice position, measurements should be taken on the mid-sagittal plane halfway between the inferior and superior end plates for L3, L4, and L5, and 2/3 of the way towards the superior end plate for S1 measurements.

iv. Grade each VB as a "hit" or "miss" based on the overlay of the ablation zone with the BVF.

If, on the basis of viewing T1, T2 and STIR images of sagittal and axial views, the measurements of A, B, and C are clearly established, a data form will be completed and the results recorded.

Results will be reported on a "per vertebral body" and a "per patient" basis, as the percentage of vertebral bodies/patients.

9.7 Long-Term Surveillance Endpoint Analyses

The additional endpoint of mean improvement from baseline to 24 months in the ODI, VAS, SF-36, and EQ-5D-5L will be evaluated with descriptive statistics in the RF ablation arm subjects only. Results for the Patient Satisfaction Survey will also be summarized.

RF Ablation arm subjects that consent to the five-year post procedure follow-up sub-study will be evaluated for the mean change from Baseline to 36, 48, and 60 months as measured by the ODI, VAS, SF-36, EQ-5D-5L, as well as the Patient Satisfaction rating. ODI, VAS, SF-36, and EQ-5D-5L will be evaluated with descriptive statistics. Results for the Patient Satisfaction Survey will also be summarized.

9.8 Analysis of Additional Outcomes of Interest

9.8.1 Health-related Quality of Life and Disability

Additional analyses of health-related quality of life and disability will be estimated via the EQ-5D-5L, SF-36, and ODI questionnaires.

9.8.2 Costs

Direct medical costs will be determined based on resource utilization (procedures, medications, hospitalizations, etc.) collected during the study and cost data obtained from published databases and records.

9.8.3 Quality-Adjusted Life Years

Health-related quality of life data from the EQ-5D-5L and SF-36, in conjunction with mortality data as appropriate, will be used to compute quality-adjusted life years (QALY).

9.8.4 Analyses

Collected resource utilization and cost data will be used to assess differences between baseline and follow-up time points for the RF ablation and Control arms, and between the RF ablation and Control arms. QALYs will be computed for the RF ablation and Control arms based on collected EQ-5D-5L utility scores and observed mortalities. Incremental cost-effectiveness will be assessed using these data and model-based projections to capture longer-term time horizons beyond follow-up observed in the trial. Further analyses might be conducted, such as exploration of potential indirect cost impact based on trial data and a comparison to data from the published literature.

9.9 Safety Endpoint Analyses

Safety will be evaluated for the Safety population, which will be comprised of all ITT subjects who attend a follow-up visit or who through some other means provide information relating to their well-being. All procedure, device, neurological and spine-related events reported in the study will be recorded and classified on the basis of MedDRA terminology for the Safety population.

Reported AEs will be tabulated by subject, detailing verbatim term given by the investigator, preferred term, system organ class, start date, stop date, severity, and device or procedure relatedness.

All reported procedure, device, neurological and spine-related SAEs will be tabulated by subject, detailing verbatim term given by the investigator, days from procedure to start of event, device or procedure relatedness, and outcome.

All Significant neurological AEs will be tabulated by subject, detailing event description by the investigator, level treated, access side, start date, stop date, severity, transient or permanent classification, and device or procedure relatedness.

10.0 SUBJECT BENEFIT AND RISKS

10.1 Risks of the Intracept System

Potential risks of the Intracept System include those of any surgical or minimally-invasive procedure performed with general anesthesia or moderate sedation. These risks include:

- Death
- Cardiopulmonary arrest
- Injury to a nerve or the spinal cord leading to increased pain, numbness, weakness, bowel/bladder incontinence, sexual dysfunction, or paralysis.
- Hypotension

- Pulmonary embolism
- Pneumonia
- Stroke
- Bleeding sufficient to cause anemia or require transfusion
- Hematoma
- Pseudoaneurysm
- Seroma
- Blood vessel injury
- Deep or superficial wound infection
- Adverse reaction to medications
- Treatment at wrong level
- Failure to treat

Potential risks from x-ray exposure used for the procedure include:

- Hair loss
- Cancer
- Skin redness
- Skin damage

Potential risks specific to the Intracept System and shared with many operative or minimally–invasive spine procedures include:

- Radiculopathy
- Failure to improve
- Operative, peri-operative, or post-operative pain associated with or resulting from the procedure (including new sensation of pain or increase in original pain)
- Thermal injury to neural, disc or paraspinal tissues
- Injury to anatomical structures adjacent to the target treatment location, including the nerve root and spinal cord
- Vertebral body fracture
- Permanent nerve damage resulting in loss of function or paralysis
- Device malfunction (separation of components, failure to reach target temperature, overheating)
- Allergic reaction to device components

All of the adverse events listed above are believed to be very rare for a procedure of this type. As noted in Section 6.13, Serious Adverse Events, Significant Neurological Events, and/or other important clinically significant adverse events, including those that are proximate events related to the device or procedure, will be recorded on the CRF and reviewed by the Medical Monitor.

