The SPACER Trial - Investigator Protocol Signature Page

Title: A Prospective, Multi-center, Randomized Study Comparing the VertiFlex® Superion® Interspinous Spacer (ISS) to the X-STOP® Interspinous Process Decompression (IPD®) System in Patients with Moderate Lumbar Spinal Stenosis – Continued Follow-Up

Short Title: The SPACER Trial
Superion® Post-Approval Continued Evaluation and Review

Protocol # 08-VISS-01
19 June 2015

Sponsor:
VertiFlex®, Inc.
1351 Calle Avanzado, Suite 100
San Clemente, CA 92673
USA

By signing this page, the Investigator acknowledges that:

He/she has read the protocol and agrees to comply with the protocol in accordance with 21 CFR Parts 50, 54, 56 and 812; Good Clinical Practices and use of the investigational products as indicated.

All subjects have provided signed Informed Consent prior to enrollment in the study.

All data relevant to the clinical evaluation and regarding the subject response and safety will be documented and forwarded to the Sponsor.

All unanticipated adverse device effects and serious adverse device effects will be reported as requested to the Sponsor within 24 hours.

The investigational products supplied by the Sponsor for this study protocol were used only for subjects enrolled for treatment under this protocol, and unused devices will be returned to the Sponsor at the close of the study or sooner as determined by the Sponsor.

_____ _____
Signature of Investigator Date

_____
Printed Name of Investigator

Clinical Investigational Plan (CIP)

A Prospective, Multi-center, Randomized Study Comparing the VertiFlex® Superion® Interspinous Spacer (ISS) to the X-STOP® Interspinous Process Decompression (IPD®) System in Patients with Moderate Lumbar Spinal Stenosis – Continued Follow-Up

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Protocol Summary Page

Title:	A Prospective, Multi-center, Randomized Study Comparing the Superion® Interspinous Spacer (ISS) to the X-STOP® Interspinous Process Decompression (IPD®) System in Patients with Moderate Lumbar Spinal Stenosis – Continued Follow-Up
Protocol Number:	08-VISS-01, 19 June 2015
Short Title:	SPACER Trial – Superion® Post-Approval Clinical Evaluation and Review
Study Treatment:	Superion® Interspinous Spacer ("Superion® ISS")
Control Treatment	Surgical implantation of the X-STOP® Interspinous Process Decompression (IPD®) System ("X-STOP® IPD®")
Study Design:	Prospective, multi-center, randomized, controlled study
Study Purpose:	To demonstrate that the success rate of the study group receiving the Superion® Interspinous Spacer is not inferior to the success rate observed in the X-STOP® IPD® Control group, and that the Superion® Interspinous Spacer is safe when used in the treatment of moderately impaired lumbar spinal stenosis (LSS) patients, at 5 years post-surgery.
Study Population:	Subjects suffering from moderate symptoms of neurogenic claudication secondary to a confirmed diagnosis of moderate LSS at one or two contiguous levels from L1 to L5 who meet all inclusion/exclusion criteria.
Number of Subjects:	Up to 470 patients were enrolled in the clinical trial as follows: Randomized Trial: • An adaptively selected sample size - range 250-350 subjects • 1:1 Randomization • A minimum of 125 to a maximum of 175 in each group. Non-randomized Trial: Prior to initiating the randomized trial, clinical sites could enroll 0-2 non-randomized patients up to a maximum of 70 Superion® ISS non-randomized "training" cases. The numbers of patients in the final primary analysis set for effectiveness and safety included 190 patients randomized to Superion® and 201 patients randomized to the X-STOP® IPD® Control group. Eight (8) Superion® patients and 12 X-STOP® IPD patients are from 2 sites that are not participating in the PAS. This reduces the analysis set to 182 and 189, respectively. Additionally, 28 training cases were enrolled.

Study Hypotheses:	The primary hypothesis of this extended follow-up post approval study is that performance of the Superion® ISS remains clinically non-inferior to X-STOP® IPD® at 5 years post-surgery using the same non-inferiority margin as was used at 2-years. The hypotheses to be tested may be symbolically described as follows: **Ho: $CCS_{Superion} - CCS_{X\text{-}STOP} \leq -0.10$ (inferior)** **Ha: $CCS_{Superion} - CCS_{X\text{-}STOP} > -0.10$ (not inferior)** At 2-years, follow-up compliance was 97% and 95%, and the observed overall success rates were 51.9% (95/183) and 49.7% (93/187) for Superion® ISS and X-STOP® IPD®, respectively. For the purpose of sample size analysis it was initially assumed: a) that at 5-years, follow-up compliance would be 85% in both groups (i.e., 155 Superion® and 161 X-STOP® IPD®); b) a device group difference equal to that observed at 2-years (i.e., 2.2%); and c) at 5-years 40% of Superion® ISS would achieve CCS (and so 37.8% is assumed for X-STOP® IPD®). In keeping with the original design, these hypotheses will be tested by determining the Bayesian posterior probability that **$(CCS_{Superion} - CCS_{X\text{-}STOP}) > -0.10$.** If the Bayesian posterior probability is at least equal to 0.95, then the hypothesis that Superion® ISS is non-inferior to X-STOP® IPD® at 5-years will be accepted. Non-informative beta(1,1) priors were assumed for both groups. With these assumptions, power is 73% and type 1 error is 0.05. However, updated Month 36 results reflect a device group difference equal to 5.7%. Conservatively assuming a 5% difference, power increases to 87% and remains above 80% for device group differences larger than about 3.5%. The following superiority hypotheses will be tested if non-inferiority is demonstrated. By the closed testing principle there is no need for multiplicity adjustment. **Ho: $CCS_{Superion} - CCS_{X\text{-}STOP} \leq 0$ (not superior)** **Ha: $CCS_{Superion} - CCS_{X\text{-}STOP} > 0$ (superior)** The posterior probability that **$(CCS_{Superion} - CCS_{X\text{-}STOP}) > 0$** will be determined using Beta(1,1) priors for 5-year e **$CCS_{Superion}$** and for 5-year **$CCS_{X\text{-}STOP}$**. If the posterior probability of superior is at least equal to 0.95, then a superiority claim will be made.
Number of Sites:	Only sites participating in the original IDE study will participate in this continued follow-up protocol. 25 IDE sites remain eligible for participation.
Study Enrollment:	Enrollment was completed in December 2011, with 391 randomized and treated patients and 28 non-randomized Superion® training patients.

Study Duration:	Subjects included in the original clinical investigation (G070118) returned for follow-up visits at 6 weeks, and 3, 6, 12, 18 and 24 months post-treatment to collect data for the primary evaluation of safety and effectiveness. Patients will be followed annually until each patient has reached the 60 month time point. Study duration is approximately 36 months as all patients have reached 24 months prior to the start of this continued follow-up protocol. Patients may potentially be followed annually for up to 10 years as part of a possible post-approval study.
Inclusion Criteria	1. Male or female subjects ≥ 45 years of age. 2. Persistent leg/buttock/groin pain, with or without back pain, that is relieved by flexion activities (example: sitting or bending over a shopping cart) 3. Subjects who have been symptomatic and undergoing conservative care treatment for at least 6 months. 4. Diagnosis of degenerative spinal stenosis of the lumbar spine, defined as the narrowing of the midline sagittal spinal canal (central) and/or narrowing between the facet superior articulating process (SAP), the posterior vertebral margin (lateral recess), and the nerve root canal (foraminal). 5. Radiographic confirmation of at least moderate spinal stenosis which narrows the central, lateral, or foraminal spinal canal at one or two contiguous levels from L1-L5. Moderate spinal stenosis is defined as 25% to 50% reduction in lateral/central foramen compared to the adjacent levels, with radiographic confirmation of any one of the following: o Evidence of thecal sac and/or cauda equina compression o Evidence of nerve root impingement (displacement or compression) by either osseous or non-osseous elements o Evidence of hypertrophic facets with canal encroachment 6. Must present with moderately impaired Physical Function (PF) defined as a score of ≥ 2.0 of the Zurich Claudication Questionnaire (ZCQ) 7. Must be able to sit for 50 minutes without pain and to walk 50 feet or more 8. Subjects who are able to give voluntary, written informed consent to participate in this clinical investigation and from whom consent has been obtained 9. Subjects, who, in the opinion of the Clinical Investigator, are able to understand this clinical investigation, cooperate with the investigational procedures and are willing to return for all the required post-treatment follow-ups.

