Clinical Protocol for Post Approval ‘Actual Conditions of Use’ Study

A 2 and 3 year comparative evaluation of clinical outcomes in the treatment of lumbar spinal stenosis with the Superion® InterSpinous Spacer or by decompression surgery for FDA Actual Conditions of Use Study.

Protocol Number: XXXXX
Version: October 2014
Sponsor/Affiliate: VertiFlex®, Inc.
1351 Calle Avanzado
San Clemente, CA 92673, USA
Device name: Superion® InterSpinous Spacer
PMA Number: P140004
Clinical Research Organization (US): TBD
Number of sites: Up to 15
Planned Start of Recruitment: January 2015
Planned End of Recruitment: December 2016
Planned End of Clinical Phases:
  Month 24: January 2019
  Month 36: January 2020
Planned Draft Interim Report: July 2019
Planned Draft Final Report: July 2020

CONFIDENTIAL
The information in this clinical protocol is for the CRO, Sponsor, investigator and staff, IRBs and health authorities. It may not be disclosed to third parties without written authorization from VertiFlex®, Inc., except to obtain informed consent from persons receiving the study treatment. Once signed, the terms of the clinical protocol are binding for all parties.
SIGNATURE PAGE

This clinical protocol was subject to a critical review and has been approved by the appropriate review committee of VertiFlex®, Inc. The information it contains is consistent with:

- The current risk/benefit evaluation of the device preparation;
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki in its current version as well as the EN ISO 14155-1 & -2;
- Good clinical practice guidelines as applicable for medical devices in their current version.

VertiFlex®, Inc.

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(Place, date) Name
Title

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(Place, date) Name
Title

All further investigators have to give their agreement with the content of this clinical protocol on a separate “investigator protocol signature page”.
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# STUDY SYNOPSIS

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<th>VertiFlex®, Inc.</th>
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<td>NAME OF PRODUCT</td>
<td>Superion® InterSpinous Spacer</td>
</tr>
<tr>
<td>CLASS OF MEDICAL DEVICE</td>
<td>Class III</td>
</tr>
<tr>
<td>STUDY TITLE</td>
<td>A 2 and 3 year comparative evaluation of clinical outcomes in the treatment of lumbar spinal stenosis with the Superion® InterSpinous Spacer or by decompression surgery for FDA Actual Conditions of Use Study.</td>
</tr>
<tr>
<td>STUDY NICKNAME</td>
<td>Superion® PAS #2</td>
</tr>
<tr>
<td>PROTOCOL #</td>
<td>XXXXX</td>
</tr>
<tr>
<td>STUDY TREATMENT</td>
<td>Stabilization with Superion® InterSpinous Spacer (Superion® ISS)</td>
</tr>
<tr>
<td>CONTROL TREATMENT</td>
<td>Decompression Surgery</td>
</tr>
</tbody>
</table>
| DURATION OF THE CLINICAL INVESTIGATION | Per Patient: 36 months  
Recruitment: 12 months  
Total: 48 months |
| STUDY GOALS              | Meet FDA mandated post-approval Actual Conditions of Use evaluation |
| OBJECTIVES               | The first objective of this ‘actual conditions of use’ study is to confirm that Superion® performance is not clinically inferior in the PAS population compared to the pivotal IDE trial population. The same Month 24 composite clinical success (CCS) endpoint used in the IDE trial will be used in primary analyses to facilitate this comparison.  
The second objective of this study is to compare clinical status of patients implanted with the Superion® device relative to surgical decompression two years post operatively.  
The third objective is to evaluate longer term (3 year) Superion® device performance in the actual conditions of use population and to compare this Month 36 composite clinical success between patients implanted with Superion® relative to decompression. |
<p>| METHODOLOGY and STUDY DESIGN | Prospective, multicenter, randomized, controlled, patient-blinded through Month 36 |
| NUMBER OF PATIENTS       | Min 150 per group, Max 250 per group; (300 to 500 total) plus 15% to account for LTF |</p>
<table>
<thead>
<tr>
<th>NUMBER OF SITES</th>
<th>Up to 15 sites</th>
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<tbody>
<tr>
<td><strong>DIAGNOSIS and INCLUSION CRITERIA</strong></td>
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</tr>
<tr>
<td>1.</td>
<td>Male or female subjects ≥ 45 years of age.</td>
</tr>
<tr>
<td>2.</td>
<td>Persistent leg/buttock/groin pain, with or without back pain that is relieved by flexion activities (example: sitting or bending over a shopping cart).</td>
</tr>
<tr>
<td>3.</td>
<td>Subjects who have been symptomatic and undergoing conservative care treatment for at least 6 months.</td>
</tr>
<tr>
<td>4.</td>
<td>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 access), and the nerve root canal (foraminal).</td>
</tr>
<tr>
<td>5.</td>
<td>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:</td>
</tr>
<tr>
<td>6.</td>
<td>Must present with moderately impaired Physical Function (PF) defined as a score of ≥ 2.0 of the Zurich Claudication Questionnaire (ZCQ).</td>
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<tr>
<td>7.</td>
<td>Must be able to sit for 50 minutes without pain and to walk 50 feet or more.</td>
</tr>
<tr>
<td>8.</td>
<td>Subjects who are able to give voluntary, written informed consent to participate in this clinical investigation and from whom consent has been obtained.</td>
</tr>
<tr>
<td>9.</td>
<td>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.</td>
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Note: In Criteria #5, all imaging used to confirm LSS should 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 may be included by requesting a deviation from the Sponsor.

