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PROTOCOL

Trialing of PM modulation therapy in patients with chronic intractable low back pain with or without leg pain

SGEN-2017PM1

Sponsor:
StimGenics
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Principal Investigator:
[_____]

Date of Protocol: 24 April 2017
Version: 1.1

The study will be conducted according to the protocol and in compliance with Good Clinical Practice and other applicable regulatory requirements.

PROTOCOL SUMMARY

Study Title: Trialing of PM modulation therapy in patients with chronic intractable lower back pain with or without leg pain.

Purpose of the study: To determine the feasibility of PM modulation therapy in patients with chronic intractable lower back pain with or without leg pain.

Objective: Demonstrate that spinal cord stimulation using multiple simultaneous waveforms provides pain relief in patients suffering chronic intractable low back pain with or without leg pain.

Trial design: This is a prospective, open label, observational cross-over study in which pain relief from a PM modulation therapy, polymodal spinal cord stimulation (PM-SCS), will be compared to conventional spinal cord stimulation. Up to 25 patients will be included in the study. Standard evaluation phase to test the subject's response to commercial SCS system will be conducted for 4 ± 1 days. After a washout period of up to 1 day, polymodal spinal cord stimulation therapy (PM-SCS) will be applied after conventional spinal cord stimulation (SCS) therapy for 4 ± 1 days.

Treatment: Enrolled patients will receive polymodal SCS therapy after receiving conventional SCS as part of their therapy trial period. Polymodal stimulation will utilize two trial leads (with eight electrodes each), which have been implanted in the epidural space following standard clinical practices and as part of a standard spinal cord stimulation trial period. Each lead will be connected to the output channel of an external neurostimulation unit (ENS) designed to safely deliver either conventional or polymodal electrical signals to the leads. During conventional SCS, arrays of electrodes in the leads will be set to deliver conventional parameters that produce paresthesia coverage of the painful area following standard programming protocols. After the conventional SCS therapy trial phase has been completed (4 ± 1 days), there will be a washout period of up to one day before the patient crosses over to polymodal SCS therapy, which will be administered for 4 ± 1 days. [redacted]

The patient will be educated and trained on operation of a remote controller that allows the patient to operate the ENS and stimulation therapy programs available within. The patient will

also be instructed on troubleshooting both the ENS and remote controller (i.e. changing batteries, etc.).

Pain relief will be assessed in terms of the level of pain before SCS therapy and in comparison with level of pain when conventional SCS and polymodal SCS were trialed.

Primary endpoint:

1. Back Pain reduction relative to baseline pain (i.e. prior to SCS) at day 5 post-initiation of a particular SCS therapy (conventional or polymodal).

[redacted]

Inclusion Criteria:

1. Capable of giving written informed consent to participate in this clinical study based on voluntary agreement after a thorough explanation of the patient's participation is provided to them.
2. Chronic intractable pain of the lower back equal to or greater than pain in lower limbs, and that has been refractory to conservative therapy for ≥ 3 months.
3. Must be older than 18 years old.
4. Average back pain intensity of ≥ 5 out of 10 on the numerical pain rating scale (NPRS).
5. Appropriate candidate for spinal cord stimulation trial.
6. Subjects must be on a stable dose of pain medication regimen for at least one month.
7. Female patients who are not pregnant and do not plan to become pregnant during the study. Females of child bearing potential must provide a negative pregnancy test and must be using reliable contraception and must continue to use reliable contraception until study completion. Non-childbearing potential is defined as postmenopausal for at least 2 years or surgical sterilization or hysterectomy at least 3 months before study start. Patients who become pregnant or who have a spouse/significant other that becomes

pregnant during the course of this study agree to report pregnancy to the study physician/staff.

8. Must be able to comply with the requirement of study visits and follow-up and phone visits.
9. Have cognitive ability of operate the remote control and follow therapy instructions and directions by clinicians.

Exclusion Criteria:

1. Systemic infection.
2. Any active implanted device.
3. Previous experience with SCS therapy either during a trial or fully implanted
4. Evidence of serious neurological, psychological or psychiatric disorders.
5. Mechanical spinal instability.
6. Patients with uncorrected coagulation disorders or who are on anticoagulation therapy and cannot interrupt the therapy.
7. Patient who are pregnant, breast-feeding or women of childbearing potential with positive pregnancy tests.
8. Human immunodeficiency virus (HIV) infection or a clinically significant infection.
9. Patients who are undergoing or will undergo therapies or diagnostics that involve electromagnetic fields such as: diathermy based therapies, electrocautery, magnetic resonance imaging (MRI), radiofrequency (RF) or microwave ablation, bone growth stimulators, electrolysis, therapeutic ultrasound, ultrasound, lithotripsy, psychotherapeutic procedures, radiation therapy, and transcutaneous electrical nerve stimulation.
10. A clinically significant disorder such as cerebrovascular disease, pulmonary infarction, ischemic heart disease, cardiac dysrhythmia, myocardial infarction, or congestive heart failure or any other as determined by the investigator.
11. Uncontrolled diabetes, uncontrolled pulmonary disease, or uncontrolled hypertension.
12. Patients who have evidence of major psychiatric disease, mental disorder, drug dependency, alcohol dependency, or substance abuse disorders.
13. Patients who have progressive neurological disease such as multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, rapidly progressive arachnoiditis, acute herniated disc, or any other as determined by investigator.
14. Medical condition or pain in other body areas that could interfere with study procedures, accurate pain reporting, and/or confound evaluation of study end points.
15. Concurrent participation in another clinical study.
16. Involvement in an injury claim under current litigation or a pending or approved workers' compensation claim.