	Note: In Criterion #5, all imaging used to confirm LSS need be completed within 3 months prior to enrollment. Radiographic confirmation of LSS may include MRI and/or CT. In the case of a transitional L5/L6 segment with a sufficiently prominent L6 spinous process, these could be included by requesting a deviation from the Sponsor.
Exclusion Criteria	1. Axial back pain only 2. Fixed motor deficit 3. Diagnosis of lumbar spinal stenosis which requires any direct neural decompression or surgical intervention other than those required to implant the control or investigational device 4. Unremitting pain in any spinal position 5. Significant peripheral neuropathy or acute denervation secondary to radiculopathy 6. Lumbar spinal stenosis at more than two levels determined pre-operatively to require surgical intervention 7. Significant instability of the lumbar spine as defined by ≥ 3mm translation or ≥ 5° angulation 8. Sustained pathologic fractures of the vertebrae or multiple fractures of the vertebrae and/or hips 9. Spondylolisthesis or degenerative spondylolisthesis greater than grade 1.0 (on a scale of 1-4) 10. Spondylolysis (pars fracture) 11. Degenerative lumbar scoliosis with a Cobb angle of > 10° at treatment level 12. Osteopenia or osteoporosis. To confirm eligibility, at the Clinical Investigator's discretion, the following subjects may have a DEXA scan performed: -Women 65 or older -Postmenopausal women < age 65 -Subjects with major risk factors for or diagnosed with osteoporosis or osteopenia If DEXA is required, exclusion is defined as a DEXA bone density measurement T score ≤ -2.5 13. Morbid obesity, defined as Body Mass Index (BMI) greater than 40kg/m^2 14. Insulin-dependent diabetes mellitus 15. Significant peripheral vascular disease (diminished dorsalis pedis or tibial pulses) 16. Prior surgery of the lumbar spine 17. *Cauda equina* syndrome (defined as neural compression causing neurogenic bowel or bladder dysfunction) 18. Infection in the disc or spine, past or present 19. Evidence of active (systemic or local) infection at time of surgery 20. Active systemic disease such as AIDS, HIV, hepatitis, etc.

	21. Paget's disease at involved segment or metastasis to the vertebra, osteomalacia, or other metabolic bone disease 22. Currently undergoing immunosuppressive therapy or long-term steroid use 23. Known allergy to titanium or titanium alloys 24. Tumor in the spine or a malignant tumor except for basal cell carcinoma 25. Known or suspected history of alcohol and/or drug abuse 26. Prisoner or transient 27. Life expectancy less than two years 28. Angina, active rheumatoid arthritis, or any other systemic disease that would affect the subject's welfare or outcome of the clinical investigation 29. Any significant psychological disturbance past or present, psychotic or neurotic that could impair the consent process or ability to complete subject self-report questionnaires 30. Involved in pending litigation of the spine or worker's compensation related to the back 31. Enrolled in the treatment phase of another drug or device clinical investigation (currently or within past 30 days) 32. Congenital defect of the spine 33. Pregnant or lactating
Composite Endpoint (Primary) - Individual Patient Success:	An individual subject will be considered a success if they meet all of the following conditions at the 60 month follow-up visit: • Clinically significant improvement in outcomes compared to baseline, as determined by meeting the following for at least two of three domains of the Zurich Claudication Questionnaire (ZCQ): o Improvement in physical function by ≥ 0.5 points o Improvement in symptom severity by ≥ 0.5 points o "Satisfied" or "somewhat satisfied" as defined by a score of < 2.5 points on the patient satisfaction domain • No re-operations, revisions, removals or supplemental fixation at the index level(s) • No major implant or procedure-related complications defined as: o No dislodgement, migration, or deformation o No new or persistent worsened neurological deficit at the index level o No spinous process fractures o No deep infection, death, or other permanent device attributed disability • No clinically significant confounding treatments: o No epidural injections or nerve block procedures at index level, spinal cord stimulators or rhizotomies

Secondary Endpoints:	• To demonstrate the superiority of Superion® ISS to X-STOP® IPD® in effectively treating moderately impaired LSS patients as measured by 60 months postoperative overall success rates, using the same criteria as 24 months. • VertiFlex® Patient Satisfaction Survey: percent of patients scoring ≤ 2.5 on a 4 point scale • Oswestry Disability Index (ODI) Version 2: compared to baseline, 15 point improvement (reduction in score) is considered clinically significant • Visual Analogue Scale (VAS): compared to baseline, an improvement in leg and/or back pain of 20 mm (on a 100 mm scale) is considered clinically significant • To evaluate generic health status pre- and postoperatively using the SF-12 Short Form Health Survey, Version 2 • To evaluate maintenance of distraction defined by ≤ 4 mm of measurable decrease in the posterior disc space height on successive radiographs obtained at 6 weeks and 24 months postoperatively
Safety Endpoints:	Data will be evaluated for safety endpoints by an independent Clinical Events Committee (CEC). Safety outcomes will be determined by evaluating the type, frequency, severity, and relationship to device of adverse events through the 60-month time point for all subjects. Adverse events will be categorized as implant-related or procedure-related. All device-related and major procedure-related failures reported by the site PIs will be adjudicated by the independent CEC. In addition, events reported as having unknown or undetermined relationship to the device by the PI will be adjudicated by the CEC.
Other Endpoints:	• Work status and time to return to work or normal (pre-operative) activities of daily living (ADL) • Narcotic use

Principal Study Contacts

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1 Introduction and Background

1.1 Introduction

Lumbar Spinal Stenosis (LSS) is characterized as a narrowing of the spinal canal and/or the intervertebral foramina that decreases space for the neural elements in the lumbar region of the spine.[1,2,3,4,5,6] As early as the 1950's it was recognized by Verbiest[7] that structural narrowing of the vertebral canal could compress the *cauda equina* and produce neurogenic claudication symptoms. These include leg pain (and occasionally weakness, numbness, or cramping) on walking or standing, which is relieved by sitting or spinal flexion.

Increasing numbers of people in the aging population that suffer from LSS symptoms have commanded the attention of both medical practitioners and industry representatives.[8,9] As such, there have been great strides to identify the least invasive treatment for patients with LSS that would successfully enhance their function and mobility, thus leading to improved, if not a restored quality of life.[10,11,12,13,14]

Nonsurgical management (NSM), or conservative care, is well-established as the first-line treatment approach for LSS patients with mild to moderate symptoms.[15,16,17,18,19,20] NSM typically involves the prescription of bed rest or controlled physical activity, physiotherapy, anti-inflammatory drugs, epidural steroid injections, the use of a lumbar corset, or some combination thereof.[23] While some patients are able to obtain relief from symptoms with these measures, many others do not obtain adequate relief over the long-term.

Surgical treatment, i.e. laminectomy with or without fusion, is generally accepted as the standard of care for LSS patients with severe symptoms.[21,22,23,24,25,26] LSS is currently the most common diagnosis for patients 55 years or older scheduled for spinal surgery.[27,28,29,30] This dramatic increase in the number of surgeries is attributable to improved diagnostic imaging techniques, improved and less invasive surgical techniques, the aging population, and improved patient education.[31,32,33,34,35] This is elective surgery to improve the quality of life for these individuals who have disabling back and leg pain and significant limitations in walking tolerance.[36,37,38] *Cauda equina* syndrome is the only absolute indication for decompressive laminectomy.[39]

The treatment algorithm for patients with moderate LSS symptoms is less well-defined. Clinical symptoms combined with radiographic findings should determine the optimal care for this group of patients. These patients may obtain partial relief from NSM measures but remain dissatisfied with their outcomes, or they may have failed an extended course of NSM but are unable or unwilling to undergo major surgery. Until recently, there were no other treatment options available for this patient population. With the first commercial introduction of interspinous spacers into the US marketplace in 2005 (X-STOP® IPD®, Medtronic, Inc., Minneapolis, MN), a new, less invasive treatment alterative became available for this patient population. Subsequently, the Superion® Interspinous Spacer (Superion® ISS) was granted FDA approval to market in the U.S. on May 20, 2015, pursuant to PMA No. P140004, and following conduct of a clinical trial randomized against the X-STOP® IPD® device conducted under IDE #G010118. This trial is intended to acquire 60 month follow-up of subjects enrolled in that IDE study.

The Superion® Interspinous Spacer is a new minimally invasive spinal implant that limits extension at the symptomatic level designed for percutaneous surgical techniques. The device is intended to treat moderate spinal stenosis in the adult spine and can be implanted under general anesthesia or local anesthesia with or without conscious sedation. Following sequential dilation, the Superion® ISS is implanted via a small dilation or incision through the supraspinous ligament. The device presents little or no risk to nervous and vascular structures. If necessary, the Superion® ISS can be easily removed through the same portal using percutaneous or minimally invasive techniques with very little alteration to the lumbar spinal anatomy.

This Conditions of Approval clinical trial is designed to evaluate the safety and effectiveness of the Superion® ISS through 60 months post-treatment, compared to the X-STOP® IPD®, in healthy adults suffering moderate spinal stenosis symptoms who have been unresponsive to at least 6 months of conservative, or non-surgical care.

1.2 Rationale for this Investigation

Interspinous spacers offer an alternative option in the treatment of adult patients with symptomatic moderate LSS. At the present time, the X-STOP® IPD® and the Superion® ISS are the only interspinous spacers commercially available to this patient population within the United States.

The Superion® ISS device is an interspinous spacer intended for use in the treatment of moderate LSS patients and is designed to limit extension at the symptomatic level, open up the spinal canal and foraminal areas, and relieve pressure on the nerve roots. The X-STOP® IPD® interspinous spacer was selected as the active control treatment because of its similarities to the Superion® ISS with respect to device design, intended patient population, indications for use, degree of invasiveness, risk profile, and anticipated clinical outcomes.