10.2 Mitigation of Risk

Operative and postoperative risks for the Intracept Intraosseous Nerve Ablation System and procedure are mitigated by:

- Restriction of the use of the Intracept Intraosseous Nerve Ablation System to skilled spine surgeons and/or interventional physicians trained in the proper surgical techniques and imaging guidance.
- Meticulous selection of patients using well-defined clinical and imaging criteria.
- Careful pre-operative planning with three-dimensional imaging studies.
- Acute and long-term clinical and imaging evaluations of treated subjects following the procedure.
- Proctoring during procedures as needed. (Proctoring is performed by any clinician or by a Sponsor-designated physician thoroughly trained in the procedure, or by Sponsor technical support personnel.)

10.3 Risk-Benefit Analysis

While the potential risks of the Intracept System listed in Section 10.1 are risks associated with a procedure of this type, review of the literature suggests that adverse events known to occur during transpedicular procedures or intraosseous tumor ablation procedures are rare. Furthermore, the incidence of AEs in the SMART trial were within an acceptable range.

The potential benefits of participating in this study are improvement of pain and associated symptoms. Having regular, frequent interaction with the physician as part of the study may also be of benefit to the subject.

The sponsor believes that the potential benefit of the Intracept procedure outweighs the risk.

11.0 STUDY OPERATIONS AND EVALUATIONS

11.1 Reporting and Recording of Data

An electronic data capture (EDC) portal/database will be provided by the Sponsor. The EDC database will be provided by a vendor with extensive clinical trial experience and will be compliant with FDA Code of Federal Regulations (CFR) 21 part 11 guidelines for electronic records in clinical trials. All data will be entered according to the instructions provided in the CRF Instructions document and ICH/GCP Guidelines.

CRFs must be completed for each subject who has provided written informed consent and begins Screening procedures under this protocol. Information will be collected on potential subjects who screen out of the study and subjects who are enrolled. At a minimum, the information collected will include date of birth and the reason the subject was not randomized.

The Sponsor and/or its delegate will verify the data entered into the CRFs against applicable source documents to ensure accuracy and completeness of the data. Source documents for this trial may include, but are not limited to, hospital records, clinic records, and any study-specific worksheets, or laboratory result reporting documents. Data may be directly entered into CRFs, and therefore source documents may not be applicable to all CRF entries. Subject study records must contain reference to the study title and assigned subject identification number. The signed consent form must be filed with the subject's study record.

CRF completion must be kept current to reflect subject status during the course of the trial. No subject may be treated unless all Screening CRFs have been completed and submitted and the subject confirmed to be eligible for treatment by the study Enrollment Monitor.

All CRF data must be reviewed by the investigator. The investigator will sign off upon completion of all CRFs for a subject.

Study subjects will be identified by subject ID number. Subject names or other personal identification (e.g., subject social security number) must be blacked out on any documents submitted to the Sponsor or their designee, with subject ID number and protocol number transcribed onto each document page.

12.0 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

12.1 Investigator Qualifications

The investigator who performs the surgical procedure should have expertise in percutaneous, transpedicular vertebral body access during surgical procedures and have a lifetime history of having performed at least 30 kyphoplasty or vertebroplasty procedures or percutaneous pedicle screw placement. All investigators who perform the surgical procedure should be fellowship-trained and certified in the field of spine surgery by a national organization (e.g., American Board of Orthopedic Surgeons; American Board of Neurological Surgeons; American Board of Interventional Pain Physicians; American Board of Physical Medicine and Rehabilitation). Physician specialty types are expected to include primarily orthopedic surgeons, neurosurgeons, anesthesiologists, interventional neuroradiologists and physiatrists. Investigator must be willing to be proctored by a clinician or Sponsor designated physician trained in the procedure or by Sponsor technical support personnel for a minimum of 3 procedures. Deviations or exceptions to these investigator qualification requirements will be made on a case by case basis by the Sponsor.