Schedule of Events:

Event\Activity	Enrollment/ Baseline (Day 0)	Start of SCS Trial (0-30 days after enrollment/baseline)	Crossover to Polymodal SCS (3-5 days after start of trial)	End of Study (3-5 days after crossover to PM-SCS)
Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Pregnancy Test[A]	X			
General Health and Pain Medications	X			
Pain NPRS	X		X	X
Informed Consent Reaffirmation	X			
Lead Implantation		X		
X-ray Fluoroscopy		X	X	X
Programming of Conventional SCS and start of trial		[X]		
Programming of PM-SCS			[X]	
Stimulation Sensation Assessment				X
Impression of Improvement and Patient Satisfaction				X
Adverse Event Assessment		X	X	X

[A] Administered only to subjects of childbearing potential

[X] Optional reprogramming (conventional or polymodal SCS) visits are allowed at the discretion of the investigator and depending on the feedback from standard of care follow up phone visits.

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SIGNATURE PAGE

Investigator Signature

I have read this protocol and agree to conduct the investigation according to the requirements of the study protocol and in accordance with Good Clinical Practice, applicable State and Federal regulations and conditions imposed by the reviewing Investigational Review Board. As the Principal Investigator of the study, I agree to supervise all sub-investigators at my site as well as the use of all of the investigational devices and to ensure appropriate informed consent is obtained for all subjects prior to inclusion in the study.

Signed: _____ Date: _____

Name: _____
Title: Principal Investigator

Confidentiality Statement

All information concerning the study device supplied by StimGenics in connection with this study, and not previously published, is considered confidential and proprietary information. This information includes the clinical protocol and its appendices, subject informed consent form, product labelling (user manuals for patient and clinician), and case report forms. This confidential information shall remain the sole property of StimGenics, and shall not be disclosed to others without previous written consent by StimGenics. This confidential information shall not be used except for the performance of the study.

All the information communicated and developed during the conduct of the study shall be considered confidential and proprietary. This information will be used by StimGenics in connection with the development of polymodal spinal cord stimulation therapy. This information may be disclosed as deemed necessary by StimGenics.

The data and information gathered from the study will not be the subject of publication by the individual study site and without prior consent from StimGenics.

LIST OF ABBREVIATIONS

A	Amplitude of electric signal (in units of current: Ampere)
AE	Adverse Event
CE	Conformité Européenne
CFT	Clinical Field Technician
CRF	Case Report Form
CRO	Contract Research Organization
EMI	Electromagnetic interference
ENS	External Neurostimulation Unit
F	Frequency of pulsed electric signals (in units of Hz)
GCP	Good Clinical Practice
Hz	Hertz, equivalent to event per second
IRB	Institutional Review Board
kHz	kilohertz (equivalent to one thousand events per second)
µC/cm^2	Microcoulomb per square centimeter (units of charge density)
µs	Microseconds (equivalent to one millionth of a second)
mA	Milliamperes (equivalent to one thousand of an ampere)
ms	Milliseconds (equivalent to one thousand of a second)
NPRS	Numerical Pain Rating Scale
PI	Principal Investigator
PM-SCS	Polymodal Spinal Cord Stimulation
PW	Pulse Width of pulsed electric signal (in units of time)
SAE	Serious Adverse Event
SCS	Spinal Cord Stimulation
ST	Sensory Threshold
UADE	Unanticipated adverse device effects
US-FDA	United States Food and Drug Administration

1. BACKGROUND/SCIENTIFIC RATIONALE

1.1 Spinal Cord Stimulation Therapy and Chronic Pain

It is estimated that about 20% percent of the population worldwide is affected by moderate to severe chronic pain[1]. Chronic pain becomes a burden to the individual as this affects a person's ability to carry out many daily life activities, such as exercising, walking, driving a car, attending social events, or performing household chores.[1] In the United States, chronic pain is considered one of the most pervasive and intractable conditions affecting at least one third of the population at an estimated cost of five hundred billion dollars per year, when combining health-related expenditure and the cost-impact on loss of productivity and income.[2]

Spinal cord stimulation (SCS) is a proven therapy that have been in use for over 40 years for various types of neuropathic pain and is a reversible, less invasive therapy that allows patients to evaluate the therapy for several days using an external stimulation (ENS) prior to receiving an implantable pulse generator (IPG).[3,22,25,28] Conventional medical management, including medication and physical therapy, is often not adequate for treating chronic pain. In some cases, surgical interventions also fail to remediate severe cases of neuropathies and intractable back pain. Spinal Cord Stimulation (SCS) utilizes a pulsed electric field that is applied to the dorsal section of the spinal cord via electrode arrays, called leads, implanted in the epidural space.[3] Conventional (also called tonic) SCS utilizes an electric field oscillating in the 40-250 Hz frequency range. The electric field stimulates neurons that induce a tingling sensation (paresthesia) that is steered by the clinician and patient to overlay with the targeted pain location by modifying the applied electric field. This therapy has been clinically utilized for about half a century. The mode of action is based on the Gate Control Theory formulated by Melzack and Wall,[4] although a full understanding of the mechanism has yet to be elucidated. The concept behind tonic SCS is that the paresthesia induced by the applied oscillating electric field masks (or "closes the gates to") pain signals travelling to the brain.