The STOP® IPD® IDE clinical study was conducted on a population of patients with mild to moderate LSS symptoms. Results from this pivotal study have shown that patients who undergo X-STOP® IPD® implantation have superior clinical outcomes when compared to patients who undergo non-surgical management.[40] Further analysis of the main study findings by that study's sponsor demonstrated that the subset of X-STOP® IPD® patients with moderately impaired physical function at baseline (defined as a Physical Function [PF] domain score $\geq$ 2.0 using the Zurich Claudication Questionnaire [ZCQ]) was the patient population most likely to benefit from the device[41]. As a result, the X-STOP® IPD® indications for use were modified at the time of PMA approval to include only those LSS patients with moderate physical function impairment at baseline.

Based on the results of the X-STOP® IPD® clinical trial and the X-STOP® IPD® PMA approval order, LSS patients with moderate physical function impairment at baseline comprised the patient population eligible for enrollment into the Superion® ISS clinical trial. Therefore, this IDE study was a prospective, controlled, randomized study comparing the Superion® ISS with X-STOP® IPD® in patients with moderate physical function impairment due to LSS.

The primary endpoint of this PAS trial is Month 60 composite clinical success (CCS). The primary effectiveness hypothesis for the PAS is that Superion® ISS is clinically non-inferior to X-STOP® IPD® (non-inferiority margin = -0.10) at Month 60. The Superion® ISS provides a minimally invasive technique, and is a single-piece design to minimize the potential for breakage or disassembly. Further, the minimally invasive technique allows the device to be delivered with minimum disruption to the soft tissue, potentially minimizing the risk of migration. Thus, although the study is designed to demonstrate non-inferiority, there are several potential advantages of the Superion® ISS that will be evaluated based on the results of the investigation at the conclusion of the 60 month follow-up.

2 Device Name

The Superion® Interspinous Spacer (ISS)

3 Intended Use of the Device

The Superion® InterSpinous Spacer (ISS) is indicated to treat skeletally mature patients suffering from pain, numbness, and/or cramping in the legs (neurogenic intermittent claudication) secondary to a diagnosis of moderate degenerative lumbar spinal stenosis, with or without Grade 1 spondylolisthesis, confirmed by X-ray, MRI and/or CT evidence of thickened *ligamentum flavum*, narrowed lateral recess, and/or central canal or foraminal narrowing. The Superion® ISS is indicated for those patients with moderately impaired physical function who experience relief in flexion from symptoms of leg/buttock/groin pain, numbness, and/or cramping, with or without back pain, and who have undergone at least 6 months of non-operative treatment. The Superion® ISS may be implanted at one or two adjacent lumbar levels in patients in whom treatment is indicated at no more than two levels, from L1 to L5.

For this intended use, moderate degenerative lumbar spinal stenosis was defined as follows:

- 25% to 50% reduction in the central canal and/or nerve root canal (subarticular, neuroforaminal) compared to the adjacent levels on radiographic studies, with radiographic confirmation of any one of the following:
  - Evidence of thecal sac and/or *cauda equina* compression
  - Evidence of nerve root impingement (displacement or compression) by either osseous or non-osseous elements
  - Evidence of hypertrophic facets with canal encroachment
- AND associated with the following clinical signs:
  - Presents with moderately impaired Physical Function (PF) defined as a score of ≥ 2.0 of the Zurich Claudication Questionnaire (ZCQ)
  - Ability to sit for 50 minutes without pain and to walk 50 feet or more.

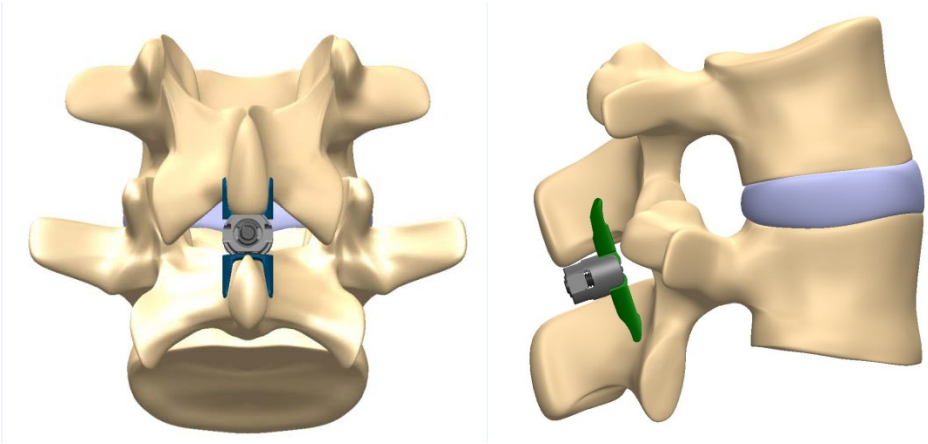
4 Device Description

4.1 Superion® Interspinous Spacer (ISS) – Study Device

The Superion® Interspinous Spacer (ISS) device is a non-fusion, spinal column load-sharing device used to stabilize the spine at the implanted level. When implanted between contiguous spinous processes, it is designed to provide distraction at the affected spinal level and reduce compression of neural elements in extension.

The Superion® ISS may be implanted under general or local anesthesia. With the spine positioned in flexed position, the Superion® ISS is inserted between adjacent vertebral spinous processes at one level, or at two contiguous levels. The degree of flexion to relieve the stenotic condition is determined by the operating surgeon using fluoroscopy. **Figure 1** illustrates the Superion® ISS device *in situ* after implantation, with the superior and inferior cam lobes engaging the lateral aspects of L3 and L4 spinous processes:

Figure 1: Superion® ISS Implant in situ



A/P View **Lateral View**

Five (5) sizes of the Superion® ISS device are available (8mm, 10mm, 12mm, 14mm, and 16mm). Implant "size" refers to the distance between the cam lobes, which corresponds to the amount of distraction the implant will provide when it is implanted between two spinous processes.

The Superion® ISS implant is composed entirely of titanium 6Al-4V ELI alloy conforming to ASTM Standard F136 (2002), *Standard Specification for Wrought Titanium-6 Aluminum-4 Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications*. This material is widely used in spinal and other orthopedic implants, and is recognized as a safe, biocompatible material after decades of use in implantable devices of many types. Manual instruments provided for use with the Superion® ISS implant are composed of durable materials traditionally employed to manufacture surgical instrumentation, and which are known to tolerate repeated cleaning, sterilization, and use. The materials include various grades of stainless steel (e.g., 300 and 400 series, 17-4 PH), aluminum, and titanium and/or polymers (RADEL) all of which conform to applicable ASTM material specifications.

The Superion® ISS implant is provided in assembled form, and is supplied sterile and intended for single-use only. Manual instruments are provided non-sterile, and are intended to be sterilized by the user before use. Complete instructions for use of the instrumentation are contained in the Superion® ISS Surgical Technique Manual.

4.2 X-STOP® Interspinous Decompression (IPD®) System – Control Treatment

The X-STOP® IPD® is an FDA-approved implant for the treatment of patients aged 50 years or older suffering from moderate symptoms of neurogenic intermittent claudication secondary to a confirmed diagnosis of LSS. The X-STOP® IPD® implant is a titanium metal implant designed to fit between the spinous processes in the lumbar spine. For additional information, please refer to the X-STOP® IPD® surgical technique supplied by the manufacturer with the device.

5 Study Overview

5.1 Purpose

The purpose of this study is to demonstrate that the success rate of the Study group receiving the Superion® Interspinous Spacer is not inferior to the success rate observed in the X-STOP® IPD® control group at 60 months follow-up, and that the Superion® Interspinous Spacer is safe when used in the treatment of moderately impaired LSS patients. This safety and effectiveness data will be used to satisfy the Agency-imposed Conditions of Approval of the Superion® Premarket Approval (PMA).

5.2 Study Endpoints

5.2.1 Composite Endpoint (Primary) – Individual Patient Success

Subjects will be evaluated for success at each follow-up interval through 60 months. The primary study endpoint is the rate of overall subject success at the 60 month follow-up visit. An individual subject will be considered a success if they meet all of the following conditions at the 60 month follow-up:

Clinically significant improvement in outcomes compared to baseline, as determined by meeting the following:

- At least two of three domains of the Zurich Claudication Questionnaire (ZCQ)
  - Improvement in physical function by ≥0.5 points
  - Improvement in symptom severity by ≥0.5 points
  - "Satisfied" or "somewhat satisfied" as defined by a score of ≤ 2.5 points on the patient satisfaction domain
- No re-operations, revisions, removals or supplemental fixation at the index level(s)
- No major implant- or procedure-related complications:
  - No dislodgement, migration, or deformation
  - No new or persistent worsened neurological deficit at the index level
  - No spinous process fractures
  - No deep infection, death, or other permanent device attributed disability
- No clinically significant confounding treatments:
  - No epidural injections or nerve block procedures at index level, spinal cord

5.2.2 Secondary Endpoints

The secondary endpoints of this investigation are:

- To demonstrate the superiority of Superion® ISS to X-STOP® IPD® in effectively treating moderately impaired LSS patients as measured by 60 months postoperative overall success rates
- VertiFlex® Patient Satisfaction Survey – percent of patients scoring ≤ 2.5 on a 4 point scale
- Oswestry Disability Index (ODI) Version 2– compared to baseline, 15 point improvement (reduction in score) is considered clinically significant
- Visual Analogue Scale (VAS) - compared to baseline, an improvement in leg and/or back pain of 20 mm (on a 100 mm scale) is considered clinically significant
- To evaluate generic health status pre- and postoperatively using the SF-12 Short Form Health Survey, Version 2
- To evaluate maintenance of distraction defined by ≤ 4 mm of measurable decrease in the posterior disc space height on successive radiographs obtained at 6 weeks and 60 months postoperatively

5.2.3 Safety Endpoints and Role of CEC

Data will be evaluated for safety endpoints by an independent Clinical Events Committee (CEC). Safety outcomes will be determined by evaluating the type, frequency, severity, and relationship to device of adverse events through the 60-month time point for all subjects. Adverse events will be categorized as implant-related or procedure-related. All device-related events and major procedure-related failures reported by the site PIs will be adjudicated by the independent CEC. In addition, events reported as having unknown or undetermined relationship to the device by the site PI will be adjudicated by the CEC.