<table>
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<tr>
<th>EXCLUSION CRITERIA</th>
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<tbody>
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<td>1.</td>
<td>Axial back pain only.</td>
</tr>
<tr>
<td>2.</td>
<td>Fixed motor deficit.</td>
</tr>
<tr>
<td>3.</td>
<td>Diagnosis of lumbar spinal stenosis which requires any direct</td>
</tr>
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</table>
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. Spondylosis (par 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/m².
15. Significant peripheral vascular disease (diminished dorsalis pedis or tibial pulses).
17. Cauda equine 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 vertebrae, 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
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 within past 30 days).
32. Congenital defect of the spine.
33. Pregnant or lactating.

INVESTIGATIONAL DEVICE;
DOSE and MODE OF
APPLICATION
The Superion® InterSpinous Spacer is an FDA approved medical
device (P140004) already being marketed in the USA. The
Superion® InterSpinous Spacer obtained marketing approval in the
US on PENDING.
The device will be implanted as described in the product brochure
in patients with spinal stenosis.

COMPOSITE CLINICAL
SUCCESS (CCS)
Month 24 Composite Clinical Success (CCS)
The identical Month 24 CCS endpoint as was used in the IDE will
be used to compare PAS results to IDE study results. Month 24
success for this comparison will require a clinically significant
improvement in at least two of the three domains of the ZCQ; no
reoperations, revisions, removals or supplemental fixation at the
index level(s); no major implant or procedure-related
complications; no device component fracture, deformation or
disassembly; no dislodgement, migration, or deformation, new or
persistent worsened neurological deficit at the index level, spinous
process fractures, and deep infection, death, or other permanent
device attributed disability; no spinal cord stimulators or
rhizotomies; and no post-operative epidural steroid injections, or
nerve block procedures performed to treat spinal stenosis at the
index level(s). The CCS is described in more detail in Section 5 of
this protocol.

The Month 24 CCS for Objective 2 (comparison of Superion® to
decompression surgery) will be modified to note that implant-
related issues are applicable to the Superion® group only.

Month 36 Composite Clinical Success (CCS)
The Month 36 CCS will be slightly modified to account for failures occurring between 24 and 36 months and to assess changes in clinical status from baseline to month 36. A different approach will be used for lumbar epidural injections in order to avoid calling transient symptom management a device failure unless there is subsequent re-operation or unless patient status is compromised as reflected in an ODI improvement from baseline that is less than 15%. Therefore, for Month 36 CCS, only lumbar injections occurring within 12 months of the Month 36 visit will indicate Month 36 CCS failure. This is because a lumbar injection within 12 months of the Month 36 visit can confound the Month 36 assessment.

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<td>▶ VertiFlex® Patient Satisfaction Survey (percent of patients scoring ≤ 2.5 on a 4-point scale)</td>
</tr>
<tr>
<td>▶ ODI change compared to baseline at 24 and 36 months and in terms of achieving at least a 15 point improvement.</td>
</tr>
<tr>
<td>▶ Change in Visual Analog Scale (VAS) for low back and leg pain (on the 100 mm scale) after 24 and 36 months compared to baseline and in terms of achieving a 20 point improvement.</td>
</tr>
<tr>
<td>▶ SF-12 generic health status compared to baseline at 24 and 36 months</td>
</tr>
<tr>
<td>▶ Maintenance of distraction defined by ≤ 4mm of measurable decrease in the posterior disc space height on successive radiographs obtained at 3 months and 24/36 months post-operatively.</td>
</tr>
<tr>
<td>▶ The CCS will be modified to examine the effect of narcotics use (opioids and/or opiates) has on treatment success rates. When comparing Superion® in conjunction with decompression to decompression alone, the Month 24 CCS will be modified to require no narcotic use at Month 24. Similarly, the Month 36 CCS will require no narcotic use at Month 36.</td>
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<table>
<thead>
<tr>
<th>SAFETY ENDPOINTS</th>
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<tbody>
<tr>
<td>Documentation of Adverse Events and SAEs and implant and surgery related complications (e.g. breaking of implants). Specific AEs will be summarized according incidence (per patient) and counts of AE over time.</td>
</tr>
<tr>
<td>Assessment of revisions and additional stabilizations.</td>
</tr>
<tr>
<td>Assessment of epidurals.</td>
</tr>
<tr>
<td>Assessment of analgesic narcotics usage.</td>
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<table>
<thead>
<tr>
<th>OTHER ENDPOINTS</th>
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</thead>
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<tr>
<td>• Length of hospital stay</td>
</tr>
<tr>
<td>• Operative time</td>
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<tr>
<td>• Estimated blood loss</td>
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</tbody>
</table>
| | Work status and time to return to work or normal (pre-operative) activities of daily living (ADL)
| | Type of anesthesia
| | Rehabilitation utilization (concomitant treatments)

**STATISTICAL METHODS**

The first objective of this “real conditions of use study” is to compare Superion® device performance in the PAS population to Superion® device performance observed in the IDE study. Patients will be enrolled at sites that were not involved in the IDE study. The likelihood of PAS patients achieving Month 24 CCS will be compared to the same likelihood as observed in the IDE study population.

In the IDE study, 95 of 183 patients (51.9%, 95% Bayesian credible interval 44.6% to 58.8%) achieved Month 24 CCS.

Objective 2 is to test the hypothesis that Superion® is superior to surgical decompression in terms of the same Month 24 composite clinical success (CCS) used in the IDE Study. The primary superiority test will involve determining the Bayesian posterior probability that the likelihood of achieving Month 24 CCS is larger for patients implanted with the Superion® device compared to patients undergoing decompression. It is hypothesized that Superion® will be superior to decompression in terms of the proportion patients expected to achieve Month 24 CCS. Symbolically this is $H_0: CCS_{Superion} - CCS_{decomp} \leq 0$ vs $H_a: CCS_{Superion} - CCS_{decomp} > 0$.

