A Prospective Post Market Observational Pilot Study to Evaluate the Effectiveness of DRG Stimulation in the Treatment of Discogenic Low Back Pain

Protocol 28-SMI-2015

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PROTOCOL SIGNATURE SHEET:

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
AIMDD	Active Implantable Medical Device Directive
BSI	British Standard Institution
CE mark	Conformité Européenne (In accordance to European Regulations)
CLBP	Chronic Low Back Pain
CMO	Commissie Mensgebonden Onderzoek
CRF	Case Report Form
CRPS	Complex Regional Pain Syndrome
CSF	CerebroSpinal Fluid
CT	Computerised Tomography
DSMB	Data Safety Monitoring Board
DRG	Dorsal Root Ganglion
EC	Ethics Committee
EQ-5D	© 1987 EuroQol Group. EQ-5D™ is a trademark of the EuroQol Group
FBSS	Failed Back Surgery Syndrome
FU	Follow Up
GCP	Good Clinical Practice
IASP	International Association for the Study of Pain
ICD	Implantable Cardiac Defibrillator
ICH	International Conference on Harmonization
INS	Implantable NeuroStimulator
ISIS	International Spine Intervention Society
ISO	International Organisation for standardisation
LBP	Low Back Pain
MEDDEV	Medical Device Directive
MRI	Magnetic Resonance Imaging
NPRS	Numerical Pain Rating Scale
ODI	Oswestry Disability Index
PGIC	Patient Global Impression of Change
PIC	Patient Informed Consent
POMS	Profile of Mood States
PSI	Pounds per Square Inch
QOL	Quality of Life
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SCS	Spinal Cord Stimulation
Sponsor	The party that commissions the organisation or performance of the research
SPSS	Statistical computer program
TNS	Trial NeuroStimulator
US	United States
VAS	Visual Analogue Scale
WMO	Wet Medisch-wetenschappelijk Onderzoek met mensen

SUMMARY

Rationale: Initial clinical studies have shown that Dorsal Root Ganglion (DRG) can significantly reduce chronic intractable pain in a variety of chronic pain conditions including Chronic Low Back Pain (CLBP). CLBP as a diagnosis represents a heterogeneous patient population, for which there are few treatments with proven long-term efficacy other than lumbar spinal surgery. This study sets out to evaluate the effectiveness of DRG stimulation in a homogenous sub population of CLBP, that being Discogenic Low Back Pain or Discogenic Pain which is chiefly driven by disruption or deterioration of the lower lumbar intervertebral discs and is believed to represent around 40% of CLBP generally.

Objective: The purpose of this prospective post market observational pilot study is to evaluate the effect of DRG stimulation in the management of chronic discogenic pain in subjects who are refractory to other available treatments. Selected subjects will not be suitable candidates for lumbar spinal surgery and will meet the standard selection process for DRG stimulation as routinely utilised in the study centres. Results from this pilot study will inform current clinical practice and future comparative studies in this specific population.

Study design: This is a prospective, single-arm, multi-centre, post market, observational pilot study to collect data on pain relief, subject satisfaction, quality of life, physical functioning and safety.

Device: Commercially available Spinal Modulation Neurostimulator System for the management of chronic intractable pain (CE 567069). The device will be used within its CE mark indication (intractable chronic pain). However, for this pilot study all devices and associated implantable equipment will be provided at no cost to the study centres as it is not reimbursed yet for this specific sub population of CLBP.

Study population: A maximum of 20 subjects will be enrolled into the pilot study but we will cease enrolment once 15 subjects have had a successful trial and proceeded to full implant. Any patient enrolled at that time will continue through the protocol. The subjects will be of either gender, between 18 and 65 years of age and suffering from confirmed discogenic Low Back Pain (LBP) (minimum duration of 6 months) and are not suitable candidates for lumbar spinal surgery.

Data Collection: Potential subjects will be enrolled after they have read and signed a Patient Informed Consent (PIC) form. Subjects enrolled will be asked to complete several questionnaires prior to their procedure and at routine follow up visits for 12 months.

Follow-up visits: Subjects will visit the hospital for the following visits: Baseline, Trial Neurostimulation (TNS) procedure, End of Trial, Implantable Neurostimulator (INS) implant, 2 week follow-up (FU), 3 month FU, 6 month FU and12 month FU.

Risks: The implantation of the system is a standard procedure in the participating hospitals and regular follow up visits for the first year after this procedure are also standard practice. While this procedure is not routinely offered to patients with Discogenic Low Back pain due to reimbursement restrictions, the use of the therapy in this patient group falls within the CE

mark indication for the treatment. As participants in this research would not be offered this therapy if they would not be enrolled in this study, a clinical trial insurance is in place to reassure coverage in case of any complications.
Subject who decided not to participate in this study will not receive a neurostimulator and will be monitored by their physician as needed in accordance with standard medical procedures.

1 INTRODUCTION AND RATIONALE

1.1 History of Therapy

Neuromodulation for the treatment of chronic pain has been used for over a century[1]. The first use of electricity in the spine for neuromodulation of pain was conducted by Norm Shealy in 1967[2]. The development of spinal cord stimulation (SCS) technology has grown rapidly in the past 40 years and is now used in over 40,000 new patients each year.