5.2.4 Other Endpoints

- Work status and time to return to work or normal activities of daily living (ADL)
- Narcotic use

5.3 Study Hypothesis

The primary hypothesis of this extended follow-up post approval study is that performance of the Superion® ISS remains clinically non-inferior to X-STOP® IPD® at 5 years post-surgery using the same non-inferiority margin as was used at 2-years. The hypotheses to be tested may be symbolically described as follows:

Ho: $CCS_{Superion} - CCS_{X\text{-}STOP} \leq -0.10$ (inferior)

Ha: $CCS_{Superion} - CCS_{X\text{-}STOP} > -0.10$ (not inferior)

At 2-years, follow-up compliance was 97% and 95%, and the observed overall success rates were 51.9% (95/183) and 49.7% (93/187) for Superion® ISS and X-STOP® IPD®, respectively. For the purpose of sample size analysis it was initially assumed: a) that at 5-years, follow-up compliance would be 85% in both groups (i.e., 155 Superion® and 161 X-STOP® IPD®); b) a device group difference equal to that observed at 2-years (i.e., 2.2%); and c) at 5-years 40% of Superion® ISS would achieve CCS (and so 37.8% is assumed for X-STOP® IPD®). In keeping with the original design, these hypotheses will be tested by determining the Bayesian posterior probability that **($CCS_{Superion} - CCS_{X\text{-}STOP}$)> -0.10.** If the Bayesian posterior probability is at least equal to 0.95, then the hypothesis that Superion® ISS is non-inferior to X-STOP® IPD® at 5-years will be accepted. Non-informative beta(1,1) priors were assumed for both groups. With these assumptions, power is 73% and type 1 error is approximately 0.05. However, updated Month 36 results reflect a device group difference equal to 5.7%. Conservatively assuming a 5% difference, power increases to 87% and remains above 80% for device group differences larger than 3.5%.

The following superiority hypotheses will be tested if non-inferiority is demonstrated. By the closed testing principle there is no need for multiplicity adjustment.

Ho: $CCS_{Superion} - CCS_{X\text{-}STOP} \leq 0$ (not superior)

Ha: $CCS_{Superion} - CCS_{X\text{-}STOP} > 0$ (superior)

The posterior probability that **($CCS_{Superion} - CCS_{X\text{-}STOP}) > 0$** will be determined using Beta(1,1) priors for 5-year e **$CCS_{Superion}$** and for 5-year **$CCS_{X\text{-}STOP}$** If the posterior probability of superior is at least equal to 0.95, then a superiority claim will be made.

5.4 Duration and Extent of Investigation

Subjects included in the clinical investigation have returned for follow-up visits at 6 weeks (± 2 weeks), 3 months (± 2 weeks), 6 months (± 1 month), 12 months (± 2 months), 18 months (± 2 months) and 24 months (± 2 months) post-treatment to collect data for the primary evaluation of safety and effectiveness. Patients will continue to be followed annually (± 3 months) until each patient has reached the 60 month time point. Study duration is anticipated to be extended by approximately 36 months to accommodate this additional follow-up.

6 Study Design

This study is a prospective, multi-center, randomized controlled clinical trial comparing the Superion® ISS to the X-STOP® IPD® in the treatment of subjects aged 45 or older suffering from moderate symptoms of neurogenic intermittent claudication secondary to a confirmed diagnosis of moderate LSS at one or two contiguous levels from L1 to L5, i.e. from the L1-L2 level to the L4-L5 level. Implantation of the X-STOP® IPD® for patients aged 45-49 years is considered investigational. A maximum of 35 investigative sites in the U.S. enrolled subjects into the trial using a 1:1 randomization assignment and an adaptively selected sample size ranging from 250 to 350 subjects (125-175 enrolled into each group).

Up to an additional 50 patients (25 per group) were allowed to be enrolled to allow for loss to follow-up. In addition, prior to initiating the randomized trial, clinical sites were permitted to enroll 0-2 non-randomized "training" patients to receive the Superion® ISS. A total of 470 subjects were enrolled into the study. An investigative site is defined as a facility or facilities in the same general geographic location if they are under the control of a local Institutional Review Board (IRB). A total of 33 sites were authorized to enroll subjects. Two (2) failed to enroll any subjects and were discontinued from the trial. Of the remaining 31 sites that enrolled one or more subjects, six (6) have since discontinued participation, leaving 25 sites actively participating in the extended follow-up described by this protocol.

The numbers of patients in the final primary analysis set for effectiveness and safety included 190 patients randomized to Superion® and 201 patients randomized to the X-STOP® IPD® Control group. Eight (8) Superion® patients and 12 X-STOP® IPD patients are from 2 sites that are not participating in the PAS. This reduces the analysis set to 182 Superion® and 189 X-STOP® IPD®, respectively. Assuming 85% follow-up for the primary effectiveness endpoint at Month 60, there will be 155 Superion® patients and 161 X-STOP® IPD patients included in the primary non-inferiority evaluation.

After implantation of the Superion® ISS or the X-STOP® IPD® device, each Investigator provided a postoperative care regimen based on the subject's specific need. The regimen may have included, but was not limited to: medications, a corset or brace, acupuncture, traction, physical therapy, chiropractic treatment, use of a TENS unit and massage therapy. The type and amount of the postoperative care were collected.

At each follow-up visit through 60 months, subjects will be interviewed to determine if they have experienced adverse events (AEs) since the previous follow-up visit. A neurological assessment will be performed for all patients at baseline and all follow-up visits. All subjects will be required to complete ZCQ, ODI, VAS, SF-12, and the VertiFlex® Patient Satisfaction questionnaires to evaluate disability, function, pain, quality of life and satisfaction at each follow-up visit. Subjects were also required to complete a VAS questionnaire to evaluate pain status at discharge.

The potential impact of spinal injections/nerve blocks use on the ZCQ was evaluated based on review of the medical literature.[1] As these are potentially confounding of the ZCQ outcomes, epidural steroid injections or nerve block procedures at the treated level(s) will be deemed failures. Further, rhizotomy procedures at the treated level(s) will be deemed failures.

[1] Campbell's Operative Orthopedics (11th ed.) at 2281: "Although epidural steroid injections have been used in the treatment of spinal stenosis for many years, no scientifically validated long-term outcomes have been reported to substantiate their use, and most prospective reports show no statistically significant benefit. A meta-analysis showed that epidural steroids have little short-term advantage over placebo for treatment of leg pain." See also Carette S, Marcoux S, Truchon R, Grondin C, Gagnon J, Allard Y, Latulippe M. (1991) A controlled trial of corticosteroid injections into facet joints for chronic low back pain. NEJM 325(14):1002-1007. Jackson RP, Jacobs RR, Montesano PX (1988). Facet joint injection in low-back pain: A prospective statistical study. Spine 13(9):966-71.

With respect to spinal cord stimulators, because the use of a permanent implant would require a surgical procedure, this will be deemed a study failure.

Radiographic evaluations were performed at discharge, and at each scheduled follow-up visit and prior to any re-operations. The Investigator may obtain x-rays at unscheduled visits or to assess adverse events, if clinically indicated.

6.1 Study Population and Source of Subjects

The study population consists of male and female subjects who are equal to or older than 45 years of age at time of enrollment, with moderate symptoms of neurogenic intermittent claudication and a confirmed diagnosis of moderate lumbar stenosis at one or two contiguous levels from L1 to L5, i.e level L1-L2 through level L4-L5, who met all inclusion/exclusion criteria and remain in follow-up from the original IDE study.

6.2 Randomization

A computer-generated random list of treatment assignments (Master Randomization List) was created using a 1:1 ratio. Randomization occurred as close to the beginning of the treatment procedure as possible. Due to differences in the procedures, incision sizes, and operative positioning, subjects were not masked to their treatment arm after the surgery, but were not advised by site staff of their treatment assignment.