12.2 Study Initiation

Before the start of this study at each study site, the essential documents as identified in the Sponsor's clinical trial SOPs must be on file in the Site Regulatory Binder as well as with the Sponsor or a Sponsor representative (i.e., IRB protocol and informed consent approval, investigator curricula vitae, investigator medical license, signed Investigator Agreement, signed protocol signature page, etc.). The investigator performing the Intracept procedure must have completed training in the use of the device. All site personnel must be trained on the study protocol and its execution, and applicable personnel must be trained on use of the EDC CRF system.

12.3 Informed Consent

Informed consent shall be obtained in writing and documented before a subject is enrolled in the clinical investigation. It is the responsibility of the investigator to ensure that written informed consent is obtained from the subject and documented before any activity or procedure is undertaken beyond standard of care assessments and procedures.

12.4 Amendments and Deviations

12.4.1 Protocol Amendments

This protocol is to be followed exactly. Changes to the research covered by this protocol must be implemented by formal protocol amendment. Amendments to the protocol may be initiated by Sponsor or at the request of the investigator. In either case, a formal amendment cannot be initiated until it has been approved by the Sponsor and the IRB, and a protocol signature page amendment has been signed by the investigator.

12.4.2 Protocol Deviations

Deviation from the clinical protocol and protocol requirements must be reported to the Sponsor in a timely fashion. All protocol deviations will be reviewed and evaluated on an ongoing basis and appropriate corrective actions implemented as necessary.

12.5 Institutional Review Board (IRB) Approval

This study will be conducted in compliance with the Declaration of Helsinki and its amendments and the applicable regulations of the country in which the study is conducted.

A properly constituted, valid IRB must review and approve the protocol, the investigator's informed consent document, and related subject information and recruitment materials before the start of the study.

12.6 Regulatory Compliance

The Intracept System has received FDA 510(k) clearance for the Indications for Use being studied under this protocol. This study will be conducted in compliance to applicable regulations contained in 21 CFR 11, 50, and 56, as well as the ICH/GCP Guidelines. The investigator and all research staff participating in this study are expected to adhere to this protocol, applicable privacy laws, and any approval requirements imposed by the Institutional Review Board. The investigator has the further responsibility of adherence to the Investigator Agreement and to maintain the contents of the Regulatory Binder.

12.7 Study Monitoring Requirements

Study monitoring will be performed according to Good Clinical Practice (GCP), the Sponsor's Standard Operating Procedures (SOPs), and the Sponsor's Monitoring Plan. The Sponsor's

Clinical Research Associates (CRA) or their delegates will conduct clinical monitoring of the study.

The investigator agrees to allow these CRAs, other authorized Sponsor personnel and Sponsor representatives access to the treatment and clinical supplies dispensing and storage area and to study documentation for the above-mentioned purpose and agrees to assist the CRAs in their activities, as requested. Requests by regulatory agencies to inspect the clinical site may be made. The investigator agrees to allow inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested and as required by law.

It is the investigator's responsibility to ensure accurate completion of the CRFs and to approve the CRFs.

12.8 Case Report Forms

Electronic CRFs will be used for this study. The CRFs contain confidential material, and the EDC system will be HIPAA and 21 CFR Part 11 compliant. Specific instructions for CRF completion as well as CRF completion training will be provided to investigational site personnel.

The investigator is responsible for reporting appropriately the requested information in the CRFs.

The Sponsor and/or its delegate will verify the data entered into the CRFs against applicable source documents to ensure accuracy and completeness of the data.

12.9 Data Management

The standard procedures for handling and processing records will be followed per GCP, the Sponsor's (and/or their designee) SOPs, and the Sponsor's Data Management Plan (DMP).

12.10 Disclosure of Data

Subject medical information obtained for this study is confidential, and disclosure to third parties other than those noted below is prohibited. Subject data will be identified by subject ID number only. Data will be de-identified in a manner compliant with HIPAA regulations.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, the Sponsor or its designee, and the IRB for each study site, if appropriate.