1.2 Spinal Cord Stimulation

Several recent systematic reviews have provided evidence that this stimulation technology is a safe and effective treatment option for patients suffering from chronic, intractable pain[3-5]. The effective rate of serious complications is quite low[3-5]. The treatment has been found to be successful in approximately 50% of patients that have a successful temporary stimulation trial period[6,7]. In the largest prospective trial published to date, Kumar and colleagues found a significant reduction in leg pain when compared to a conventional medical management control group in the Failed Back Surgery Syndrome (FBSS) population[6,8]. In a similar manner, Kemler and colleagues found that SCS can be effective in the treatment of complex regional pain syndrome (CRPS)[9-11]. Despite varying levels of success in the literature, approximately 50% of patients will not receive adequate pain relief from traditional spinal cord stimulation. The Spinal Modulation Neurostimulation System allows a novel method of Spinal Cord Stimulation by specifically stimulating the Dorsal Root Ganglion (DRG). There are, to date, five published clinical studies on the use of the Spinal Modulation Neuromodulation System that demonstrate that DRG stimulation is a safe and effective treatment for a variety of chronic pain conditions including FBSS and Low Back Pain (LBP) generally[12-16].

1.3 Therapy Description

DRG stimulation with the Spinal Modulation Neurostimulation System consists of a two-phase treatment process: 1) a trial phase and 2) a permanent implant phase. The first phase involves implanting stimulation electrodes (or “leads”) into the epidural space, which are connected to an external Trial NeuroStimulator (TNS) to electrically stimulate the Dorsal Root Ganglion (DRG). If the subject experiences sufficient pain relief, defined as a reduction in pain intensity of ≥50%, during this trial stimulation phase they will progress to receive a fully Implantable NeuroStimulator (INS) system (phase 2).

1.4 Rationale

Low Back Pain (LBP) generally and Chronic Low Back Pain (CLBP) particularly, represents a significant clinical challenge with a one year incidence rate or 10-15% and a point prevalence of 15-30% of the US population[17]. Incremental healthcare costs attributable to LBP were estimated at $US 26.3 billion in 1998[18]. Furthermore, 75% of costs associated with LBP are accumulated by just 5% of the LBP population further highlighting the need for effective treatment options for CLBP sufferers[19].

Discogenic LBP describes LBP originating from one or more intervertebral discs as depicted below in Figure 1.

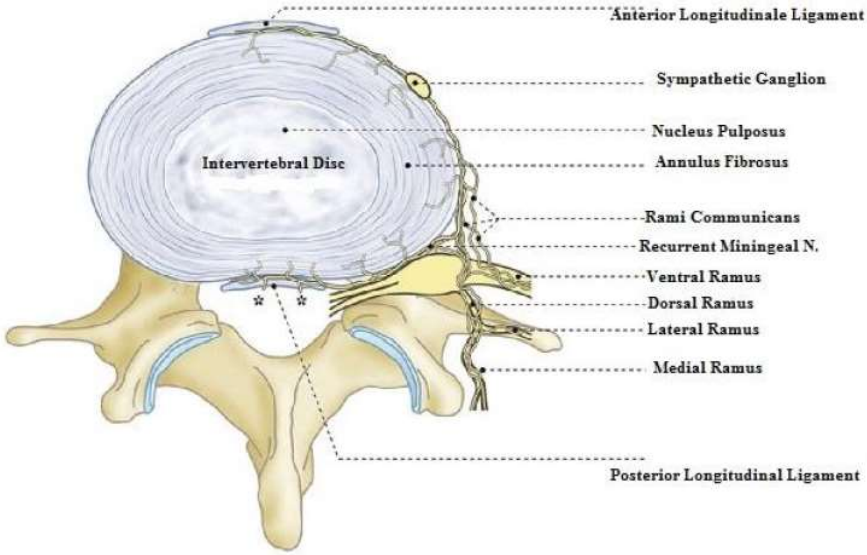

Figure 1.

The Intervertebral Disc with Innervation.

Image taken from Chapter 15: Discogenic Low Back Pain (Kallewaard et al) in Evidence Based Interventional Pain Medicine – According to Clinical Diagnosis Wiley Blackwell 2012. J. Van Zundert et al

Intervertebral discs can become painful when nociceptive afferent (pain sensing) fibres present in the outer layer of the annulus fibrosus are activated due to disruption of the disc, usually caused by injury or degeneration. Figure 2 shows different degrees of disc disruption as seen during discography (intra-disc injection of dye under fluoroscopy or computerised tomography (CT)).

Discogenic low back pain is believed to account for 26-42% of CLBP[20]. Currently, aside from spinal surgery, there are few effective treatments for this common, debilitating condition, which justifies the need for further research into potential therapy options[20].