Sites used a web-based system to obtain treatment randomization assignment. The clinical sites were provided with system usage instructions, usernames, passwords, and technical support contact information. Randomization assignments were not re-used in the event that a subject withdrew from the study prior to surgery or became a study treatment failure.

6.3 Subject Eligibility Criteria

The Principal or Sub-Investigator (PI or Sub-I) at each site was responsible for verifying that a potential study subject met all eligibility criteria and had none of the exclusion criteria. All patients who satisfied the inclusion and exclusion criteria and sign the Informed Consent were eligible to proceed to randomization and enrollment.

6.3.1 Inclusion Criteria

*Candidates for this study met **ALL** of the following criteria:*

34. Male or female subjects ≥ 45 years of age.
35. Persistent leg/buttock/groin pain, with or without back pain, that is relieved by flexion activities (example: sitting or bending over a shopping cart)
36. Subjects who have been symptomatic and undergoing conservative care treatment for at least 6 months.
37. Diagnosis of degenerative spinal stenosis of the lumbar spine, defined as the narrowing of the midline sagittal spinal canal (central) and/or narrowing between the facet superior articulating process (SAP), the posterior vertebral margin (lateral recess), and the nerve root canal (foraminal).

38. Radiographic confirmation of at least moderate spinal stenosis which narrows the central, lateral, or foraminal spinal canal at one or two contiguous levels from L1-L5. Moderate spinal stenosis is defined as 25% to 50% reduction in lateral/central foramen compared to the adjacent levels, with radiographic confirmation of any one of the following:
    - Evidence of thecal sac and/or *cauda equina* compression
    - Evidence of nerve root impingement (displacement or compression) by either osseous or non-osseous elements
    - Evidence of hypertrophic facets with canal encroachment
39. Must present with moderately impaired Physical Function (PF) defined as a score of ≥ 2.0 of the Zurich Claudication Questionnaire (ZCQ)
40. Must be able to sit for 50 minutes without pain and to walk 50 feet or more
41. Subjects who are able to give voluntary, written informed consent to participate in this clinical investigation and from whom consent has been obtained
42. Subjects, who, in the opinion of the Clinical Investigator, are able to understand this clinical investigation, cooperate with the investigational procedures and are willing to return for all the required post-treatment follow-ups.

Note: In Criterion #5, all imaging used to confirm LSS need be completed within 3 months prior to enrollment. Radiographic confirmation of LSS may include MRI and/or CT. In the case of a transitional L5/L6 segment with a sufficiently prominent L6 spinous process, these could be included by requesting a deviation from the Sponsor.

6.3.2 Exclusion Criteria

*Candidates were excluded from the study if **ANY** of the following applied:*

8. Axial back pain only
9. Fixed motor deficit
10. Diagnosis of lumbar spinal stenosis which requires any direct neural decompression or surgical intervention other than those required to implant the control or investigational device
11. Unremitting pain in any spinal position
12. Significant peripheral neuropathy or acute denervation secondary to radiculopathy
13. Lumbar spinal stenosis at more than two levels determined pre-operatively to require surgical intervention
14. Significant instability of the lumbar spine as defined by ≥ 3mm translation or ≥ 5° angulation
8. Sustained pathologic fractures of the vertebrae or multiple fractures of the vertebrae and/or hips
9. Spondylolisthesis or degenerative spondylolisthesis greater than grade 1.0 (on a scale of 1-4)
43. Spondylolysis (pars fracture)
44. Degenerative lumbar scoliosis with a Cobb angle of > 10° at treatment level
45. Osteopenia or osteoporosis. To confirm eligibility, at the Clinical Investigator's discretion, the following subjects may have a DEXA scan performed:
    -Women 65 or older
    -Postmenopausal women < age 65
    -Subjects with major risk factors for or diagnosed with osteoporosis or osteopenia

    If DEXA is required, exclusion is defined as DEXA bone density measurement T score ≤ -2.5
46. Morbid obesity, defined as Body Mass Index (BMI) greater than 40kg/m^2

47. Insulin-dependent diabetes mellitus
48. Significant peripheral vascular disease (diminished *dorsalis pedis* or tibial pulses)
49. Prior surgery of the lumbar spine
50. *Cauda equina* syndrome (defined as neural compression causing neurogenic bowel or bladder dysfunction)
51. Infection in the disc or spine, past or present
52. Evidence of active (systemic or local) infection at time of surgery
53. Active systemic disease such as AIDS, HIV, hepatitis, etc.
54. Paget's disease at involved segment or metastasis to the vertebra, osteomalacia, or other metabolic bone disease
55. Currently undergoing immunosuppressive therapy or long-term steroid use
56. Known allergy to titanium or titanium alloys
57. Tumor in the spine or a malignant tumor except for basal cell carcinoma
58. Known or suspected history of alcohol and/or drug abuse
59. Prisoner or transient
60. Life expectancy less than two years
61. Angina, active rheumatoid arthritis, or any other systemic disease that would affect the subject's welfare or outcome of the clinical investigation
62. Any significant psychological disturbance past or present, psychotic or neurotic that could impair the consent process or ability to complete subject self-report questionnaires
63. Involved in pending litigation of the spine or worker's compensation related to the back
64. Enrolled in the treatment phase of another drug or device clinical investigation (currently or within past 30 days)
65. Congenital defect of the spine
66. Pregnant or lactating

6.4 Study Enrollment

Each site evaluated consecutive spine patients for potential eligibility for study participation based on their age and medical symptoms. Patients could be prescreened and preliminarily excluded because of failure to meet basic inclusion or exclusion criteria. The Investigator could have approached patients who were considered be suitable for entry into this study.

Patients were only considered evaluable after informed consent was obtained, eligibility for study entry had been verified by the Principal Investigator (PI) or designee at each site, randomization assignment had been provided, and treatment anesthesia administration had begun. Patients that were randomized, and had an anesthesia start time recorded, but were not treated with the control device or the investigational device due to unforeseen circumstances were considered in the Intent to Treat protocol analysis as a failure in his or her randomized treatment group. Patients that were randomized, but did not have a treatment administered, or an anesthesia start time recorded, were exited from the trial, and the reason for their screen failure was recorded and tallied.

6.5 Study Procedures

6.5.1 Screening

All potential subjects were screened for eligibility and were listed on the Screening/Enrollment Log. The Screening/Enrollment Log documented the date of screening, the results of screening, and the primary reason for excluding the subject (e.g. subject does not satisfy enrollment exclusion criteria or subject declined).

Eligible patients who agreed to participate in the study were required to sign an Informed Consent prior to undergoing any study-related screening procedures that were not standard of care. If the patient did not meet all eligibility criteria after signing Informed Consent and undergoing additional evaluation, the patient was considered a "screen failure" and was not be entered into the study. The reason for all screen failures was tabulated.

6.5.2 Baseline Assessment

The following baseline assessments were performed:

Subject Self-Report Questionnaires will be administered: • Zurich Claudication Questionnaire (ZCQ) • Visual Analogue Scale (VAS) • SF-12 version 2 Health Related Quality of Life • Oswestry Disability Index (ODI)
Demographic/History and Physical Assessment: • Date of birth, race, ethnicity • Gender, weight, height, and body mass index (BMI) • Work status • Nicotine use • Leg and back pain • Medical treatment • Previous surgeries, co-existing diseases, any disabilities and concomitant medication
Neurological Assessment: • Muscle strength • Sensory and Reflexes • Range of motion • Palpation of pulses • Straight leg raise • Femoral Stretch
Radiographic studies performed within 3 months of baseline: • Standing Anterior/Posterior Lumbar Spine view • Lateral Lumbar Spine view • Flexion/Extension Lateral Lumbar Spine views • MRI or CT Scan • DEXA Scan (If indicated)

6.5.3 Randomization and Enrollment

Randomization assignment was conducted at the end of the baseline period. After a patient had signed Informed Consent, and demonstrated eligibility based upon ALL inclusion/exclusion criteria, the patient was randomly assigned to a treatment group and surgery was scheduled. The randomization occurred as close as possible to the date of the treatment procedure.

Patients were only considered evaluable after Informed Consent had been obtained, eligibility for study entry had been verified by the Principal Investigator (PI) or designee at each site, randomization assignment had been provided, and treatment anesthesia administration had begun. Patients that were randomized, and had an anesthesia start time recorded, but were not treated with the control device or the investigational device due to unforeseen circumstances were considered in the Intent to Treat protocol analysis as a failure in his or her randomized treatment group. Patients that were randomized, but did not have an anesthesia start time recorded, were exited from the trial and the reason for their screen failure was recorded and tallied.

Treatment Procedures: **Investigational (Superion® ISS) and Control (X-STOP® IPD®) groups**

Surgical procedure:

- Follow the applicable surgical procedure: Superion® ISS Surgical Technique Manual or X-STOP® IPD® Surgical Technique Manual (Manufacturer's Instructions)
- Perform the procedure under fluoroscopic guidance
- Surgery under local anesthesia with or without conscious sedation is recommended. General anesthesia is allowed at the discretion of the Investigator.