12.11 Retention of Records

The Sponsor requires that records and documents pertaining to the conduct of this study and the distribution of investigational device, including CRFs, consent form, laboratory test results, and study device management records, be retained by the investigator for 2 years after marketing application approval, or longer as required by governing local and national regulations. If no application is filed, the Sponsor requires that these records must be retained for 2 years after the

investigation is discontinued, or longer as required by governing local and national regulations. The Sponsor will notify the investigator of these events.

12.12 Data Quality Assurance

Steps to assure the accuracy and reliability of data include the selection of qualified clinical investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel prior to the study, and periodic monitoring visits by the Sponsor. The Sponsor and/or its delegate will review data accuracy and completeness during and after the study, and any discrepancies will be resolved with the clinical investigator or designee as appropriate.

13.0 APPENDIX 1: INVESTIGATOR SIGNATURE PAGE

Title:	**A Prospective, Randomized, Multi-Center Study of Intraosseous Basivertebral Nerve Ablation for the Treatment of Chronic Low Back Pain**
Protocol Number:	**CIP 0006, REV E**
Date:	**OCTOBER 17, 2018**

I have received and read the protocol listed above. I agree to undertake the protocol as defined therein and in accordance with the relevant parts of the ICH Guidelines for GCP, ISO 14155, the Declaration of Helsinki, and any other pertinent individual country laws/regulations. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or consent form must first be approved by the Sponsor and the Institutional Review Board, except those changes necessary to eliminate apparent immediate hazards to patients, or purely administrative changes, which must first be approved by the Sponsor. Failure to adhere to these stipulations may constitute a breach of United States Federal Regulations and may result in my termination of the study. In addition, when applicable, we agree to enlist sub-investigators who also agree to perform and conduct the study as described in the protocol.

Principal Investigator (Print Name) _____

Principal Investigator (Signature) _____

Date: _____

14.0 APPENDIX 2: MAIN STUDY SCHEDULE OF ASSESSMENTS

Visit or data collection period	**Screening Visit**	**Baseline**	**Procedure**	**6 Week MRI**	**3 Months Visit**	**6 Months Visit**	**9 Treatment Visit***	**12 Months Visit***	**24 Months Post-Treatment Visit***
Timeframe	Up to 3 months before Baseline	1-21 days before Treatment Visit		6 weeks (±4 days) after Treatment or Baseline Visit	3 months (± 1 week) after Treatment or Baseline Visit	6 months (± 1 week) after Treatment or Baseline Visit	9 months (± 1 week) after Treatment or Baseline Visit	12 months (± 2 weeks) after Treatment or Baseline Visit	24 months (± 2 weeks) after Treatment or Baseline Visit
Study activities									
Consent	x								
I/E criteria review	x								
Demographics	x								
Medical History	x								
Review densitometry	x								
Pregnancy test, if necessary	x	x							
BDI	x								
Standing lateral x-ray	x								
Review MRI	x			x					
ODI	x	x			x	x	x	x	x
VAS	x	x			x	x	x	x	x
Physical / neurological exam	x	x			x	x	x	x	x
LBP Concomitant Meds	x	x			x	x	x	x	
LBP Concomitant Therapies	x	x			x	x	x	x	
EQ-5D-5L		x			x	x	x	x	x
SF-36		x			x	x	x	x	x
Intracept Treatment			x						
Patient Satisfaction					x	x	x	x	x
AEs			x		x	x	x	x	x

*Post-Treatment visit to be performed in RF Ablation arm subjects only

15.0 APPENDIX 3: SUB STUDY ADDITIONAL FOLLOW-UP SCHEDULE OF ASSESSMENTS

Visit or data collection period	**36 Months Post-Treatment Visit***	**48 Months Post-Treatment Visit***	**60 Months Post-Treatment Visit***
Timeframe	36 months (± 4 week) after Treatment	48 months (± 4 weeks) after Treatment	60 months (± 4 weeks) after Treatment
Study activities			
Consent			
I/E criteria review			
Demographics			
Medical History			
Review densitometry			
Pregnancy test, if necessary			
BDI			
Standing lateral x-ray			
Review MRI			
ODI	x	x	x
VAS	x	x	x
Physical / neurological exam	x	x	x
LBP Concomitant Meds	x	x	
LBP Concomitant Therapies	x	x	
EQ-5D-5L	x	x	x
SF-36	x	x	x
Intracept Treatment			
Patient Satisfaction	x	x	x
AEs	x	x	x

*Post-Treatment visit to be performed in RF Ablation arm subjects who consent to participate in the Sub-study only

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