$H_0$ will be rejected in favor of $H_a$ if the Bayesian posterior probability of superiority exceeds the Objective 2 posterior probability study success criterion. A Bayesian predictive probability sample size re-estimation will be employed.

The third objective is to test the hypothesis that Superion® is superior to surgical decompression in terms of Month 36 composite clinical success (CCS). The Month 36 endpoint will be slightly modified so that only epidural lumbar injections occurring within 12 months of the Month 36 endpoint will be counted as a Month 36 CCS failure.
CLINICAL INVESTIGATION PLAN

1. BACKGROUND INFORMATION

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. As early as the 1950’s it was recognized by Verbiest that structural narrowing of the vertebral canal could compress the cauda equina and produce neurogenic claudication symptoms. 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.

Nonsurgical management (NSM) or conservative care is well-established as the first-line treatment approach for LSS patients with mild to moderate symptoms. 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. 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. LSS is currently the most common diagnosis for patients 55 years or older scheduled for spinal surgery. This dramatic increase in the number of

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surgery is attributable to improved diagnostic imaging techniques, improved and less invasive surgical techniques, the aging population and improved patient education.\textsuperscript{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.\textsuperscript{36, 37, 38} However, cauda equina syndrome is the only absolute indication for decompressive laminectomy.\textsuperscript{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. However, with the first commercial introduction of interspinous spacers into the US marketplace in 2005 (X-STOP\textsuperscript{®} Interspinous Process Decompression [IPD\textsuperscript{®}] System, Kyphon, Inc., Sunnyvale, CA), a new, less invasive treatment alternative became available for this patient population.

The Superion\textsuperscript{®} 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\textsuperscript{®} 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\textsuperscript{®} 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 proposed Post Approval Study (PAS) is designed to evaluate the safety and effectiveness of the Superion\textsuperscript{®} ISS in a real conditions of use setting and compare clinical outcomes to a control group comprising patients undergoing surgical decompression-in healthy adults suffering moderate spinal stenosis symptoms who have been unresponsive to at least 6 months of conservative care.

For further details, including indications, contraindications and associated risks please see the Product Brochure and instructions for use.

\section{RATIONALE}

In a clinical study to support US market approval, 419 patients (28 Superion\textsuperscript{®} training, 190 Superion\textsuperscript{®} and 201 X-STOP\textsuperscript{®}) from 21 sites in the United States were enrolled between 2007 and 2011. Subjects received the Superion\textsuperscript{®} Interspinous Spacer or the X-STOP\textsuperscript{®} Interspinous Process Decompression (IPD) System in a 1:1 ratio. Overall device success required a clinically significant improvement in at least two of the three domains of the ZCQ; no reoperations, revisions, removals or supplemental fixation at the index level(s); no

\begin{thebibliography}{99}
\item Herno A, et al. computed tomography findings 4 years after surgical management of lumbar spinal stenosis. Spine (1999); 24(21): 2234-2239.
\end{thebibliography}
major implant or procedure-related complications; no device component fracture, deformation or disassembly; no dislodgement, migration, or deformation, new or persistent worsened neurological deficit at the index level, spinous process fractures, and deep infection, death, or other permanent device attributed disability; no spinal cord stimulators or rhizotomies; and no post-operative epidural steroid injections, or nerve block procedures performed to treat spinal stenosis at the index level(s).

Using this primary endpoint, non-inferiority of Superion® compared to X-STOP® was established in the primary effectiveness cohort based on a Bayesian Posterior Probability of 0.9927, which is greater than the 0.958 success criterion as described in the statistical analysis plan, using the modified intent-to-treat cohort that included all patients with an anesthesia start time in the Superion® IDE. Further, this demonstration of non-inferiority in the per protocol cohort (Bayesian Posterior Probability of 0.9927) provides confirmation of the non-inferiority result of the Superion® IDE and demonstrates the robustness of the overall statistical determination. By overwhelmingly meeting the a priori endpoint, Superion® demonstrated that it is reasonably safe and effective.

This randomized multicenter study has not generated any peer-reviewed publications:
3. STUDY OBJECTIVES AND ENPOINTS

3.1. Study Objectives

The first objective of this ‘actual conditions of use’ study is to confirm that the Superion® device performance is not clinically inferior in the PAS population compared to the pivotal IDE trial population. The same Month 24 composite clinical success (CCS) endpoint used in the IDE trial will be used in primary analyses to facilitate this comparison. The first objective will be achieved by conducting a frequentist test of the null hypothesis that PAS device performance is inferior to IDE device performance ($\delta = -0.10$). Rejection of this null hypothesis naturally provides evidence supporting the use of the PAS results to update the Bayesian posterior probabilities that were determined in the IDE trial and are documented in the Superion® SSED. The Bayesian posterior probabilities of non-inferiority and superiority relative to the X-STOP® control at the end of the Superion® IDE trial was 0.9927 and 0.6879, respectively. These probabilities will be updated using the new Superion® enrollments into this PAS.

The second objective of this study is to compare clinical status of patients implanted with the Superion® device relative to surgical decompression surgery two years post-operatively. This second objective will be achieved by conducting a Bayesian test of the null hypothesis that the likelihood of achieving Month 24 CCS among patients implanted with the Superion® device in conjunction is no larger than that for patients undergoing surgical decompression. The alternative hypothesis to be proved is that Superion® is superior to decompression surgery with regard to Month 24 CCS. The second objective will be met using an informative prior for the investigational device based on the results summarized in the Superion® SSED. Clinical trial simulation of the frequentist operating characteristics of the Bayesian hypothesis test guide the selection of the posterior probability threshold needed to conclude superiority.