In recent years, new modalities have been developed in which the stimulation is done effectively and safely with pulses oscillating at frequencies larger than conventional ones (i.e. 1,200 Hz) including high frequency (10 kHz),[5,6,7] as well as oscillating bursts of pulses (5 pulses at 500 Hz).[8,9] A unique aspect of these treatments is that pain may be relieved without the need of the often uncomfortable paresthesias.

There are currently various Spinal Cord Stimulation (SCS) systems which have received CE mark and are approved by the FDA for use in the U.S. These devices are indicated as a sole mitigating agent or as an adjunct to other modes of therapy used in a multidisciplinary approach

for chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with failed-back surgery syndrome, intractable low back pain and leg pain.

1.3 General Description of a Trial Stage for Spinal Cord Stimulation Therapy

SCS therapy may not be suitable for all patients that suffer intractable chronic pain conditions. In order to assess if a patient qualifies for SCS therapy, they must be enrolled in a trial stage as prescribed by a physician. The beginning of the trial stage period involves the

implantation of the trial leads and initial programming of therapy. A trained physician introduces, percutaneously, a set of trial leads within the epidural space along vertebral levels appropriate to stimulate segments of the spinal cord associated to the painful dermatome. The leads are connected to a commercial external neurostimulator (ENS) that is programmed by a clinician to deliver pulsed oscillatory signals to particular sets of electrodes in the leads using parameters that provide pain relief within an established safety range. A pulsed electric signal is characterized by three parameters: pulse frequency (F), pulse width (PW), and amplitude (A). The ENS allows the clinician to set various therapy options to be tried by the patient during the SCS trial stage period. A signal with a specific combination of parameters (F, PW, A) that is delivered to a specific array of electrodes in the leads is called a program. A combination of programs, called a group, constitutes a therapeutic SCS option to be tried. The patient is discharged from the clinic with an active therapy group and the clinician would follow up and may instruct the patient to select a different therapy group, which may provide better pain relief. At the end of the trial stage, the physician and patient assess the level of pain relief as well as the level of comfort of the patient with the treatment received by one or various therapy groups. The temporary leads are then removed from the patient. If the trial stage is considered successful, then the patient may return for surgical implantation of permanent leads and an implantable programmable stimulator device.

Programming with PM-SCS will occur during the trial stage period after the patient has undergone a trial of the therapy using conventional SCS. PM-SCS will utilize the same trial leads, interface trial cable, and remote controller that had been used during the conventional SCS period. The leads, interface trial cable and remote controller are commercial products (i.e. FDA approved). The ENS for PM-SCS is an investigational device based on a commercial platform which has been modified and tested to safely provide programs and therapy groups with the proper parameter sets (F, PW, A). The patient will try conventional SCS therapy at the beginning of the trial stage period for up to five days and then, after a brief washout period, will receive PM-SCS therapy for up to five days.

2. RISKS AND BENEFITS

SCS have been used therapeutically since 1967.[21] Over the years, SCS has been proven to be effective and safe, and to improve the quality of life of thousands of patients suffering from chronic pain who have failed other treatments, including conservative therapies (i.e. pharmacological, physical therapy) and surgery.[22]

2.1 Risks

It is anticipated that stimulation programs used when administering PM-SCS therapy will exhibit a safety profile equivalent to that exhibited by a stimulation programs used during conventional SCS therapy, considering that the ENS used is based on a commercially available platform which has been cleared by CE mark and approved by the US-FDA. It is anticipated that no additional risk is introduced with the treatment with polymodal SCS.

[redacted]

There is a substantial body of evidence that indicates that SCS is safe and that serious adverse events are rare, while most common complications can be resolved with minor interventions. This large body of evidence has stimulated professional societies such as the International Neuromodulation Society (INS) and the American Society of Interventional Pain Physicians (ASIPP) to commission a body of experts to review the available body of evidence and provide recommendations intended to be a guide for proper and safe practice of SCS therapy.[22,25,26] This study will follow these guidelines.

Complications of SCS therapy have been previously reviewed and listed in Table 1.[25,26,27,28,29] These are associated with the implantation of the temporary leads and include superficial infection, deep infection, dural puncture with associated comorbidities, epidural hematoma, and

spinal cord damage. Dural puncture is a well-known complication with any procedure that accesses the epidural space. A significant post-dural puncture headache would be treated with fluids, analgesics, and bed rest; while a recalcitrant one may require an epidural blood patch.

Unlikely risks and complications associated to the leads include pain at the implant site, and tissue reaction to leads. Serious complications such as paralysis, nerve injury and death are very unlikely risks.

Possible risks associated with stimulation include malfunctioning of the ENS, undesirable sensations, increased pain (other than at implant site), uncomfortable stimulation of muscle and skin, and development of pain symptoms in a new location. Unlikely risks include an increase in the intensity, duration, or frequency of pain to be treated. Seizures, paralysis, nerve injury or death are very unlikely to occur as a result of stimulation.

Electromagnetic interference (EMI) is a field of energy generated by equipment that can be found in medical, work, home or public environments and that is strong enough to interfere with the device function. Both the commercial and investigational devices (ENSs) used in this study include features that has been tested to provide protection from EMI. Most electrical devices and magnets encountered by a patient in a normal day are unlikely to affect the operation of the ENS or remote controller. However, sources of strong EMI can result in the following adverse events: serious injury or death, lead migration, operational changes of the device, and unexpected changes in stimulation therapy. In order to minimize the risk of EMI, patients will be instructed to avoid exposure to defibrillators, diathermy based therapies, electrocautery, arc welding, power stations, magnetic resonance imaging (MRI), radiofrequency (RF) or microwave ablation, bone growth stimulators, electrolysis, therapeutic ultrasound, ultrasound, lithotripsy, psychotherapeutic procedures, radiation therapy, theft detectors, therapeutic magnets, and transcutaneous electrical nerve stimulators. Patients that may require the use of certain therapies or devices that generate strong EMI during the study will not be admitted to participate. Patients with other active implanted devices will not be admitted in the study.