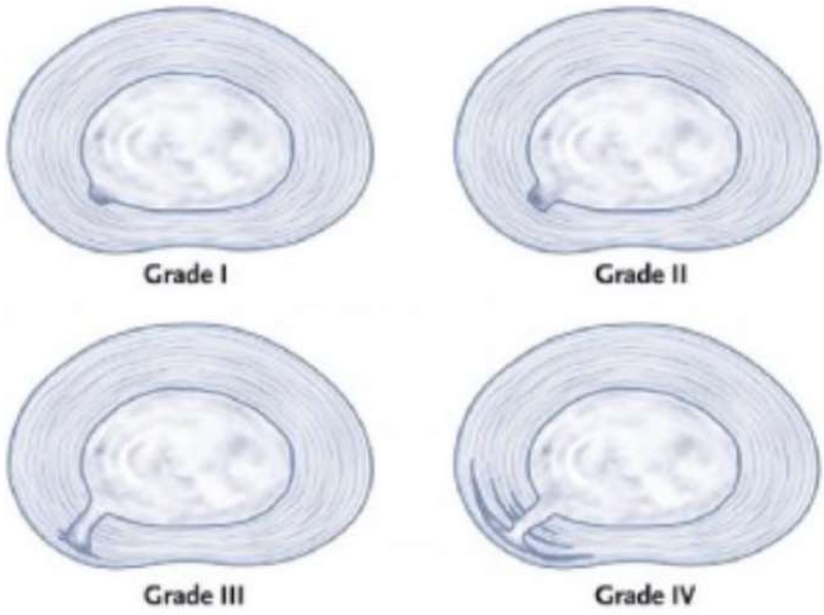

Figure 2. The Dallas Discogram Scale to Classify Grades of Disc Disruption.
Image taken from Chapter 15: Discogenic Low Back Pain (Kallewaard et al) in Evidence Based Interventional Pain Medicine – According to Clinical Diagnosis Wiley Blackwell 2012. J. Van Zundert et al

Early clinical results on the use of DRG stimulation in LBP are encouraging and in line with other neuromodulation therapies[12-14]. However, the results for SCS in this diverse patient population are generally mixed[3, 6-8]. We wish to study the effectiveness of DRG stimulation in this homogenous sub-population of CLBP in whom the pathophysiology of chronic pain has been properly elucidated. The neuroanatomical mapping of nociceptive afferent neurons from the lower lumbar (L4/5 and L5/S1) Intervertebral discs through the sympathetic trunk and L2/L1 DRG(s) suggests that these levels may be a good target for interventional therapies[21]. Indeed anecdotal observations from the previously treated populations suggest that this may hold true and as such the L2 and or L1 DRG(s) will be targeted with treatment to assess this.

In 2007 a consensus article was published on the clinical relevance of changes in pain intensity as measured by commonly utilised research instruments such as a visual analogue scale (VAS) and a numerical pain rating scale (NPRS) in chronic pain[22]. While standard practice is to judge the success of a neurostimulation trial procedure as a reduction in pain intensity of ≥50% the mentioned consensus article denotes that a reduction in pain intensity of ≥30% or 2 points on a VAS/NPRS is clinically relevant[21]. As such the treatment in this observational post market study will follow standard practice and only subjects who experience ≥50% pain relief during the temporary trial procedure will go on to receive the implantable stimulator but we will judge the long term effectiveness of the therapy against the ≥30% or 2 point reduction as recommended.

2. OBJECTIVES

2.1 Primary Objective:

- To determine the number (percentage) of subjects who achieve a sustained and clinically meaningful reduction in the intensity of LBP of ≥30% or 2 points on a numerical pain rating scale (NPRS)[22] in the implanted subjects at 6 and 12 month follow up visits as compared to baseline.

2.2 Secondary Objectives:

- Subject Satisfaction with treatment will be assessed using the Patient Global Impression of Change (PGIC), a 7 point Likert scale
- Number (percentage) of subjects who achieve a ≥50% reduction in the intensity of the LBP at 6 and 12 months FU
- Pain relief (≥30% and ≥50%) in other painful anatomy related to the back pain (e.g. Leg, buttock or foot)
- [redacted]

3. STUDY DESIGN

This is a prospective, observational, multi centre, single arm pilot study designed to assess the effectiveness of DRG stimulation using the Axium® SCS system for the treatment of discogenic LBP over a 12 month follow up period.
Eligible subjects for DRG stimulation will be asked to participate in this study. If they decide to participate, they will be treated with the Axium® SCS system and prospectively followed for 12 months following implantation. If they decide not to participate, they will not receive the Axium® SCS system and will be monitored by their physician as needed in accordance with standard medical procedures.

In line with standard practice the system will be implanted in two stages. The first stage is the Trial NeuroStimulation (TNS) phase during which epidural leads are implanted at the L2 and/or L1 level (to treat the back pain) and L3 and/or L4 to treat any leg pain and temporarily tunnelled to an external trial stimulation device. Subjects will then utilise the temporary system for period of time in line with usual practice (typically 5-10 days). If, at the end of this TNS phase, the subject has experienced a reduction of ≥50% in their LBP they will proceed to the second treatment stage when the Implantable NeuroStimulator (INS) will be implanted and connected to existing epidural leads. Following INS insertion subjects will be followed prospectively for 12 months as shown in Figure 3 below

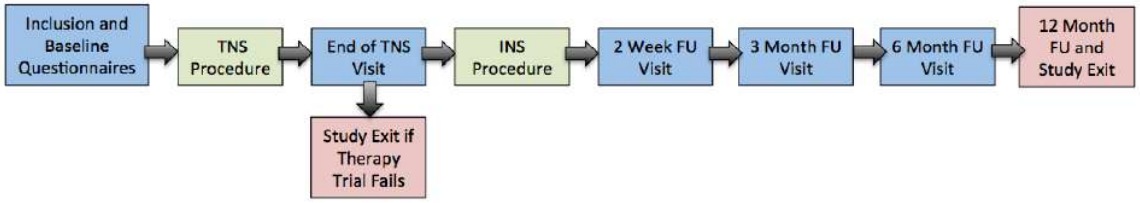

Figure 3: Study Flowchart; Questionnaires administered at the Follow Up (FU) visits in blue and the final 12 month visit

4 STUDY POPULATION

4.1 Population

A maximum of 20 subjects will be enrolled but we will cease enrolment once 15 subjects have had a successful trial and proceeded to full implant. Any patient enrolled at that time will continue through the protocol. The subjects will be of either gender, between 18 and 65 years of age and suffering from confirmed discogenic LBP (minimum duration of 6 months) and are not suitable candidates for lumbar spinal surgery.