The third objective is to evaluate longer term (i.e., 3 year) Superion® device performance in the real conditions of use population and to compare this Month 36 composite clinical success between patients implanted with Superion® relative to decompression.

3.2. Composite Clinical Success (CCS)

The identical Month 24 CCS endpoint as was used in the IDE will be used to compare PAS results to IDE study results, and to update the Bayesian posterior probabilities of non-inferiority and superiority relative to the IDE control device, X-STOP®. This CCS definition requires a clinically significant improvement in at least two of the three domains of the ZCQ; no reoperations, revisions, removals or supplemental fixation at the index level(s); no major implant or procedure-related complications; no spinal cord stimulators or rhizotomies; and no post-operative epidural steroid injections, or nerve block procedures performed to treat spinal stenosis at the index level(s). The CCS is described in more detail in Section 5 of this protocol.

The Month 24 CCS for Objective 2 (comparison of Superion® to decompression surgery at Month 24) will be modified to note that implant-related issues are applicable to the Superion® group only.

The Month 36 CCS for Objective 3 (comparison of Superion® to decompression surgery at Month 36) will be modified to account for failures occurring between 24 and 36 months and to include evaluation of changes in clinical status from baseline to Month 36. A different approach will be used for lumbar epidural injections. This is to avoid calling transient symptom management a device failure unless there is subsequent re-operation or unless patient status is compromised as reflected in an ODI improvement from baseline that is less than 15%. Therefore, for Month 36 CCS, only lumbar injections occurring within 12 months of the Month 36 visit will indicate Month 36 CCS
failure. This is because a lumbar injection within 12 months of the Month 36 visit can confound the Month 36 assessment.

3.3. Secondary Endpoints

The following outcome measures will be evaluated as secondary endpoints:

- VertiFlex® Patient Satisfaction Surgery; percent of patients scoring ≤ 2.5 on a 4 point scale.
- ODI change compared to baseline at 24 and 36 months and in terms of achieving at least a 15 point improvement.
- Change in Visual Analog Scale (VAS) for low back and leg pain (on the 100 mm scale) after 24 and 36 months compared to baseline and in terms of achieving a 20 point improvement.
- SF-12 generic health status compared to baseline at 24 and 36 months.
- Maintenance of distraction defined by ≤ 4mm of measurable decrease in the posterior disc space height on successive radiographs obtained at 3 months and 24/36 months post-operatively.

The CCS will be modified to examine the effect narcotics use (opioids and/or opiates) has on treatment success rates. When comparing Superion® to decompression, this modified Month 24/36 CCS will include:

- No use of a narcotic (opioids or opiates) at month 24/36.

3.4. Safety Endpoints

The safety endpoint will include documentation of adverse events and serious adverse events (SAEs) and implant- and surgery-related complications (e.g., breaking of implants). Specific AEs will be summarized according to incidence (per patient) and counts of AE over time. The endpoint will also assess revisions and additional stabilizations, epidurals, and analgesic narcotics usage.

3.5. Other Endpoints

- Length of hospital stay
- Operative time
- Estimated blood loss
- Work status and time to return to work or normal (per-operative) activities of daily living (ADL)
- Type of anesthesia
- Rehabilitation utilization (concomitant treatments)

3.6. Crossing Over

Patients who are randomized to the control arm (decompression surgery) and require further treatment due to failure of the initial surgery, may receive a Superion® implant if the investigator determines that to be a potentially beneficial option. In these cases, the surgery should be noted in the patient’s eCRF and reported as an adverse event, and then these patients should continue to be followed up within the study. Such patients will be considered a failure for the treatment they were initially randomized to.
4. SUBJECTS AND METHODS

4.1. Study Design

This is a prospective randomized, multicenter clinical study, involving up to 15 centers in the US to assess the safety and effectiveness of the Superion® InterSpinous Spacer (ISS) for the treatment of at least moderate leg and low back pain in patients with moderate spinal stenosis.

4.2. Number of Subjects

The number of subjects is determined on basis of Objective 2, the Month 24 comparison between Superion® and decompression. It is then shown that the minimum sample size for Objective 2 is appropriate to meet Objective 1, the comparison of Month 24 CCS between Superion® in the PAS and IDE populations. To meet Objective 2, a Bayesian predictive probability sample size re-estimation (BPP-SSR) design will be used. The initial commitment is to evaluate 150 patients per group (300 total). This total will be increased by 15% to account for loss-to-follow-up. Therefore, the initial total to be randomized is 345. When 100 of initially planned patients per group are evaluable for Month 24 follow-up, the Bayesian predictive probability of Study Success will be determined. The design permits up to a 100 patient increase per group if the interim analysis results are "promising" (e.g., predictive probability between 50% and 80%). With adjustment for LTF, the expanded sample size may be up to 115 patients per group. Therefore, the maximum randomized enrollment is 575.

Patients will be randomized to one of the treatment groups (Group A, decompression surgery, Group B, Superion® InterSpinous Spacer (ISS), ratio 1:1 for allocation to the treatment groups). Patients will be blinded to the treatment received at the time of surgery. Due to differences in the procedures, incision sizes, and operative positioning, subjects may not be masked to their treatment arm after the surgery.

Recruitment of about 3-4 patients per month and center is expected. If a center does not include the planned amount of patients, other centers can be asked to enroll more patients in order to reach the required number of trial patients in a reasonable time. Each site will be required to enroll at least 5 patients.