In summary, the study has been designed to minimize the potential for injury to the subject. The procedures used in this study are all routine medical procedures using standard products as aforementioned. Also, the list of exclusion criteria includes a few that will mitigate the risk of EMI or mishandling of the devices by potential patients. The potential risks for this study are identical to risks seen with standard commercially approved SCS systems. Following standard practices of care, subjects will be trained and educated about avoiding or minimizing their exposure to EMI, proper operation of the device and remote control, and to contact the investigators when they suspect a complication.

All procedures, including implantation and programming, will be conducted by experienced and properly trained personnel following routine medical procedures and standard techniques, which would make the risks associated with this study to be the same as the risks associated with commercially approved SCS systems.

Table 1. Risks associated with SCS therapy

Type of Risk	***Level of Risk***	***Risk and Occurrence***
Lead Implant Risks	Possible	Lead migration (13.2%) Failure/malfunction of leads (9.1%) Superficial site infection (4.5%) Procedure complications, including infection & fever (3.4%)
	Unlikely	Persistent pain at lead implant site (0.9%) Temporary pain at implant site (0.9%) Tissue reaction to leads (0.3%) Epidural hematoma (0.3%) Skin erosion around the leads (0.2%)
	Very Unlikely	Allergic reaction to leads (0.1%) Paralysis (0.003%) Nerve injury Death
Stimulation Risks	Possible	Malfunction of stimulation system (4.5%) Undesirable sensations (2.4%) Increased pain in area other than implant site Uncomfortable stimulation of tissue around leads Development of pain in a new location
	Unlikely	Increase in pain intensity, duration, or frequency
	Very Unlikely	Seizure Paralysis Nerve injury Death

2.2 Benefits:

Because of the short-term of the study, there is no opportunity for long-term benefits to patients in this study beyond those associated with the outcome of the trial of conventional SCS therapy. A patient that experiences a successful outcome with trialing conventional SCS therapy

will be eligible for a permanent implant. Participation in this study will provide information that will add to our understanding of treatment options for patients with back pain.

3. OBJECTIVES

3.1 Purpose:

To determine the feasibility of polymodal spinal cord stimulation therapy in patients with chronic intractable lower back pain with or without leg pain.

3.2 Objective:

To demonstrate that spinal cord stimulation using multiple simultaneous waveforms provides pain relief in patients suffering chronic intractable low back pain with or without leg pain.

3.3 Primary endpoint:

3.3.1 Back pain score reduction relative to baseline pain score (i.e. prior to SCS) at day 5 post-initiation of a particular SCS therapy (conventional or polymodal).

[redacted]

4. ELIGIBILITY

4.1 Inclusion Criteria:

4.1.1 Capable of giving written informed consent to participate in this clinical study based on voluntary agreement after a thorough explanation of the patient's participation is provided to them.

4.1.2 Chronic intractable pain of the lower back equal to or greater than pain in lower limbs, and that has been refractory to conservative therapy for ≥ 3 months

4.1.3 Must be older than 18 years old.

4.1.4 Average back pain intensity of ≥ 5 out of 10 on the numerical pain rating scale (NPRS)

4.1.6 Appropriate candidate for spinal cord stimulation trial

4.1.7 Subjects must be on a stable dose of pain medication regimen for at least one month.

4.1.8 Female patients who are not pregnant and do not plan to become pregnant during the study. Females of child bearing potential must provide a negative pregnancy test and must be using reliable contraception and must continue to use reliable contraception until study completion. Non-childbearing potential is defined as postmenopausal for at least 2 years or surgical sterilization or hysterectomy at least 3 months before study start. Patients who become pregnant or who have a spouse/significant other that becomes pregnant during the course of this study agree to report pregnancy to the study physician/staff

4.1.9 Must be able to comply with the requirement of study visits and follow-up and phone visits

4.1.10 Have cognitive ability of operate the remote control and follow therapy instructions and directions by investigator

4.2 Exclusion Criteria:

4.2.1 Systemic infection

4.2.2 Any active implanted device

4.2.3 Previous experience with SCS therapy either during a trial or fully implanted

4.2.4 Evidence of serious neurological, psychological or psychiatric disorders.

4.2.5 Mechanical spinal instability

4.2.6 Patients with uncorrected coagulation disorders or who are on anticoagulation therapy and cannot interrupt the therapy

4.2.7 Patient who are pregnant, breast-feeding or women of childbearing potential with positive pregnancy tests

4.2.8 Human immunodeficiency virus (HIV) infection or a clinically significant infection

4.2.9 Patients who are undergoing or will undergo therapies or diagnostics that involve electromagnetic fields such as: diathermy based therapies, electrocautery, magnetic resonance imaging (MRI), radiofrequency (RF) or microwave ablation, bone growth stimulators, electrolysis, therapeutic ultrasound, ultrasound, lithotripsy, psychotherapeutic procedures, radiation therapy, and transcutaneous electrical nerve stimulation.