Subjects must meet all of the inclusion and none of the exclusion criteria to be enrolled in the post market pilot study. Subjects will read and sign an informed consent prior to data collection. Subjects will be recruited from the sites existing patient population and through new patient contacts as normally progresses in standard clinical practice.

4.2 Inclusion criteria

1. Subject of either gender between 18 and 65 years of age
2. Subject is able and willing to comply with the follow-up schedule and protocol
3. Subject is able to provide written informed consent
4. Chronic low back pain of at least 6 months
5. History consistent with discogenic low back pain (e.g. Pain produced on lumbar motion, significant functional limitation in sitting duration and tolerance)
6. Neurologic exam without marked motor deficit.
7. Definite/Highly Probable/Discogenic Pain as confirmed by provocative discography according to IASP/ISIS guidelines*
8. Low Back Pain intensity should be 6 or higher measured on a NPRS at baseline
9. Meets all the inclusion criteria for the implantation of a neurostimulation system as typically utilised in the study centre
10. Subject has been screened by a multi-disciplinary panel including a psychologist and deemed suitable for implantation

* Guidelines summarised in Appendix B

4.3 Exclusion criteria

1. Female subject of childbearing potential is pregnant/nursing or plans to become pregnant during the course of the study
2. Escalating or changing pain condition within the past month as evidenced by investigator examination
3. BMI ≥35
4. Subject has had injection therapy or radiofrequency treatment for their low back pain within the past 3 months
5. Subject currently has an active implantable device including ICD, pacemaker, spinal cord stimulator or intrathecal drug pump
6. Subject is unable to operate the device
7. Severe disc degeneration at the affected level as evidenced by >50% disc height loss on plain anteroposterior and lateral lumbar radiographs or CT/MRI.
8. Extruded or sequestered herniated nucleus pulposus at the affected level(s).
9. Previous lumbar back surgery (e.g. Laminectomy, discectomy or fusion) at the affected level(s)
10. Moderate to severe spinal stenosis due to osteophyte and/or ligamentous overgrowth as evidenced by MRI or CT in the previous 6 months
11. Moderate to severe endplate degenerative changes at the affected levels
12. Grade 1-2 spondylolisthesis
13. Previous Neurostimulation therapy

4.4 Sample size calculation

For this post market pilot study no formal sample size estimation has been made, we will enrol a maximum of 20 subjects.

5 TREATMENT OF SUBJECTS

5.1 Implant Procedure

The *Physician Implant Manual*, to be found in the packages of the components, provides a detailed description of the implant and surgical technique; this is also described briefly in Section 3. Following informed consent and baseline measurements, subjects will begin the two-phase treatment process in line with standard practice. Following INS insertion subjects will be followed prospectively for 12 months as shown in Figure 3.
As a result of the device design, the therapy is fully reversible and can be removed through a similar minor procedure.

5.2 Use of pre-existing therapies

Subjects will be allowed to continue using medication and other non-invasive therapies for the treatment of their pain condition. The Principal Investigators and/or sub-investigator as per standard of care will dictate the prescription of such treatments for pain.

6 DESCRIPTION OF THE DEVICE

6.1 Name and description of Neurostimulator System

The Spinal Modulation Neurostimulator System consists of the following components:

- Trial Neurostimulator
- Implantable Neurostimulator
- Trial Lead Kit
- Implant Lead Kit
- Connector Cable Kit
- Tunnelling Tool Kit
- Clinical Programmer
- Patient Programmer
- Auxiliary Magnet Kit
- Programmer Charger Kit
- Programmer Carrying case
- Lead Accessories Kit
- 22 cm Small Curve Delivery Sheath Kit
- 22 cm Big Curve Delivery Sheath Kit
- Lead Extension Kit

A detailed description of the components can be found in the Physician Implant Manual, included in the packages of the components.

On 16 November 2011, BSI granted Spinal Modulation, Inc. CE mark for the Spinal Modulation Neurostimulator System for the management of chronic intractable pain (CE 567069). The system has been registered with the CIBG in the Netherlands on 24 November 2011 and will be utilised within its CE marked indication.

6.2 Summary of known and potential risks and benefits of the therapy

A summary of the known and potential risks and benefits can be found in the accompanying manuals that are included in the package of the components. The general risks associated with the Spinal Modulation Neurostimulator System are similar to those associated with other Spinal Cord Stimulator systems. Possible risks to the subjects include both device and procedural based risks.