4.3. Inclusion Criteria

The following criteria must be met for inclusion into the study:

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 access), or 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:
• Evidence of thecal sac and/or cauda equine compression
• Evidence of nerve root impingement (displacement or compression) by either osseous or non-osseous elements
• 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 Criteria #5, all imaging used to confirm LSS should 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 may be included by requesting a deviation from the Sponsor.

4.4. 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. Spondylosis (par 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/m².
15. Significant peripheral vascular disease (diminished dorsalis pedis or tibial pulses).
17. Cauda equine 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 vertebrae, 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 within past 30 days).
32. Congenital defect of the spine.
33. Pregnant or lactating.

4.5. Restriction to Subjects
There are no study specific restrictions for patients’ diet or habits (smoking, etc....).

4.6. Study Conduct
The study will be performed in up to 15 study centers in the US. All centers will be experienced in the treatment of spinal stenosis with decompression surgery and thoroughly trained to use the Superion® InterSpinous Spacer (ISS), but no site was included in the IDE study. All treatments will be carried out in each center according to the routine procedures for decompression surgery in the control group and based
on the Superion® surgical technique described in labeling. Only investigators that are thoroughly trained in the implantation of the study device will perform the surgeries for this trial.

Subjects participating in this study will be recruited from the investigators’ standard patient populations. Subjects must meet all of the above inclusion criteria and none of the exclusion criteria. The investigator maintains exclusive responsibility for the inclusion and exclusion of any potential study participant.

All patients presenting for treatment of symptomatic spinal stenosis that have not responded to conventional medical therapy for 6 months will be evaluated for study participation based on the inclusion/exclusion criteria listed above. In total 345 to 575 patients are planned to be included in the trial. Each center should recruit at least 5 patients.

The schedule of study related actions is summarized in the Study Visits Table (see Section 4.7).

<table>
<thead>
<tr>
<th>Patients who fulfil the inclusion/exclusion criteria are randomly allocated to one of the two parallel treatment groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A:</strong> Decompression surgery without any further stabilization (control group)</td>
</tr>
<tr>
<td><strong>Group B:</strong> Stabilization using the Superion® InterSpinous Spacer (ISS) (treatment group)</td>
</tr>
</tbody>
</table>

Blood sampling is not planned as a part of the trial but might be performed as part of the routine procedures of each center. Blood parameters will not be documented in the CRF – except if necessary for SAEs.

For the implantation of the Superion® InterSpinous Spacer (ISS) the product brochure and implantation instructions provided by the manufacturer have to be followed.

4.7. Description of Study Procedures

4.7.1. Surgical Technique:

Within the Superion® group, patients will have their device implanted via a percutaneous or mini-open procedure. The “mini open” technique is actually an “optional approach” described in Step 1 (page 5) of the surgical technique manual. The normal “percutaneous” technique involves placing the first dilator through the supraspinous ligament entirely under fluoroscopic guidance. The optional (“mini open”) approach allows the surgeon to make a skin incision to directly visualize the supraspinous ligament for placement of the first dilator. Therefore, the only difference is how the dilator is introduced to the surgical site to penetrate the ligament. In the first approach, it is fluoroscopic, and in the second it is under direct visualization of the ligament.

4.7.2. X-ray Imaging:

X-ray images will be made in standing position in both cohorts.

During visit 1, visit 3, visit 4, visit 5, and visit 6 x-rays will be taken in the following positions: antero-posterior, lateral, flexion and extension.

During visit 2 (surgery) X-rays will be taken only in group B (with Superion® InterSpinous Spacer) for the following two positions: antero-posterior and lateral.
In total 27 X-ray images will be made in the course of the trial for group B (with Superion® InterSpinous Spacer).

In total 25 X-ray images will be made in the course of the trial for group A (decompression surgery).

X-ray images from Visit 2, which are only performed in test group B, will not be evaluated on a regular basis, but may be consulted on demand for potential assessment of spinous process fractures, implant function and potential migration.

Additional radiographs may be taken in between regularly scheduled visits at the discretion of the investigator/patient's surgeon due to new symptoms. This additional information makes an earlier intervention possible, which could result in an early reduction of the pain and/or in a delay in progression of the illness.

4.7.3. CT Imaging

CT imaging will be captured at 24 months for subjects with a confirmed or suspected spinous process fracture and at 36 months for subjects with a confirmed spinous process fracture. CT imaging will utilize lateral views to observe spinous process fractures. CT imaging will be used to investigate the incidence of spinous process fractures in both Superion® and decompression patients.

4.7.4. Questionnaires:

- The Zurich Claudication Questionnaire (ZCQ) will be used as a self-rating patient questionnaire to assess the impact of pain on patient’s everyday life. The ZCQ includes questions that are used to produce indices of symptom severity, physical functional status and patient satisfaction. The ZCQ is used as part of the primary effectiveness endpoint of this trial.

- The Oswestry Low Back Pain Disability Index (ODI) will be used. The ODI is a self-rating patient questionnaire developed to assess the impairment on patient’s life by low back pain.

- Visual Analog Scales (VAS) will be used. The VAS is comprised of a 100 mm horizontal line which is scaled from 0 (left end) to 10 (right end). Every VAS is associated with a single question. The patient will be asked to mark his subjective impression about the question asked by a small vertical line on the VAS. For evaluation the distance of this marking from the left end of the VAS will be measured in mm with a ruler. VAS questions include right leg pain, left leg pain, and back pain.

- The SF-12 general health survey will be used. The SF-12 is used to measure functional health and well-being from the patient’s point of view.

- The VertiFlex® Patient satisfaction questionnaire will be used. This is a questionnaire to determine the patient’s subjective satisfaction (4 point scale) with the result of the treatment.