The following information was collected at the time of surgery:

- Date of admission
- Date of surgery
- Type of anesthesia
- Level(s) treated
- Device information
- Operative time
- Estimated blood loss
- Intra-operative adverse events

6.5.4 Post-Procedure Visits

The following was collected at the Discharge Assessment for treated patients (0-7 days)

Most patients were discharged the day of procedure. If clinically indicated, some patients stayed for up to 23 hours or were admitted based on co-morbid conditions.

Discharge Assessment: • Visual Analogue Scale (VAS) to assess leg and back pain • Medical treatment • Adverse event • Concomitant medication and treatment • Length of hospital stay • Type of anesthesia
Neurological Assessment: • Muscle strength • Sensory and Reflexes • Range of motion • Palpation of pulses • Straight leg raise • Femoral Stretch
Radiographic studies: • Standing Anterior/Posterior Lumbar Spine X-ray • Lateral Lumbar Spine X-ray

The following information was/will be collected at the Follow-up Visits for treated patients at *6-week (± 2 weeks), 3-month (± 2 weeks), 6-month (± 1 month), 12-month (± 2 months), 18-month (± 2 months), 24-month (± 2 months), and will be collected annually (± 3 months) thereafter through 60 months as required by this protocol**:***

Subject Self-Report Questionnaires: • Zurich Claudication Questionnaire (ZCQ) • Visual Analogue Scale (VAS) • SF-12 version 2 Health Related Quality of Life • Oswestry Disability Index (ODI) • VertiFlex Patient Satisfaction Questionnaire
Neurological Assessment: • Muscle strength • Sensory and Reflexes • Range of motion • Palpation of pulses • Straight leg raise • Femoral Stretch
Follow-up Assessment: • Work status and time to return to work or normal ADL (activities of daily living) • Leg and back pain • Medical treatment • Adverse event • Concomitant medication and treatment, including narcotic usage

Radiographic studies :

- Standing Anterior/Posterior Lumbar Spine X-ray
- Lateral Lumbar Spine X-ray
- Flexion/Extension Lateral Lumbar Spine X-rays

The Study Visit Schedule (**Appendix A**) provides an overview of activities to be performed at each annual study visit through 60 months.

7 Termination of Subject Participation

Subjects may voluntarily withdraw from the study at any time for any reason. The Investigator(s) may elect to withdraw a subject from the study at any time due to lack of compliance or for any reason unrelated to the study treatment if such a decision is in the subject's best medical interest. If a subject withdraws from the study, or is withdrawn by the Investigator(s), as much follow-up data as possible will be obtained, particularly regarding possible adverse events. The primary reason for termination or discontinuation will be documented on the End of Study Case Report Form.

If the Investigator(s) reports a subject to be lost to follow-up, the monitor will ensure that documentation is complete regarding the reason(s) this has occurred and will ensure that every attempt is made by the Investigator(s) to contact the subject or significant other persons associated with the subject to determine subject status. Appropriate documentation will consist of at least two documented attempts at contact via telephone, followed by an attempt to contact via registered U.S. Mail.

8 Study Deviation

A study deviation is defined as an event where the clinical investigator or site personnel did not conduct the study according to the Clinical Protocol or the Investigator Agreement. Deviations will be classified as follows:

Major Deviation: Any deviation from patient inclusion and exclusion criteria or patient informed consent procedures.

Minor Deviation: Deviation from a protocol requirement, such as incomplete or missed patient evaluations, follow-up performed outside specified time windows, etc.

Investigators will be required to obtain proper approval from the Sponsor before initiating major deviations from the Clinical Protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval will be documented in writing and maintained in the study files. Although prior approval is generally not expected for minor deviation, the event must still be reported.

Deviations will be reported to the Sponsor regardless of whether medically justifiable, pre-approved by the Sponsor, or taken to protect the subject in an emergency. Subject-specific deviations will be reported on the Protocol Deviation CRF. Non-subject-specific deviations, (e.g. unauthorized use of a study device outside the study) will be reported in writing. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures.

9.0 Adverse Events

9.1 Definitions

An **Adverse Event (AE)** is any undesired clinical response or complication experienced by a subject. All operative and postoperative AEs, whether device-related or not, will be recorded on the AE Case Report Forms.

The Investigator, on the basis of his or her clinical judgment and the following definitions, will determine the severity of the AE and the relationship to the device and/or procedure:

- Not related: The AE is clearly not related
- Unknown/Undetermined: The AE is unknown or undetermined to be related
- Related: The AE is clearly related
    - Device related: The AE is related to the study device or the control device
    - Procedure related: The AE is related to the procedure to implant the study or control device

The **severity** of an AE may be mild, moderate or severe. Severity is determined by the Clinical Investigator, using the following definitions, and is not necessarily the subject's interpretation:

Mild	The AE is transient or causes mild discomfort. There usually is no intervention/therapy required and the AE does not interfere with the subject's normal activities.
Moderate	The AE causes some limitation in activity and some assistance may be needed. There is no or minimal medical intervention/therapy required.
Severe	The AE causes marked limitation in activity. The subject's usual daily activity is interrupted. The subject may require medical intervention/therapy, hospitalization is possible.

The term "severe" is used to describe intensity (severity) of a specific event. An event itself may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on event outcomes or actions taken to prevent or treat an event and is usually associated with events that pose a threat to the patient's life or functioning.

The AE is regarded as a **Serious Adverse Event (SAE)** if the injury or illness:

A) Results in death
B) Is life-threatening,
C) Results in or prolongs hospitalization
D) Results in permanent impairment of a body function or permanent damage to a body structure, or
E) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

A **Serious Adverse Device Effect (SADE)** is a device related adverse event that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made.

An **Unanticipated Adverse Device Effect (UADE)** is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the Risks identified for the study or control device; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The Sponsor's Clinical Research group must be notified of all **Unanticipated Adverse Device Effects** and **Serious Adverse Device Effects** within 24 hours at:

VertiFlex®, Inc., Clinical Research
1351 Calle Avanzado, Suite 100
San Clemente, CA 92673 USA
Tel: (866) 355-4675
Fax: (949) 940-1475
clinical@vertiflex.net

9.2 Anticipated Adverse Events

All AEs identified for the study or control device in Section 12 are considered 'anticipated'.

9.3 Subsequent Surgical Interventions

If the patient requires a subsequent surgical intervention at the index level(s), the Investigator should exit the patient from the study and document the reason on the End of Study CRF. The patient should be followed until discharge from post-operative care or resolution of any adverse events up to a maximum of 30 days. Subsequent surgical interventions are defined as:

- A revision is a procedure that adjusts or in any way modifies or removes part of the original implant configuration, with or without replacement of a component. A revision may also include adjusting the position of the original configuration.
- A removal is a procedure where all of the original system configuration are removed with or without replacement.

- A reoperation is any surgical procedure at the involved level(s) that does not include removal, modification, or addition of any components to the system.
- A supplemental fixation is a procedure in which additional instrumentation not under study in the protocol is implanted (e.g., supplemental placement of a rod/screw system or a plate/screw system).

9.4 Device Explant and Retrieval

In the event of a Superion® device removal, the device and the Investigator's written explanation of the event will be sent to the Sponsor following instructions from the Sponsor. The Investigator(s) will also be required to document the failure mode of the device and submit it to the Sponsor.

10 Statistical Considerations and Methodology

10.1 Clinical Trial Objective

The objective of this trial is to show that the Superion® Interspinous Spacer is safe and non-inferior in efficacy compared to the X-STOP® IPD® device in patients with moderate lumbar spinal stenosis at 60 months post-treatment.

10.2 Primary Outcome

The *treatment arm* (Superion® ISS) is compared to a control comprising surgical implantation of the X-STOP® IPD® device. The primary efficacy analysis is a responder analysis at 60-months post-op where a subject is a responder if each of the following are satisfied:

- Clinically significant improvement in outcomes compared to baseline, as determined by meeting the following for at least two of three domains of the Zurich Claudication Questionnaire (ZCQ):
  - Improvement in physical function by ≥ 0.5 points
  - Improvement in symptom severity by ≥ 0.5 points
  - "Satisfied" or "somewhat satisfied" as defined by a score of < 2.5 points on the patient satisfaction domain
- No re-operations, revisions, removals or supplemental fixation at the index level(s)
- No major implant or procedure-related complications defined as:
  - No dislodgement, migration, or deformation
  - No new or persistent worsened neurological deficit at the index level
  - No spinous process fractures
  - No deep infection, death, or other permanent device attributed disability
- No clinically significant confounding treatments:
  - No epidural injections or nerve block procedures at index level, spinal cord stimulators or rhizotomies

10.3 Randomization

1:1 for treatment to control. A randomized block design at each site was used.

10.4 Analysis Populations

The study contains two treatment arms with patients receiving either the Superion® ISS or the X-STOP® IPD® device. The following subject groups or analysis populations will be used to complete the analysis of data:

Modified Intent-to-treat patient population (mITT): The mITT patient population will include all patients randomized, and with an anesthesia start time recorded, where patients will be classified by the group in which they are randomized, regardless of the treatment received.

Per protocol patient population (PP): The PP patient population will include all subjects with 60-month follow-up data and no major protocol deviations and subjects that failed before 60 months and subsequently did not complete 60 months.