The most common side effects and risks are:

- Pain (where the needle is to be inserted)
- Pain caused by under stimulation due to lead migration
- Pain over the implantable neurostimulator site (only applicable in Phase 2)
- Escalating pain
- Bleeding (where the needle has been inserted)
- Headache
- Infection
- Localized collection of serous (clear) fluid at injection site
- Discomfort during the treatment
- Allergic or rejection response to implant materials
- Constant pain at the lead site
- Stimulation of the chest wall
- Lead migration (movement) and/or local skin breakage
- Weakness
- Clumsiness
- Numbness
- Temporary muscle activation

Very rare risks and side effects include:

- Cerebral Spinal Fluid (CSF) leakage
- Tissue damage
- Nerve damage
- Spinal cord compression
- Swelling
- Paralysis
- Hematoma
- Seroma
- Sensory loss
- Skin erosion around the INS or leads
- Battery failure and/or battery leakage
- Lead breakage requiring replacement of the lead
- Hardware malfunction requiring replacement of the neurostimulator
- Pain from a non-injurious stimulus to the skin (allodynia)
- An exaggerated sense of pain (hyperesthesia)

6.3 Device utilization

A detailed description of device utilization can be found in the Physician Implant Manual. Investigators involved in the study have been trained on the use of the Spinal Modulation Neurostimulator System and already have experience with the use of the commercially available products.

6.4 Devices

The devices that will be used in the post market observational pilot study are commercially available products, used within their licensed indication (intractable chronic pain). However, for this pilot study all devices and associated implantable equipment will be provided at no cost to the study centres as the device is not yet reimbursed for this specific subpopulation with CLBP.

The selected subjects will not be suitable candidates for lumbar spinal surgery and at the moment one of the requirements for reimbursement is having had a lumbar spinal surgery without success before receiving neurostimulation. A label of the products used will be added to the subject files to document and identify the devices.

Following completion of the study, any patient implanted during the course of the study will be eligible to receive free of charge replacement equipment, if necessary, while the therapy is still not reimbursed for CLBP. As soon as this indication will be reimbursed, equipment needs to be purchased in the usual manner.

7 METHODS

7.1 Assessments

During the scheduled follow-ups the following assessments will be performed. Table 1 in appendix A gives a detailed description of the assessments per follow-up.

- Pain, assessed by an 11 point (0-10) numerical pain rating scale (NPRS)
- Subject Satisfaction with treatment will be assessed using the Patient Global Impression of Change (PGIC), a 7 point Likert scale
- [redacted]

7.2 Randomisation, blinding and treatment allocation

As this is a single-arm observational study, no randomisation or blinding will occur. All eligible subjects recruited into the study will undergo treatment in the usual manner and complete questionnaires at routinely scheduled follow up appointments.
Subject who decided not to take part in this study will not receive a neurostimulator and will be monitored by their physician as needed in accordance with standard medical procedures.

7.3 Data Collection

During the post market pilot study, data will be collected on Case Report Forms (CRFs).

Subject Screening and baseline

Subjects presenting with discogenic CLBP of at least 6 months duration and not being suitable candidates for lumbar spinal surgery will be screened for possible entry into the post market pilot study. Subjects will be screened according to the Inclusion/Exclusion criteria and only subjects meeting all Inclusion criteria and none of the Exclusion criteria will be enrolled. The study will be explained to all subjects and subjects will provide informed consent prior to any data collection. Subjects will be allowed to discuss their participation in the study with the study physician, clinical staff, family, friends and personal or external physician.

Following subject screening and acquisition of Informed Consent, subjects will undergo a baseline assessment to collect clinical data prior to lead implantation and stimulation.

Trial Stimulation Lead Implant Procedure

Following collection of baseline measurements, subjects will begin Phase 1 of the two-step treatment process.

End of TNS Trial Phase

At the end of the Trial Phase, pain relief will be assessed to determine whether a subject should receive an INS implant. In line with standard clinical practice only subjects who experience ≥50% pain relief during the trial phase will go on to receive the INS. The duration of the trial phase will be at the investigators discretion and in line with current, clinical practice (usually 5-10 days) but should be no longer than 30 days.

INS Implant Procedure

Eligible subjects willing to continue with the implant will undergo surgery to insert the fully implantable neurostimulator (INS). If the epidural leads were removed during the trial period, new leads will also be implanted at this time (see Physician Implant Manual for detailed information regarding the procedure). Each subject will receive a hand-held Patient Programmer that can be used to adjust stimulation amplitude as needed.

Regular Follow-ups

Subjects will be followed according to the follow-up schedule for 12 months following implant at regular intervals: 2-week (±5 days), 3 month (±2 weeks), 6 month (±4 weeks) and 12 month (±4 weeks). The given time-windows are advisable and coincide with routine follow up

visits for patients receiving treatment with DRG stimulation, therefore, visits outside the time windows will not be seen as a protocol deviation.

Prior to completing the required assessments, the subject will have his/her stimulator reprogrammed if needed (if applicable).

12-month follow-up (Study Exit)

The study will end 12 months following INS implantation. At this visit, the regular follow-up assessments as outlined in appendix A will be acquired and a trial exit form will be completed.

Following completion of the study, subjects will continue to use the Spinal Modulation Neurostimulator System. The subjects will be monitored by their physician as needed in accordance with standard medical procedures.

Interim Programming/Revision/Replacement/Explant (if necessary)

During the course of the study, subjects will have the option to return to the study site at any time to have their neurostimulator re-programmed to achieve maximal benefit. If any part of the Spinal Modulation Neurostimulator System becomes dysfunctional or requires adjustment following implantation, it is up to the investigator to perform an interim visit. In appendix A, the assessments for an interim visit and a revision are listed (if applicable).

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.5 Replacement of individual subjects after withdrawal

Subjects who are withdrawn during the study will not be replaced.

7.6 Follow-up of subjects withdrawn from the study

Subjects who are withdrawn will continue to receive normal, standard of care follow-up by the study physician.

7.7 Premature termination of the study

The Post Market pilot Study will be terminated prematurely if the Investigators feel there is a risk to the subjects enrolled. Subject safety will continue to be monitored by the Investigators for the duration of the device.