- Information of patients on questionnaires: All questionnaires and VAS will be explained to the patient extensively by the investigator. The patients will not have access to the questionnaires / VAS which they have filled in during prior visits. The questionnaires / VAS should be filled in by the patients themselves; they should not be influenced by the investigator or other persons.

4.7.5. Direct Data Capture:
All documents that are used on site are considered source. All patient questionnaires are defined as direct data capture pages and they represent the source of the captured data (for monitoring they will be monitored as source data and there will be no other source for these data). The study coordinator will enter the source data onto the eCRFs. The monitors will verify the source documents match the eCRFs. Once this has been verified the monitor will lock the field so the data cannot be changed unless requested from the data manager.

The data will be entered into a validated electronic database capture (EDC) system: SYSTEM NAME. The data manager will be responsible for programming of the database and data management. The Investigator or his/her designee is responsible for data entry at the time of the subject visit. The site CRA and data manager will review the data for completeness and accuracy compared to source documents (e.g. medical charts, hospital records, etc.). The CRA, data manager, or Sponsor can initiate queries where data is inconsistent or incorrect. Queries are entered, tracked, and resolved through the EDC system directly.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

4.7.6. Neurological status:

The following parameters will be collected with regards to the patient’s neurological status:

- Muscle strength
- Sensory and reflexes
- Range of motion
- Palpation of pulses
- Straight leg raise
- Femoral stretch

4.7.7. Central Evaluation of Radiological Images:

Only sites with digital x-ray capability will enroll patients into this study.

In order to achieve a comparable evaluation, all radiological images will be evaluated by a core lab. X-ray images will be sent electronically to the core lab, either on a CD or via email or via FTP site. Anonymized electronic copies will be stored at sponsor and might be used for external reading and evaluation in the future.

Preoperative MRI images will also be collected.

4.7.8. Assessment of Concomitant Medication:

Pain management:

The investigator will ask the patient for detailed information on all pain killers taken. The investigator will enter in the CRF which type of pain killers are used by the patient (visit 1 – visit 6). It will be differentiated between the following types of pain killers: Class II narcotics, other narcotics (“Tramadol”, “Tilidin”), NSAIDs including acetylsalicylic acid (“Aspirin”) and acetaminophen (“Paracetamol”). It will be analyzed if pain killers were not used any more or if less strong pain killer classes are used. Other kind of pain management such
as epidural steroid injection, facet injection or nerve root block will be documented in the CRF (visit 1, visit 3, visit 4, visit 5, visit 6).

*Other concomitant medication:*
Concomitant medication will not be recorded except if they are related to an SAE or might have impact on the study evaluation according to the investigators decision.

### 4.7.9. Physical Examination

A detailed physical examination will be performed at visit 1. In the following visits only a routine physical examination will be performed and changes compared to screening will be recorded. The investigator is free to perform a complete physical examination.

Medical history will be documented in the medical history form only. The entries into this form will be regarded as source documents and will not be verified against patient files. Concomitant diseases and medications related to concomitant diseases will not be documented and monitored, except if they are related to an SAE or might have impact on the study evaluation according to the investigators decision.

### 4.7.10. Follow Up Treatment After Discharge

There are no study related limitations to the routine follow up treatment (e.g. use of orthoses, physiotherapy). The follow up treatment will be recorded in the CRF.

### 4.7.11. Informed Consent

Before any trial related action will be performed, a **written informed consent** will be obtained from each patient or the legal representative after adequate patient information; this includes the handing over of the written patient information and informed consent form that was approved by the IRB. During this procedure the investigator informs the patient extensively about all aspects of the trial especially about the fact that patients are randomly allocated to the two treatment groups with a chance of 50% to be allocated to one of each groups. The patient will have an opportunity to ask questions.

### 4.8. Study Visits

**Visit 1: Screening (< 4 weeks before Day 0)**

This visit can be performed up to 4 weeks before day 0 (day of surgery) or even at the same day of surgery as long as the patient gets sufficient time to think over the study participation after being informed by the investigator.

- During the screening visit the **ZCQ, ODI, SF-12, VAS back pain** and **VAS leg pain** of the patient will be assessed as baseline level (baseline for ZCQ patient satisfaction is assessed at the first post-operative visit at visit 3 as these questions only concern post-operative aspects). A questionnaire about **status of employment / pension** will be filled in by the patient.

- Demographic and medical history data (including weight, height, race, etc.), data about pain **management** as well as a **physical examination** will be assessed as routinely done at each center.

- It will be documented in the CRF which prior therapy had been performed for back and leg pain (epidural injection, facet injection, nerve root block).
• The **Body mass index** (BMI) will be determined by the investigator as this is one of the exclusion criteria. BMI = body weight/(body height in m)². The unit of the BMI is kg/m².

• Only if all **inclusion/exclusion criteria** are fulfilled (as far as assessable before surgery) the patient will receive a patient number by the center (randomization). In case any inclusion/exclusion criterion is not fulfilled this patient will be judged as a screening failure and will not receive a patient number (no CRF will be filled in). For screening failures only the informed consent, patient identification data and the reason for failure will be monitored by the study monitor. Screen failures will be replaced by new patients in order to achieve 300-500 treated study patients.

• **X-ray imaging before inclusion**: X-ray images necessary for inclusion must be available in anterior-posterior position as well as in lateral position and in flexion and extension and should not be older than 6 months.

  Images will be made before randomization to evaluate inclusion/exclusion criteria (e.g. exclusion of isthmic spondylolisthesis or spondylolysis). Translatory instability has to be excluded utilizing functional X-rays (≤ 3 mm). **All X-ray images are made in standing position**.