4.2.10 A clinically significant disorder such as cerebrovascular disease, pulmonary infarction, ischemic heart disease, cardiac dysrhythmia, myocardial infarction, or congestive heart failure or any other as determined by the investigator

4.2.11 Uncontrolled diabetes, uncontrolled pulmonary disease, or uncontrolled hypertension

4.2.12 Patients who have evidence of major psychiatric disease, mental disorder, drug dependency, alcohol dependency, or substance abuse disorders

4.2.13 Patients who have progressive neurological disease such as multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, rapidly progressive arachnoiditis, acute herniated disc, or any other as determined by investigator

4.2.14 Medical condition or pain condition in other body areas that could interfere with study procedures, accurate pain reporting, and/or confound evaluation of study end points

4.2.15 Concurrent participation in another clinical study

4.2.16 Involvement in an injury claim under current litigation or a pending or approved workers' compensation claim

4.3 Withdrawal:

Subjects may voluntarily withdraw from the study at any time. Withdrawing from the trial will not carry out any sanction and will not affect patient's access to other treatments.

4.4 Terminating Participation:

A patient's participation in the study may be terminated if continued participation in the study is not in the subject's best interest, according to the Principal Investigator's opinion or if the subject withdraws participation from the study. Therapy will be stopped and leads will be removed. Any patient who suffers an adverse event whether or not related to study treatment may withdraw voluntarily from the study.

5. DESIGN AND PROCEDURES

5.1 Study Design

This is a prospective, observational cross-over study that will compare conventional SCS and polymodal SCS during two different time windows during an SCS trial period. Up to 25 patients will be included in the study. Figure 1 illustrates a general diagram of the study process. A screening/enrollment visit will assess the eligibility of a potential subject who has already given adequate time to evaluate and discuss the informed consent form. Patients that meet all the inclusion and exclusion criteria and who reaffirm voluntary informed consent to participate in the study will be enrolled. Patients enrolled in the study will visit the clinic to start the SCS trial period which involves the implantation of the stimulation leads and programming of conventional SCS therapy. Conventional SCS therapy will be administered before PM-SCS therapy for 4 ± 1 days. [redacted]

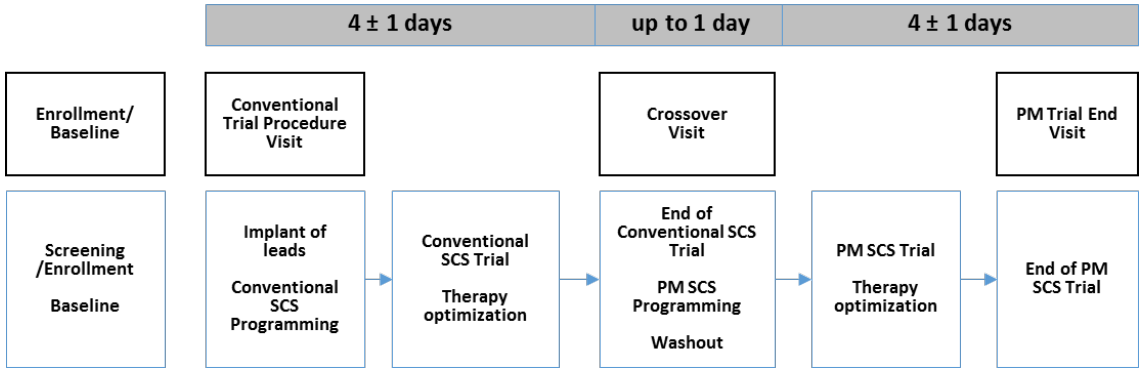

Figure 1. Flow diagram of the study process.

After the patient has trialed conventional SCS therapy, there will be a washout period which is expected to last no more than one day. This will allow analgesic effects of the conventional therapy to wear off. The patient will visit the clinic to crossover to PM-SCS therapy and will trial it for 4 ± 1 days. After the trial period is over, the implanted temporary leads will be disconnected from the ENS and removed from the patient and the trial period will end. The trial period during the study will not extend longer than ten days. Table 2 shows a schedule of events.

Table 2. Schedule of Events.

Event\Activity	**Enrollment/ Baseline (Day 0)**	**Start of SCS Trial (0-30 days after enrollment/baseline)**	**Crossover to Polymodal SCS (3-5 days after start of trial)**	**End of Study (3-5 days after crossover to PM-SCS)**
Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Pregnancy Test[A]	X			
General Health and Pain Medications	X			
Pain NPRS	X		X	X
Informed Consent Reaffirmation	X			
Lead Implantation		X		
X-ray Fluoroscopy		X	X	X
Programming of Conventional SCS and start of trial		[X]		
Programming of PM-SCS			[X]	
Stimulation Sensation Assessment				X
Impression of Improvement and Patient Satisfaction				X
Adverse Event Assessment		X	X	X

[A] Administered only to subjects of childbearing potential

[X] Optional reprogramming (conventional or polymodal SCS) visits are allowed at the discretion of the investigator and depending on the feedback from standard of care follow up phone visits.

5.2 Recruitment and Consent:

The investigator will discuss participation in the study with a patient who is already qualified and approved for a SCS therapy trial and who may qualify to be enrolled in the study according to inclusion and exclusion criteria. The patient will be given the opportunity to read an informed consent form (ICF) and get answers to all questions before consenting participation (see Appendix A for details on the Informed Consent Process).