8 SAFETY REPORTING

8.1 Applicable local laws and regulations

For the reporting of events in this trial, applicable international standards and guidance documents for CE marked products will be followed (AIMDD, MEDDEV 2.12/2 rev2 and MEDDEV 2.12-1 rev 8), the applicable local laws and regulations, and the SMI/SJM internal operating procedures on complaint reporting, whichever is the most stringent.
In this regard investigators will only need to report device related Adverse Events (AE) and device related Serious Adverse Events (SAE).

Additionally, all reported device related AEs and SAEs will be reviewed internally at Spinal Modulation Inc./St. Jude Medical according to the criteria for incidents to be reported by manufacturers to competent authorities, as defined in section 5.1.1 in the MEDDEV 2.12-1 Rev 8.

8.2 Definitions

We will use the ISO14155:2011 as reference for the definitions of events.

Adverse Event (AE):
Any untoward medical occurrence, unintended disease or injury, or untoward clinical sigs (including abnormal laboratory findings) in subjects, users or persons, whether or not related to the investigational device.

Serious Adverse Event (SAE):
Any AE that leads to:

- Death
- Serious deterioration in the health of the subject, that either resulted in
- A life threatening illness or injury, or
- A permanent impairment of a body structure or body function, or
- In-patient or prolonged hospitalisation, or
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or body function - foetal distress, foetal death or a congenital abnormality or birth defect

Planned hospitalization for a pre-existing condition, prolonged hospitalization as a result of a revision procedure, which is allowed in the protocol or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

8.3 Reporting timelines

All reportable events shall be documented in a timely manner throughout the trial by entering the required information into the appropriate CRF, provided to the site by the sponsor. The completed AE and/or SAEs CRF can be sent to the assigned person within Spinal Modulation/St. Jude Medical (cwensing@SJM.com).

8.4 Follow-up of adverse events

All reported device related events will be followed until they have abated, or until a stable situation has been reached, unless the subject is lost to follow-up.

8.5 Data Safety Monitoring Board (DSMB)

This post market pilot study is purely observational using a routinely utilised therapy within its licensed indications. According to the DSMB risk classification ('Kwaliteitsborging mensgebondenonderzoek 2.0', from www.NFU.nl on 13th May 2014) this study represents negligible risk to participants and therefore a DSMB will not be necessary for this study.

9 STATISTICAL ANALYSIS

9.1 Descriptive statistics

Descriptive statistics will be used to evaluate the means and standard deviations of data collected as well as to compute the changes in the outcomes compared to baseline.

9.2 Analysis

Univariate, multivariate and covariate statistical analyses will be conducted as appropriate to statistically tests for both primary and secondary objectives. Statistical analyses will be conducted utilizing SAS and/or SPSS statistical software. *Post-hoc* power analyses will also accompany the omnibus testing and *post-hoc* analyses determining differences between baseline and treatment means. All levels of significance will be deemed to occur at $p<0.05$.

10 ETHICAL CONSIDERATIONS

10.1 Regulation statement

The current Post Market pilot Study will adhere to the ethical principles of the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and will use the Medical Research Involving Human Subjects Act (WMO), the ISO 14155:2011, the MEDDEV 2.12/2 rev 2, as well as standards set forth in GCP/ICH guidelines according to US 21 CFR, Part 50 as guidelines.

10.2 Recruitment and consent

All proposed subjects will be recruited for this study once the “Commissie Mensgebonden Onderzoek (CMO) regio Arnhem Nijmegen” has approved the study and the “Raad van Bestuur” of the Rijnstate Ziekenhuis and the “Raad van Bestuur” of the MUMC+ approved the performance of this study. Potential subjects will be identified from the investigator’s patient population and will be informed about the purpose, nature, and duration of the Study. Interested volunteer subjects will then have the protocol, the treatment, the follow-up regimen, and the risks and benefits fully explained to them by the investigator. The potential subject will be given as much time as needed to read the consent form and have the study procedures and alternative therapies discussed prior to signing the Informed Consent form. An example of the Informed Consent form and patient information letter is provided. The subject must read the information letter, the subject’s questions answered, and the form signed by the subject before any study related activity can be performed. All subjects will receive copies of their signed informed consent documents.

10.3 Benefits and risks assessment

The benefits of this pilot study could enable improved treatment of chronic, discogenic LBP. Feedback from this study will inform future practice of interventional pain medicine and improve physicians understanding of the beneficial effect of DRG stimulation in a homogenous sub-population of CLBP who are no suitable candidates for lumbar spinal surgery.

The results from this pilot study will inform future clinical practice and inform the need and design of future research in this specific population.

The device is CE mark approved and will be used within its licensed indications.

Careful monitoring of subjects will ensure that any potential side effects or adverse events are noticed and treated as quickly as possible. Reporting of adverse events will adhere to local regulatory requirements.

10.4 Compensation for injury

The implantation of the system is a standard procedure in the hospital and regular follow up visits for the first year after this procedure are also standard practice. While this procedure is not routinely offered to patients with Discogenic low back pain due to reimbursement restrictions, the use of the therapy in this patient group falls within the CE mark indication for the treatment. As participants in this research would not be offered this therapy if they would not be enrolled in this study, a clinical trial insurance is in place to reassure coverage in case of any complications.
In addition, the sponsor/investigator has a liability insurance that provides cover for damage to subjects through injury or death caused by the use of the device

10.5 Compensation

Subjects that participate in the Study will receive the device at no costs and they will be compensated for additional travel expenses which would not have been incurred had they not been part of this study. Subjects will not be provided compensation above and beyond reasonable travel expenses.
Following completion of the study, any patient implanted during the course of the study will be eligible to receive free of charge replacement equipment, if necessary, while the therapy is still not reimbursed for CLBP. As soon as this indication will be reimbursed, equipment needs to be purchased in the usual manner.