• **MRI imaging**: Necessary routine MRI (Post-Myelo-CT) is also permitted in the event that the patient already has one that is <6 months old) images must be available before randomization and should not be older than 6 months. They are obligatory for a clear definition of the medical indication (spinal stenosis) of the study patient. Further MRI imaging is not planned for this trial.

**Visit 2: Surgery**

• Randomization: During the surgery the investigator will be provided the planned randomization cohort for that patient and allocate the patient to one of the treatment groups (see Section 4.6).

• Surgery

• Hospitalization information will be collected such as duration of surgery, blood loss and number of days in hospital.

• Discharge Information: Date of discharge, neurological status, pain management, follow-up treatment. X-rays have to be performed before discharge only in group B (with implant) in anterior-posterior and lateral position.

• (Serious) Adverse Events: all (S)AEs will be recorded

• **Exclusion during the surgery:**

  In case the surgeon identifies during surgery any circumstance that contradicts to the patient's participation in the trial, the surgeon has to exclude the patient from the trial participation. Possible exclusion reasons are:
Instabilities assessed during surgery that requires stabilization by spinal fusion.

- Partial resection or resection of disc tissue.
- (S)AEs assessed during surgery that rule out the implantation of Superion® (e.g. breakage of a spinal process, local osteoporosis).

As these patients had been randomized a CRF will be filled in. The study monitor will only check the signed informed consent form and patient demographics as well as the reason of failure. The patient will be a dropout and the dropout reason will be recorded in the CRF.

Visit 3: 3 Months Follow Up (±2 weeks)

- VAS leg pain
- VAS back pain
- Questionnaires ZCQ, ODI, SF-12, patient satisfaction, status of employment / pension
- Physical examination
- Neurological status
- Pain management
- Hospitalization
- Follow up treatment
- X-ray images for both groups in all four positions
- (Serious) Adverse Events: all (S)AEs will be recorded

Visit 4: 12 Months Follow Up (±2 months)

- VAS leg pain
- VAS back pain
- Questionnaires ZCQ, ODI, SF-12, patient satisfaction, status of employment / pension
- Physical examination
- Neurological status
- Pain management
- Hospitalization
- Follow up treatment
- X-ray images for both groups in all four positions
- (Serious) Adverse Events: all (S)AEs will be recorded
Visit 5: 24 Months Follow Up (±2 months)

- VAS leg pain
- VAS back pain
- Questionnaires ZCQ, ODI, SF-12, patient satisfaction, status of employment / pension
- Physical examination
- Neurological status
- Pain management
- Hospitalization
- Follow up treatment
- X-ray images for both groups in all four positions
- CT Scan (if spinous process fracture is detected / suspected via X-ray)
- (Serious) Adverse Events: all (S)AEs will be recorded

Visit 6: 36 Months Follow Up (±4 months)

- VAS leg pain
- VAS back pain
- Questionnaires ZCQ, ODI, SF-12, patient satisfaction, status of employment / pension
- Physical examination
- Neurological status
- Pain management
- Hospitalization
- Follow up treatment
- X-ray images for both groups in all four positions
- CT Scan (if confirmation of spinous process fracture at 24 months)
- (Serious) Adverse Events: all (S)AEs will be recorded
1) A detailed physical examination will be performed at visit 1. In the following visits only a routine physical examination will be performed and changes compared to screening will be recorded. The investigator is free to perform a complete physical examination.

2) Only group B (with Superion® implant: anterior-posterior, lateral)

3) After surgery, before discharge

4) Only subjects with detected/suspected spinous process fracture via radiograph.

5) Only subjects with confirmed spinous process fracture.

<table>
<thead>
<tr>
<th>Visits</th>
<th>Screening</th>
<th>Treatment Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 2 weeks before Day 0</td>
<td>Day 0; surgery</td>
</tr>
<tr>
<td></td>
<td>Patient information and Informed consent</td>
<td>X</td>
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<tr>
<td></td>
<td>Demographics</td>
<td>X</td>
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<tr>
<td></td>
<td>Medical history</td>
<td>X</td>
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<tr>
<td></td>
<td>Pain management</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Physical examination</td>
<td>X(1)</td>
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<tr>
<td></td>
<td>Neurological status</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Inclusion/exclusion criteria</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>X-ray in standing position (AP, lateral, flexion, extension)</td>
<td>X</td>
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<tr>
<td></td>
<td>CT Scan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRI and/or Post Myelo CT (not older than 6 months)</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Diagnosis</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>VAS back pain, VAS leg pain</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>ZCQ; ODI; SF-12</td>
<td>X</td>
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<tr>
<td></td>
<td>Randomization</td>
<td>X</td>
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<tr>
<td></td>
<td>Surgery</td>
<td>X</td>
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<tr>
<td></td>
<td>Patient satisfaction questionnaire</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>(S)AEs and device related complications</td>
<td>X</td>
</tr>
</tbody>
</table>

1) A detailed physical examination will be performed at visit 1. In the following visits only a routine physical examination will be performed and changes compared to screening will be recorded. The investigator is free to perform a complete physical examination.

2) Only group B (with Superion® implant: anterior-posterior, lateral)

3) After surgery, before discharge

4) Only subjects with detected/suspected spinous process fracture via radiograph.

5) Only subjects with confirmed spinous process fracture.
4.9. Loss To Follow-Up

Loss to follow-up will be minimized by utilizing experience CRAs to actively engage the sites and motivate study staff. Additional support can be provided with documentation of anticipated follow-up windows to ensure patients are returning for visits and returning for visits in window.