5.3 Clinic Visit 1: Enrollment/Baseline Visit

A patient will be enrolled in the study upon signing the ICF, verifying that all inclusion and exclusion criteria are met (using CRF01) and reaffirming voluntary participation, and. Medical history, including pain management, and baseline pain will be collected and recorded in the appropriate CRFs (CRF02, CRF03, and CRF04).

5.4 Clinic Visit 2: Lead Implantation, Conventional SCS Programming and Training Procedure:

Patients will be implanted with commercially available temporary leads as part of the regular SCS trial period and using standard clinical practice. The patient will be placed on a surgical bed in a supine position and may be mildly sedated. The back of the patient will be draped and cleaned using sterile techniques. A properly trained physician will guide and place two percutaneous leads into the epidural space using introducers and steering stylets while under fluoroscopic x-ray guidance. Once the leads are placed above the dorsal aspect of the cord at the proper vertebral level, the introducers and stylets are removed. The exterior portion of the leads will be anchored with sutures or taped firmly to the skin and the proximal ends of the leads connected to an interface cable, which will be plugged into the ENS. The leads and cables will be properly secured to minimize migration of the leads and prevent accidental disconnection. An AP and lateral radiograph of the implanted leads in reference to the vertebral levels will be collected. After the patient has recovered from sedation, programming of conventional SCS therapy will be performed using standard clinical practice.

5.4.1 Conventional SCS Therapy:

For Conventional SCS Therapy, the ENS will be programmed to deliver pulses at a frequency in the 20-200 Hz range with a maximum pulse width of 1 ms. The amplitude of

the electrical signal and the arrays of electrodes used for delivering therapy will be set in order to elicit paresthesia as reported by the patient. Once paresthesia is reported, this will be used to guide the programmer to cover the proper pain dermatome. These parameters and electrode arrangements will be noted and saved in the remote controller. The patient will be educated and trained on operation and troubleshooting the ENS and remote controller.

Following a satisfactory demonstration on ENS and remote controller operation, the patient will be discharged to home with an emergency 24-hour contact information should the patient have any issues or questions. Programming and training procedure should be approximately 1.5 to 2 hours long. The patient will be scheduled to return to the clinic for the crossover reprograming visit 4 ± 1 days after the initial programming.

5.5 Clinic Visit 3: Crossover visit:

After 4 ± 1 days of trialing conventional SCS therapy, the patient will return to the clinic for a reassessment of the lead location using x-ray fluoroscopy, and crossover to PM-SCS therapy. Pain level obtained with conventional SCS will be assessed and recorded in CRF05 before crossing over to PM-SCS therapy. The study physician may reposition the leads if deemed necessary upon comparison to the initial x-ray image. If leads have migrated and cannot be re-adjusted, the patient will be exited from the study and subject data will be excluded from the final analysis. After x-ray assessment, stimulation parameters will be programmed as described below for PM-SCS. No therapy will be given for up to one day to allow washout of the conventional SCS therapy.

5.5.1 Polymodal SCS Therapy:

In this case the ENS will be programmed to deliver multiple simultaneous signals with different stimulation parameters to different electrode arrays in the leads. Stimulation signals will be in the 20-1,200 Hz range and a maximum pulse width of 1 ms, which is within the CE Mark and FDA approved parameters. The parameters of each program will be saved in the remote controller. The patient will be educated and trained on operation and troubleshooting the ENS and remote controller as it pertains to PM-SCS therapy.

5.6 Standard of Care Follow up phone visits:

It is standard practice that during a SCS trial period, a Clinical Field Technician (CFT) will contact the patient by phone to track the status of therapy and comfort of the patient.

Accordingly, follow up phone visits will be performed as needed during the study. After the first day of therapy and depending on the extent of pain relief reported by the patient, the CFT may instruct the patient to adjust the level of stimulation as deemed appropriate by patient to obtain optimum pain relief. The patient may also be instructed to use a different therapy group in case a therapy cannot be optimized with the previously tried therapy group. This process may be repeated during trial days for both the conventional SCS part of the trial and the PM-SCS part of the trial. Depending on feedback from the phone visits, the PI may decide to schedule a visit to the clinic for reassessing lead position and reprogramming, or to address an adverse event.

5.7 Optional unscheduled clinic visit:

If lead migration is suspected, the PI may schedule a reprogramming visit. In this visit, the PI may evaluate the position of the leads inside the epidural space using x-ray fluoroscopy and reposition and/or reprogram as needed. The PI may also change stimulation parameters using patient feedback as done during the initial visit or during the crossover visit. This visit may also be used to address any other mild or moderate adverse events related to SCS therapy.

5.8 Clinic Visit 4: End of trial period visit:

The patient will return to the clinic as scheduled for an end of trial period visit, in which the stimulation will be stopped, the hardware disconnected from the leads, and the temporary leads removed. Before stimulation is stopped, the patient will be asked to provide feedback about pain status, subjective satisfaction, and paresthesia sensation, which will be recorded in the appropriate CRFs (CRF06, CRF07, and CRF08). This visit may take place any time if the PI deems necessary to exit a patient from the trial and study, or if the patient voluntarily decides to withdraw.

5.9 Other therapies:

As per standard of care practice the patient may continue on prophylactic antibiotics as prevention for bacterial skin infection. Patient will also follow the investigating physician's protocol for anticoagulant therapy, other medications, as well as over-the-counter medications and supplements.