11 ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents

The Sponsor and their designated representatives will make every reasonable effort to protect the confidentiality of the subjects participating in the pilot Study. Except as required by law, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. A unique identification code will be assigned to each subject participating in this Study. Information about the code will be kept in a secure location. All subject data will be stored in locked offices. All electronic data will be password-protected on computers stored in locked offices. Access to subject information will be limited to study personnel only. Any data, including photographs, videos, and interviews with the subject that may be published in abstracts, scientific journals, marketing material or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity without the express approval of the subject. Subjects will be asked for approval at the start of the Study as part of the patient informed consent. It is possible that subject personal health records may be disclosed to other agencies such as regulatory bodies as per country regulations.

Data storage will reside at both the study site and with the Sponsor Company, Spinal Modulation/SJM. Sites will retain data collected during the post market pilot study for a minimum of 5 years. Sponsor will retain data per company Standard Operating Procedures.

11.2 Amendments

Amendments are changes made to the post market pilot Study after approval by the CMO regio Arnhem Nijmegen. The CMO regio Arnhem Nijmegen will be notified of all study amendments according to its stated requirements.

11.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the pilot Study to the CMO regio Arnhem Nijmegen, the "Raad van Bestuur" of the Rijnstate Ziekenhuis and the "Raad van Bestuur" of the MUMC+ as required by local law and regulations.

11.4 End of study report

The Investigator will provide the CMO regio Arnhem Nijmegen, the "Raad van Bestuur" of the Rijnstate Ziekenhuis, the "Raad van Bestuur" of the MUMC+ and other regulatory bodies, as needed by law, a final report following the end of the pilot Study. The timing of this submission will be in accordance with the reporting requirements.

In case the pilot Study is ended prematurely, the investigator will notify the CMO regio Arnhem Nijmegen, the "Raad van Bestuur" of the Rijnstate Ziekenhuis and the "Raad van Bestuur" of the MUMC+ including the reasons for the premature termination.

11.5 Public disclosure and publication policy

Per national guidelines (where applicable) and medical journal editorial board guidelines, the post market pilot Study will be registered with a public clinical trial registry. Publication of the data collected during this Study will be in accordance with clinical trial agreements.

12 REFERENCES

1. Gildenberg, P.L., *History of Electrical Neuromodulation for Chronic Pain.* Pain Medicine, 2006. **7**(S1): p. S7-S13.
2. Shealy, C.N., J.T. Mortimer, and J.B. Reswick, *Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report.* Anesth Analg, 1967. **46**(4): p. 489-91.
3. Cameron, T., *Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review.* J Neurosurg, 2004. **100**(3 Suppl Spine): p. 254-67.
4. Taylor, R.S., J.P. Van Buyten, and E. Buchser, *Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: a systematic review and analysis of prognostic factors.* Spine (Phila Pa 1976), 2005. **30**(1): p. 152-60.
5. Taylor, R.S., J.P. Van Buyten, and E. Buchser, *Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors.* Eur J Pain, 2006. **10**(2): p. 91-101.
6. Kumar, K., et al., *Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome.* Pain, 2007. **132**(1-2): p. 179-88.
7. North, R.B., et al., *Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial.* Neurosurgery, 2005. **56**(1): p. 98-106; discussion 106-7.
8. Kumar, K., et al., *The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation.* Neurosurgery, 2008. **63**(4): p. 762-70; discussion 770.
9. Kemler, M.A., et al., *Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy.* N Engl J Med, 2000. **343**(9): p. 618-24.
10. Kemler, M.A., et al., *The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial.* Ann Neurol, 2004. **55**(1): p. 13-8.
11. Kemler, M.A., et al., *Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial.* J Neurosurg, 2008. **108**(2): p. 292-8.
12. Deer T.R., Grigsby E., Weiner R.L., Wilcosky B., Kramer J.M. 2012. *A Prospective Study of Dorsal Root Ganglion Stimulation for the Relief of Chronic Pain*. Neuromodulation 2013; 16: 67–72
13. Liem L., Russo M., Huygen F.J.P.M., Van Buyten J.-P., Smet I., Verrills P., Cousins M., Brooker C., Levy R., Deer T., Kramer J. 2013. *A Multicenter, Prospective Trial to*

Assess the Safety and Performance of the Spinal Modulation Dorsal Root Ganglion Neurostimulator System in the Treatment of Chronic Pain.: Neuromodulation 2013; e-pub ahead of print. DOI: 10.1111/ner.120