The primary efficacy analysis will be conducted on the mITT patient population. Secondary efficacy analyses will be done on the PP population. All safety data will be analyzed based on the mITT patient population.

The numbers of patients in the mITT analysis set included 190 patients randomized to Superion® and 201 patients randomized to the X-STOP® IPD® Control group. Eight (8) Superion® patients and 12 X-STOP® IPD patients are from 2 sites that are not participating in the PAS. This reduces the analysis set to 182 Superion® and 189 X-STOP® IPD®, respectively. Assuming 85% follow-up for the primary effectiveness endpoint at Month 60, there will be 155 Superion® patients and 161 X-STOP® IPD patients included in the primary non-inferiority evaluation.

10.5 Primary Statistical Analysis

The primary hypothesis of this extended follow-up post approval study is that performance of the Superion® ISS remains clinically non-inferior to X-STOP® IPD® at 5 years post-surgery using the same non-inferiority margin as was used at 2-years. The hypotheses to be tested may be symbolically described as follows:

Ho: $CCS_{Superion} - CCS_{X\text{-}STOP} \leq -0.10$ (inferior)

Ha: $CCS_{Superion} - CCS_{X\text{-}STOP} > -0.10$ (not inferior)

At 2-years, follow-up compliance was 97% and 95%, and the observed overall success rates were 51.9% (95/183) and 49.7% (93/187) for Superion® ISS and X-STOP® IPD®, respectively. For the purpose of sample size analysis it was initially assumed: a) that at 5-years, follow-up compliance would be 85% in both groups (i.e., 155 Superion® and 161 X-STOP® IPD®); b) a device group difference equal to that observed at 2-years (i.e., 2.2%); and c) at 5-years 40% of Superion® ISS would achieve CCS (and so 37.8% is assumed for X-STOP® IPD®). In keeping with the original design, these hypotheses will be tested by determining the Bayesian posterior probability that **$(CCS_{Superion} - CCS_{X\text{-}STOP}) > -0.10$.**

If the Bayesian posterior probability is at least equal to 0.95, then the hypothesis that Superion® ISS is non-inferior to X-STOP® IPD® at 5-years will be accepted. Non-informative beta(1,1) priors were assumed for both groups. With these assumptions, power is 73% and type 1 error is equal to 0.05. However, updated Month 36 results reflect a device group difference equal to 5.7%. Conservatively assuming a 5% difference, power increases to 87% and remains above 80% for device group differences larger than about 3.5%.

10.6 Superiority

The following superiority hypotheses will be tested if non-inferiority is demonstrated. By the closed testing principle there is no need for multiplicity adjustment.

Ho: $CCS_{Superion} - CCS_{X\text{-}STOP} \leq 0$ (not superior)

Ha: $CCS_{Superion} - CCS_{X\text{-}STOP} > 0$ (superior)

The posterior probability that **($CCS_{Superion} - CCS_{X\text{-}STOP}) > 0$** will be determined using Beta(1,1) priors for 5-year **$CCS_{Superion}$** and for 5-year **$CCS_{X\text{-}STOP}$**. If the posterior probability of superior is at least equal to 0.95, then a superiority claim will be made.

10.7 Missing Data and Loss-to-Follow-Up

In order to best preserve an intent-to-treat philosophy, the primary analysis will be done on the mITT group. Those subjects who withdraw, or who are lost (LTFU) after randomization, will be included in the analysis using Bayesian imputation. This analysis will be the primary analysis, but recognizing that there is no way, statistically, to handle these subjects without possibly introducing bias, a tipping point analysis will be conducted.

The tipping point sensitivity analysis will be conducted in which missing values in each group are separately assumed to be either successes or failures. Treatment group differences will be computed based on all possible combinations of assigning success or failure to the primary overall success endpoint to the patients in the two groups. For example, one scenario will be that all missing Superion device observations are failures and all missing X-STOP observations are successes. The next scenario would have one success and the remaining missing values as failure for Superion and all missing X-STOP as successes. For each scenario, the Bayesian posterior probability of non-inferiority will be determined. These results will be plotted using a dot plot with the number of missings assumed as failures for Superion on the x-axis and the number of missing assumed as failures for controls on the Y-axis. The dots will be color coded to indicate whether or not the primary statistical conclusion changes under each individual scenario. If the fraction of scenarios in which the statistical conclusion changes is small, the primary results will have been shown to be robust against assumptions concerning missingness.

10.8 Stratified Analysis for Multiple-Level Analysis

A logistic regression analysis will be conducted with level (one-level and two-level) and treatment as additive factors. Additionally an interaction effect between level and treatment will be included.

10.9 Secondary Endpoints

Secondary continuous effectiveness endpoints will be summarized by treatment group over time and as changes over time with descriptive statistics including means, standard deviations, median, minimum and maximum values. Secondary categorical effectiveness endpoints will be summarized by treatment group over time using counts and percentages. Descriptive effect size measures such as standardized mean differences will be presented as an aid in comparing magnitudes of groups differences across endpoints measured on different scales. Secondary endpoints analyses may also include other traditional frequentist confidence intervals and p-values for superiority.

10.10 Safety Analyses

Assessment of safety will primarily be based on the incidence and severity of complications and adverse reactions associated with the treatment. Adverse event rates will be summarized by type of AE and for specific AEs in two ways: 1) per patient using counts and percentages and 2) by event, summarizing event counts by visit interval over time. Device and procedure related events will be summarized by severity. Events listings will be provided that include details such as relatedness, severity, onset and resolution status will be provide for all events and for relevant subsets of events such as serious events and related events.

10.11 Site Heterogeneity

Site poolability will be evaluated using a random effects meta-analysis approach using the R package ***metafor*** to implement the analysis. True effects are assumed to be normally distributed with mean μ and variance σ^2.

By imposing a specified distribution on the site-to-site variability, i.e. a normal distribution with mean m and variance t^2, sensitivity to small sample sizes in individual sites is reduced and the parameters reflecting the magnitude of site-to-site variability are naturally derived. The quantitative measure of the magnitude of heterogeneity is I^2. I^2 is the fraction of t^2 that is due to effect size heterogeneity, as opposed to sampling variance. Fractions 25% and less are considered small. If there is significant site to site variability, the impact on this variability will be evaluated using a Bayesian hierarchical model estimated using ***WinBUGS***.

This will be done by translating hypotheses of interest to the log odds ratio scale and using MCMC to determine the Bayesian posterior probabilities of the described results. Poolability according to baseline demographic and disease severity status will be evaluated in descriptive stratified analyses.

11 Risks

The potential risks for subjects enrolled in the trial include those related to surgery, lumbar spine surgery, interspinous spacers (including the X-STOP® IPD®, Superion® ISS and other interspinous spacers) and instrumentation, the Superion® ISS, or radiographs for the study that are not standard of care. There is always a chance that unforeseen risks may occur.

Risks generally associated with any surgery include:

- anesthetic medication reactions
- surgery at the incorrect location, side or level
- blood loss, blood vessel damage, phlebitis or hematoma
- blood transfusion which may cause circulatory collapse, blood incompatibility, kidney damage, hepatitis, infection with HIV
- myocardial infarction or circulatory problems
- deep vein thrombosis, pulmonary embolism or thrombus formation in other vessels
- stroke
- fever or infection
- pneumonia
- injury to muscle, soft tissues or nerves
- wound swelling, draining or delayed healing
- discomfort and rehabilitation associated with recovery from surgery
- inability to perform certain tasks, such as lifting, exercising etc.
- death

Risks associated with lumbar spine surgery include:

- damage to nerve roots or the spinal cord causing partial or complete sensory or motor loss (paralysis)
- loss of bladder and/or bowel functions
- dural leaks (tears in the tissue surrounding and protecting the spinal cord)
- instruments used during surgery may break or malfunction which may cause damage to the operative site or adjacent structures
- fracture, damage or remodeling of adjacent anatomy, including bony structures or soft tissues during or after surgery
- new or worsened back or leg pain

Risks associated with lumbar spine implants (including the X-STOP® IPD®, Superion® ISS and other interspinous spacers) and associated instruments include:

- sensitivity or allergy to the implant material
- failure of the device/procedure to improve symptoms and/or function
- pain and discomfort associated with the operative site or presence of implants
- implant malposition or incorrect orientation
- spinous process fracture
- wear debris which may damage surrounding soft tissues including muscle or nerve
- scar tissue may form at implant site
- migration or dislodgement of the implant from the original position so that it becomes ineffective or causes damage to adjacent bony or soft tissues including nerve
- implant may loosen, fatigue, deform, break or disassemble which may require another operation to remove the implant and may require another method of treatment
- re-operation to remove or replace the implant

Risks specifically associated with the Superion® ISS include:

- implant may deform, break or disassemble; specifically the cam lobes may collapse or fail to lock
- other unexpected reactions may also occur

Risks Associated with Radiographs of the Lumbar Spine

The series of radiographs required for this study are similar to the standard of care for patients with Lumbar Spinal Stenosis treated with traditional surgical procedures such as laminectomy with or without spinal fusion. The risk of any side effects from this low level of exposure is very small. A 4-view X-ray of the lumbar spine (AP, lateral, flexion, extension) will be obtained at baseline, and at 6 weeks, 3, 6, 12, 18 and 24 month follow-up visits with a 2-view at the immediate post-operative time point. It is estimated that the total millirems will be less than 200 millirems per visit (for a 4 view x-ray) or no more than 1300 millirems for this study. This exposure can be compared to the allowable annual radiation dose for nuclear medicine/radiation oncology workers of 1800 millirems per year.[51]

Fluoroscopy Exposure

Fluoroscopy was used intra-operatively to ensure correct placement of the Superion® ISS device, and the X-STOP® IPD® device, between the spinous processes. Doses are similar to those used during fusion surgery or to administer non-operative treatments such as epidural injections, facet blocks or nerve root blocks. Sources of morbidity associated with the use of fluoroscopic guidance include, but are not limited to: early transient erythema, main erythema reaction, temporary epilation, permanent epilation, and dermal necrosis. These are usually associated with longer radiation exposures and higher doses than expected during the study surgery.