6. DATA COLLECTION AND ANALYSIS

6.1 Effectiveness:

A statistical analysis based on analysis of variance will be carried out. Given that this is an early-stage observational study, with a small population size, the analysis may not provide appropriate power and significance of endpoint measurements. Standard statistical analysis including the number of observations, mean, ranges for quantitative variables and relative percent for some categorical variables will be reported as appropriate.

During and at the end of the trial stage, patients will be asked to provide feedback regarding sensations and pain relief as a result of the polymodal stimulation therapy and in comparison with conventional therapy.

Pain intensity will be rated using the numerical pain rate scale (NPRS). Patients will score the severity of pain using this 11-point scale, with zero (0) indicating no pain and ten (10) indicating the worst pain imaginable. The patient will be asked to evaluate the average level of pain experienced during a particular time window between visits. The primary endpoint of record will correspond to the average NPRS score reported at the end of each therapy period. Patients will serve as their own control.

6.2 Paresthesia, Patient Impression, and Satisfaction

At the end of the trial period, patients will also be asked about their paresthesia experience, therapy preference, and their global impression of improvement and satisfaction. Questionnaires will be administered for such effects.

6.3 Safety

Adverse events (AE) related to the stimulation therapies will be tracked during the study period to address any safety outcomes. Any AE encountered using the conventional SCS therapy will also be noted in the patient's medical history. All device and/or procedural adverse events will be reported.

AEs will be tracked and categorized by the PI as related to implant (leads) or activation of the stimulation program. It is expected that the polymodal SCS will have a safety profile similar to conventional SCS.

All AEs will be recorded in the corresponding Case Report Form (CRF). The PI will also rate the AE in terms of its severity. Any AE considered by the PI to be a serious adverse event (SAE) will be reported immediately (within 24 hours) to the sponsor and to the IRB within five (5) days after the PI first learns of the event.

6.3.1 Adverse Events (AEs):

The following is a list of potential adverse events associated to SCS therapy and the indwelling leads with reported risk and frequency of occurrence:

- Related to Lead implant:
  - Movement of lead (possible, 13.2%)
  - Malfunction or failure of lead (possible, 9.1%)
  - Superficial site infection (possible, 4.5%)
  - Complications related to implantation procedure including infection; fever (possible, 3.4%)
  - Persistent or temporary pain at the implant site (unlikely, 1.8%)
  - Tissue reaction to leads (unlikely, 0.3%)
  - Hematoma (unlikely, 0.3%)
  - Bleeding (unlikely, 0.3%)
  - Skin erosion over the leads (unlikely, 0.2%)
  - Allergic reactions to leads (very unlikely, 0.1 %)
  - Paralysis (very unlikely)
  - Nerve injury (very unlikely)
  - Death (very unlikely)
- Related to stimulation:
  - Malfunction of stimulation system (possible, 4.5%)

- Undesirable sensations (possible, 2.4%)
- Increased pain (possible)
- Uncomfortable stimulation of tissue around the leads (possible)
- Development of pain symptoms in a new location (possible)
- Increase in pain intensity, duration, or frequency (unlikely)
- Seizure (very unlikely)
- Paralysis (very unlikely)
- Nerve injury (very unlikely)
- Death (very unlikely)

AEs related to stimulation with the trialed therapy are expected to be comparable to those associated to others encountered with other SCS therapies (such as HF-10 or Burst) or ENS.

At each evaluation the PI will determine whether any AE have occurred, keeping in mind that an AE is any undesirable medical occurrence in the patient. If it is determined that an AE has occurred, the PI should obtain all information required to complete the AE form of the CRF (CRF09). Patients should also be encouraged to contact the PI if any significant AEs occur between visits.

6.2.2 Serious Adverse Events (SAEs):

All serious SAEs must be reported to the sponsor (or designee) and IRB within 24 hours after the PI first learns of the event and to the IRB within 5 days after the PI first learns of the event. An adverse event is considered serious if:

- Leads to death
- Leads to a serious deterioration of the health of the patient that results in:
  - Life-threatening illness or injury
  - Permanent impairment of a body structure or body function

- Inpatient hospitalization or prolongation of existent hospitalization
- Medical or surgical intervention to prevent permanent impairment to body structure or body function

All SAEs will be followed until the event is resolved. The PI will decide if additional follow up information is needed in case the event is not resolved at study completion. In case of death, all possible information available, e.g. autopsy or other post-mortem findings, including the possible relationship to the procedure or treatment should be provided.

6.2.3 Unanticipated adverse device effects (UADEs):

Unanticipated adverse device effects are defined as serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with a device, if that effect, or problem, or death was not previously identified in the protocol.

The PI must submit to sponsor (or designee) any UADE within 24 hours after the PI first learns of the effect. The PI must also report the UADE to the IRB according to local regulations.

7. DEVICES

7.1 Stimulation leads:

Commercially available SCS leads will be used. Since leads are manufactured with variable dimensions and number of electrode arrays, the study will utilize leads with the following specifications in order to avoid outcome variability. The patient will be implanted with two in line eight-contact percutaneous cylindrical leads, each with a diameter of 1.3 mm, an edge-to-edge inter-electrode distance of 6 mm or 4 mm, and an electrode length of 3 mm. These specifications are met by leads available from Medtronic (Minneapolis, MN, USA; Reference 3873 1x8 Standard or 3874 1 x 8 Compact). The same leads will be used during both conventional and polymodal SCS therapy.