14. Liem L., Russo M., Huygen F.J.P.M., Van Buyten J.-P., Smet I., Verrills P., Cousins M., Brooker C., Levy R., Deer T., Kramer J. 2014. *One-Year Outcomes of Spinal Cord Stimulation of the Dorsal Root Ganglion in the Treatment of Chronic Neuropathic Pain*. Neuromodulation 2014; E-pub ahead of print. DOI: 10.1111/ner.12228
15. Van Buyten J.P, et al., *Stimulation of Dorsal Root Ganglia for the Management of Complex Regional Pain Syndrome: A Prospective Case Series*. Pain Practice 2014 epub
16. Schu, C. et al., *Spinal Cord Stimulation of the Dorsal Root Ganglion for Groin Pain – A Retrospective Review*. Pain Practice 2014 epub
17. Slipman, C.W., Shin, C.H., Patel, R.K., Isaac, Z., Huston, C.W., Lipetz, J.S., Lenrow, D.A., Braverman, D.L. and Vresilovic, E.J. (2002), *Etiologies of Failed Back Surgery Syndrome*. Pain Medicine, 3: 200–214
18. Luo X., Pietrobon R., Sun S.X., Liu G.G., Hey L. *Estimates and patterns of direct health care expenditures among individuals with back pain in the United States*. Spine. 2004;29:79-86. [PMID: 14699281]
19. Frymoyer J.W., Cats-Baril W.L.. *An overview of the incidences and costs of low back pain*. Orthop Clin North Am. 1991;22:263-71. [PMID: 1826550]
20. N. Bogduk, C. Aprill, R. Derby**:** *Lumbar Discogenic Pain: State-of-the-Art Review*. Pain Medicine 2013; 14: 813–836
21. S-I. Nakamura, K. Takahasi, Y. Takahasi, M. Yamagata, H. Moriya: The Afferent Pathways of Discogenic Low-Back Pain – Evaluation of L2 Spinal Nerve Infiltration. The J of Bone and Joint Surgery 1996; Vol. 78-B, No 4. Pp 606-612
22. Dworkin, R.H., Turk, D.C., Wyrwich, K.W., Beaton, D., Cleeland, C.S., Farrar, J.T., Zavisic, S. (2008). *Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations*. The Journal of Pain : Official Journal of the American Pain Society, 9(2), 105–21. doi:10.1016/j.jpain.2007.09.005
23. Kallewaard. J.W., Terheggen. M.A.M.B., Groen. G.J., Sluijter. M.E., Derby. R., Kapural. L., Mekhail. N., van Kleef. M. *15. Discogenic Low Back Pain*: Pain Practice 2010; Vol 10. Issue 6. pp 560-579

Appendix A: Table 1

Follow-up Schedule 28-SMI-2015, Version 4.0_19Oct2015

A Prospective Post Market Observational Pilot Study to Evaluate the Effectiveness of DRG Stimulation in the Treatment of Discogenic Low Back Pain

CRF #	Assessment	Baseline	Trial Procedure	End of Trial	Final Implant	2-week F/U +/- 1 week	3-month F/U +/- 2 weeks	6-month F/U +/- 4 weeks	12-month F/U +/- 4 weeks	Interim Visit	Revision
	Informed Consent Form	x									
CRF - 1Q	Inclusion / Exclusion Criteria	x									
CRF - 2Q	Medical History	x									
[redacted]	[redacted]	■						■	■		
[redacted]	[redacted]	■		■		■	■	■	■	■	
CRF - 43Q	Pain Measurement	x		x		x	x	x	x	x	
[redacted]	[redacted]	■				■	■	■	x		
CRF - 39Q	Pain Assesment (Pain DETECT)	x						x	x		
[redacted]		■						■	■		
[redacted]		■						■	■		
[redacted]			■		■						■
CRF - 16Q	Programming		x		x	x	x	x	x	x	x
[redacted]				■		■	■	■	■		
[redacted]				■		■	■	■	■	■	
CRF - 17Q	AE Reporting	+	+	+	+	+	+	+	+	+	+
CRF - 18Q	SAE Reporting	+	+	+	+	+	+	+	+	+	+
CRF - 25Q	Protocol Deviation	+	+	+	+	+	+	+	+	+	+
CRF - 14Q	Revision										x
CRF - 21Q	Trial Exit			+					x	+	+

Required = x
Only if needed = +

Appendix B: IASP/ISIS Guidelines on the Diagnosis of Discogenic Pain

Consolidated Criteria taken from Kallewaard et al 2010[23]

1. Absolute discogenic pain:
    - Stimulation of target discus reproduces con-cordant pain.
    - The intensity of this pain has a Numeric Rating Scale (NRS) score of at least 7 on an 11-point scale.
    - The pain is reproduced by a pressure of less than 15 psi above the opening pressure.
    - Stimulation of the two adjacent discs is not painful.

2. Highly probable discogenic pain:
    - Stimulation of target discus reproduces con-cordant pain.
    - The intensity of this pain has a NRS score of at least 7 on an 11-point scale.
    - The pain is reproduced by a pressure of less than 15 psi above the opening pressure.
    - Stimulation of *one* of the adjacent discs is not painful.

3. Discogenic pain:
    - Stimulation of target discus reproduces con-cordant pain.
    - The intensity of this pain has a NRS score of at least 7 on an 11-point numerical scale.
    - The pain is reproduced by a pressure of less than 50 psi above the opening pressure.
    - Stimulation of the two adjacent discs is not painful.

4. Possible discogenic pain:
    - Stimulation of target discus reproduces con-cordant pain.
    - The intensity of this pain has a NRS score of at least 7 on an 11-point numerical scale.
    - The pain is reproduced by a pressure of less than 50 psi above the opening pressure.
    - Stimulation of one of the adjacent discs is not painful, and stimulation of another discus is painful at a pressure greater than 50 psi above the opening pressure, and the pain is discordant.