12 Benefit Analysis

The clinical benefits of the Superion® ISS have been documented through clinical study under IDE No. G070118, and may include the relief of symptoms associated with LSS. The potential benefit for subjects who are enrolled in the clinical investigation and receive the FDA-approved X-STOP® IPD® may include the relief of symptoms associated with LSS. An additional potential benefit for subjects who are enrolled in the clinical investigation and who receive the Superion® ISS is the possibility of less patient morbidity and tissue trauma, since the device can be percutaneously inserted through a 15 mm incision compared to the 4 cm (40 mm) incision needed to implant the X-STOP® IPD® device.

Although subjects enrolled in the clinical investigation may receive no direct benefit from participating, the knowledge gained from this investigation may benefit both physicians treating patients and patients who have LSS by generating data regarding the safety and outcome of the treatments.

13 Investigator Responsibilities

13.1 IRB Approval

This study must have initial and continuing approval (at least annual) from an Institutional Review Board (IRB) responsible for approving clinical studies. This can be a local or central IRB.

Screening or enrollment of subjects into the trial did not commence until the IRB approval letter was received by the Sponsor. In addition, a copy of the IRB approval letter must be filed on-site in the Investigator's study binder. Where appropriate, amendments to the protocol will be submitted for IRB review and approval before implementation.

13.2 Protocol Adherence

The Investigator(s) agree to conduct the study in accordance with this protocol. Prior to beginning the study, the Investigator(s) must sign the *Investigator Agreement* and the *Protocol Signature Page* of this protocol.

An Investigator must not make any changes in the study without first receiving approval in writing from the Sponsor and IRB, except when necessary to eliminate apparent immediate hazards to a subject.

13.3 Review of Source Documents

The Investigator(s) agrees that the Sponsor's employees or designees, as well as FDA designees will have the right to audit and review pertinent medical records relating to this clinical trial.

13.4 Record of Device Inventory

The Investigator(s) will maintain a Device Accountability Log of all investigational devices received, used, or returned during this study. The Device Accountability Log should be available during monitoring visits. All investigational devices not used in this study must be returned to the Sponsor before or at the completion of the study or at the Sponsors request.

13.5 Data Recording and Record Retention

1. All data will be recorded on Case Report Forms for each subject enrolled in the study as well as in the subject records (source documentation).
2. The Sponsor or Sponsor's designee will review completed Case Report Forms, along with source documentation. The Investigator(s) will ensure that the medical records are made available for review by the study monitor or FDA, as required.
3. All subject study records are to be maintained in a secure storage facility until notified by the Sponsor that the records may be discarded. This includes the following documentation:

i) Case Report Forms, Informed Consents and enrollment logs

ii) Device Accountability Logs and device shipment receipts of all devices shipped to the site

iii) Correspondence with the IRB, Sponsor, FDA, Monitor, or other Investigators

iv) Study protocol and any amendments issued

v) Protocol and Informed Consent approvals from the IRB

vi) Clinical Study Agreement and curricula vitae of Investigator(s), and the site personnel signature form

13.6 Notification Reporting

The Investigator(s) is responsible for all reporting required per the IRB.

14 Sponsor Obligations

14.1 Investigator(s) Training

Prior to the first procedure, the Sponsor provided appropriate training to each Investigator that included didactic and hands on elements, e.g., cadaver lab, sawbones, model. Training addressed topics including surgical procedures, selection of appropriate implant sizes, instrumentation for implantation, indications for use of the device, contraindications and management of complications. The Sponsor also provided appropriate training to the operating room staff at each investigational site. Investigators were trained on use of the control device. Each site was permitted to enroll up to 2 non-randomized patients to receive the Superion® ISS as training cases prior to randomizing the first patient.

14.2 Sponsor Study Termination

The Sponsor may close enrollment or terminate the study at any site, at any time, for any of the reasons listed below. If a site was closed to enrollment or terminated before enrolling randomized patients, the site could be replaced in the study. Patients identified as training cases that receive implants will be followed until they reach their 60 month follow-up or the study is terminated.

1. Non-compliance to GCP guidelines or protocol
2. Failure to enroll subjects in a timely manner
3. Protocol deviations
4. Inaccurate or incomplete data
5. Unsafe or unethical practices
6. Safety or efficacy considerations
7. Administrative decision

14.3 Study Monitoring and Frequency of Monitoring Visits

Study monitoring will be carried out in compliance with FDA regulations (21CFR 812) and all GCP guidelines. The clinical investigation will be monitored throughout its active phase, i.e., until 60 month follow-up is complete for all subjects. The first Monitoring Visit occurred shortly after the first subject was enrolled and treated at the site. Subsequent Monitoring Visits will occur as the frequency of follow-up dictates, but no less than annually.

Periodic Monitoring Visit Activities

1. The Monitor's visit to the clinical site will include review of:
    a. Subject Source Documentation
    b. Case Report Forms
    c. Informed Consents
    d. Protocol Adherence
    e. Investigational Device Accountability
2. Reports:
    a. The Monitor should complete a report documenting completion of each Periodic Monitoring visit.
3. Site Close-out Activities
    a. When the study has been completed or terminated, the Monitor will assure that all site Close-out activities have been completed.
    b. The Monitor should complete a report documenting completion of site Close-out Monitoring visit.

15 Informed Consent

A copy of the proposed Informed Consent document should be submitted to Sponsor for review and approval before submission to the IRB. Study enrollment may not have begun until Sponsor reviewed the document and it was approved by the IRB.

All subjects enrolling in the study:

a. Were informed of the investigational nature of the study
b. Were given the opportunity to ask any questions regarding the study treatment
c. Voluntarily and willingly signed the Informed Consent prior to study treatment
d. Were given a copy of the Informed Consent

List of Appendices

Appendix A: Visit Schedule

Appendix B: Patient Questionnaires

Zurich Claudication Questionnaire
Oswestry Disability Index
Visual Analog Scale
SF-12
VertiFlex® Patient Satisfaction Survey

Bibliography

Appendix A: Visit Schedule												
	Screening -Baseline	**Surgical Treatment**	**Discharge (±0-7 days)**	**6-week (±2 weeks)**	**3-month (±2 weeks)**	**6-month (±1 month)**	**12-month (±2 months)**	**18-month (±2 months)**	**24-month[c] (±2 months)**	**36-month[c] (±2 months)**	**48-month[c] (±2 months)**	**60-month[c] (±2 months)**
Study Visit Window		Day 0	0-7 days	4-8 wks	10-14 wks	5-7 mos	10-14 mos	16-20 mos	22-26 mos	22-26 mos	22-26 mos	22-26 mos
Signed Informed Consent	X											
Demographic Information	X											
Complete History & Physical	X											
Randomization	X											
Standing AP & Lateral Lumbar Spine X-rays	X[a]		X	X	X	X	X	X	X	X	X	X
Flexion / Extension Lateral Lumbar Spine X-rays	X[a]			X	X	X	X	X	X	X	X	X
Lumbar Spine MRI/CT Scan	X[a]											
DEXA Scan[b]	As needed											
SF-12 –Health Survey (v2)	X			X	X	X	X	X	X	X	X	X
Zurich Claudication Questionnaire (ZCQ)	X			X	X	X	X	X	X	X	X	X
Oswestry Disability Index (v2)	X			X	X	X	X	X	X	X	X	X
Neurological Status	X		X	X	X	X	X	X	X	X	X	X
Visual Analogue Scale	X		X	X	X	X	X	X	X	X	X	X
VertiFlex® Patient Satisfaction Questionnaire				X	X	X	X	X	X	X	X	X
Assess Adverse Events		X	X	X	X	X	X	X	X	X	X	X

[a]Lumbar spine x-rays and MRI/CT taken within 3 months of enrollment can be used to confirm eligibility.

[b]In order to confirm eligibility, at the Investigator's discretion, subjects previously diagnosed with osteoporosis, osteopenia, osteomalacia, female subjects over the age of 65, and post-menopausal female subjects under the age of 65 with any of the risk factors for osteoporosis, will have DEXA scans performed prior to study entry.

Appendix B: Patient Questionnaires

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