7.2 Multi-lead trialing cable:

The proximal end of each lead is terminated by eight metal contacts that deliver electrical signals to the electrodes in the distal end. These contacts are interfaced to an ENS unit using a cable that is fully compatible with both the stimulation leads and ENS unit. A commercially

available cable from Medtronic (Minneapolis, MN, USA; Reference 355531) will be used. The same cable will be used during either conventional or polymodal SCS therapy.

7.3 External Trial Stimulator (ENS) unit:

The trialing cable is connected to the ENS unit which is the device that delivers the stimulating electrical signals. A commercially available external trial neurostimulator from Medtronic (Minneapolis, MN, USA; Reference 37022) will be used during the conventional SCS. An investigational device based on this commercial unit will be used for PM-SCS (Medtronic, Minneapolis, MN, USA; Reference 37022-MRS). [redacted]

7.4 Clinician Programmer:

The ENS unit is programmed by a trained CFT using a computer-based interface and software. The programmer is fully compatible with the ENS unit described above and uses short-distance telemetry protocols to safely communicate with the ENS unit. For conventional SCS, commercially available N'Vision® Clinician Programmer (Medtronic, Minneapolis, MN, USA; Reference Model 8840) will be used by the CFT or clinician to program the commercial ENS unit. [redacted]

7.5 Patient Remote Controller:

Spinal cord stimulation therapy (either conventional SCS or PM-SCS) can be adjusted by the patient using the parameters set by the clinician during programming. This can be done using a handheld device that communicates with the ENS via short-distance telemetry. The remote controller allows the patient to turn the therapy on or off, adjust the level of stimulation (i.e. the amplitude of the electric field), and switch from a therapy group to other one as previously set by the CFT and clinician. The patient remote controller is fully compatible with both the ENS, and the clinician programmer described above. A commercially available device from Medtronic (Minneapolis, MN, USA; Reference MyStim® 97740) will be provided to the patient to carry on during the trial. The CFT will train the patient on using the remote controller and will provide

printed operating instructions as well as contact information in case the patient should have any questions about operating the device. Refer to Appendix D2 for a detailed product description.

7.6 Device Accountability Procedures:

All non-disposable devices (ENS, patient remote controller, and clinician programmer) will be under the control of the CFT who will program the ENS once the leads have been attached to it. The serial numbers of the investigational ENS and remote controller will be annotated in the corresponding CRF (CRF10). The CFT will be available 24-hours a day at a location near the study site during the length of the therapy. The CFT will retrieve the devices once a subject has completed therapy or exited the study. No devices will be left in the custody of the study site; thus study sites will not carry an inventory of devices.

Use of an investigational device outside the described study protocol is strictly forbidden and will constitute grounds for removal of the operator or institution from the study.

8. CONDUCT OF STUDY

8.1 Statement of Study Compliancy:

The study will be performed in accordance with Good Clinical Practice (GCP) guidelines and recommendations guiding physicians in biomedical research involving humans. As required by IRB timelines, the PI is responsible for reporting annually a study progress to the IRB. The PI/sponsor, as required by local regulations, is required to report in writing to the IRB, notice of completion, termination, or discontinuation of the study. If the study is discontinued for safety concerns, the PI will notify the IRB immediately.

8.2 Sponsor:

StimGenics will serve as the Sponsor of the study. It is the responsibility of StimGenics as the Sponsor of the study to ensure proper monitoring of the investigation and to see that all the clinical requirements are met. The study will be conducted under GCP guidelines and applicable regulatory requirements. All data used in the analyses and reporting of this investigation will be coded without identifiable reference to the subject. Access to confidential and private files will be given to only authorized personnel and representatives of the Sponsor and regulatory authorities as required.

8.3 Monitoring Activities:

Stimgenics will assign a contract research organization (CRO) to conduct monitoring activities of the study according to a monitoring plan. The monitoring plan will facilitate compliance with GPC guidelines and other relevant guidelines. The CRO will assign qualified monitors to verify that:

- The rights and well-being of participants are protected
- Reported data are accurate, complete and verifiable from source documents
- The study is conducted in compliance with currently approved protocol and other applicable regulatory requirements

The monitoring plan identifies key monitoring activities and specifies the data to be reviewed over the course of the clinical study. The clinical study monitors will conduct monitoring visits in accordance with this plan.

8.4 Quality Control and Quality Assurance:

All documents and data will be produced and maintained in such a way to assure control of documents and data to protect the patient's privacy as far as reasonably practicable. The Sponsor, CRO and representatives of regulatory authorities are permitted to access study documents (e.g. protocol, CRFs, medical records/files) as needed. All attempts will be made to preserve patients' privacy and confidentiality.

8.5 Data Handling and Record Keeping:

Source documents will be maintained by the PI. Data will be transcribed on to paper study CRFs and the original data will be secured by the PI and made available to Sponsor and CRO. PI is required to maintain records for a period of five (5) years. All CRFs pages will be subject to initial inspection for omitted data, data inconsistencies, illegible data and deviations by the monitoring body. All hard copies of CRFs and media will be stored in a secure location.

PI is responsible for submitting data and reports as follows:

- AEs: In an ongoing basis. This will be reported in the proper section of the CRF.

- SAEs or UADEs: Report within 24 hours of knowledge of event to Sponsor and report to IRB within five days as per their regulations.
- Deviations, exceptions, violations of protocol: Report to Sponsor within 5 days and report to IRB per their regulations.
- Protocol Progress report: Provide a copy to Sponsor and IRB as per regulations.
- Study Closure report: Provide a copy to Sponsor and IRB as per regulations.

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10. APPENDICES

[1] [redacted]