4.10. Travel Cost Compensation

Every patient will receive travel cost compensation up to $100 pending IRB approval. The travel expenses will be provided to the patient by the investigator/coordinator.

4.11. Sample Storage and Shipment

There are no study related collections of blood samples or any other body fluids. If required, blood samples, etc. will be collected and processed according to the routine procedures of the centers.

4.12. Randomization

During visit 2, just before surgery the patient will be randomized to one of the two groups [group A: decompression surgery without any further stabilization by an implant (control group), group B: stabilization with the Superion® implant (treatment group)].

A computer generated random list of treatment assignments (Master Randomization List) will be created using a 1:1 ratio. Randomization will occur as close to the beginning of the treatment procedure as possible. Due to differences in the procedures, incision sizes, and operative positioning, subjects may not be masked to their treatment arm after the surgery.

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

Patients who received the wrong intervention according to the randomization scheme will be analyzed as treated.

4.13. Analysis Sets

- ITT Analysis Set:
  All randomized patients classified according to the intended treatment constitute the ITT analysis set.

- All Treated Analysis Set:
  The All Treated analysis set will be defined as all randomized patients receiving a study treatment (treatment A or treatment B) classified according to the treatment actually received. Secondary safety analysis will be performed in the All Treated analysis set. All adverse events in the All Treated analysis will be described.

- mITT Analysis Set:
  Primary effectiveness and primary safety analyses will be performed in a modified intent-to-treat (mITT) analysis which will be defined as randomized patients with an anesthesia start time classified according to treatment received (treatment A or treatment B) or treatment intended for intra-operative failures; and with no clinically significant major violation of inclusion/exclusion criteria.
• Per Protocol Analysis Set:

The Per Protocol (PP) analysis set is similar to the mITT analysis set except that patients with clinically significant protocol violations occurring after randomization may be excluded if such protocol violations are expected to threaten valid evaluation of clinical status according to protocol. Patients may also be excluded from PP analysis for important violations of inclusion/exclusion that do not rise to the level of significant major violations. Secondary effectiveness and/or safety analyses may be performed in the Per Protocol (PP) analysis set.

4.14. Subject Discontinuation

Patients which did not receive a patient number will be replaced – they will be judged as screening failures. At the end of the initial recruitment phase of 345 patients that fulfill all inclusion/exclusion criteria should be allocated to the study.

The patient is entitled to terminate the clinical investigation at any time without giving any reason and without having to expect any disadvantages by the Investigator.

Reasons for withdrawal of a patient from the clinical investigation may be:

• Insufficient cooperation of the patient (non-compliance with study procedures);
• Technical or administrative reasons (change of Investigator, move of the patient);
• Withdrawal of Informed Consent;
• Death

Pregnancy will not be a reason for discontinuation. The number of x-rays taken will be limited.

For patients who terminate the clinical investigation prematurely, a complete final examination has to be performed if the patient is still available for an examination.

For this final examination all assessments as planned for visit 5 have to be carried out.

If the patient cannot come to a final examination the Investigator should clarify the reason and time point for discontinuation/drop out by phone and document this in the source document used at the site. In case of drop outs due to an (S)AE the Adverse Event has to be documented sufficiently in the SAE form and the Investigator has to report the SAE to the sponsor within 24 hours (see section about SAE reporting).

4.15. Trial Materials

4.15.1. Description of the Device

As the Superion® implant is approved for market, the devices used for the study originate from the normal production and have to be handled according to the product brochure and manufacturer’s information.

Labeling:

As the study device (Superion® Implant) is already PMA approved, the devices used for this trial will not be labeled separately for this trial, i.e., no text like “for clinical investigation only” will be mentioned. Devices from the normal production will be used and the legal requirements for labelling PMA-approved (US) will be fulfilled.

4.15.2. Device Accountability
There will be no device shipments because of the trial. The devices routinely available at each center will be used for the study patients.

A device accountability form will therefore not be filled in. Any Superion® device used with a patient will be documented (lot no. and size) in the CRF.

4.16. Trial Documents

The following documents have to be available at the trial center:

- A signed protocol and amendment(s), if any;
- A copy of the dated and signed written approval from the IRB of the protocol, amendment(s) (if any), Informed Consent Form, and any applicable recruiting materials. This approval must clearly identify the trial by title and number;
- A statement if the IRB is compliant with ICH-GCP guidelines, the names of the current members or composition of the IRB and their position in the health-care institution or their credentials, and the working procedures of the committee;
- Regulatory authority approval;
- Signed Investigator’s agreement (modified FDA Form 1572), if applicable;
- FDA Financial Disclosure Questionnaire, if applicable;
- A copy of the Signature Authorization Log that enlists all people involved in the trial at a center;
- The curricula vitae of the Investigator, co-Investigators and other study material (if any);
- The signed Financial Agreement.

4.16.1. Case Report Form (CRF)

Electronic Case Report Forms (CRFs) are to be completed for all subjects.

All data is entered into the Electronic Clinical Data Management System by the Study Coordinator or by the patient directly (patient questionnaires).

The Investigator must verify that all data entries in the CRFs are accurate and correct. If certain information is “Not Done”, “Not Available” or “Not Applicable”, the Investigator must enter that information in the appropriate space.

All data will be reviewed for consistency and correctness with the protocol by the Data Management team at the CRO. All discrepancies requiring verification via an examination of the source documents will be sent to the study site for resolution or resolved during Monitoring visits. During monitoring visits, the Clinical Research Associate (CRA) will also review all data, evaluate for completeness and have the study coordinator enter missing information and/or resolve errors with the Investigator. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee.

An electronic audit trail will be maintained to track all changes to the database.

4.16.2. Documentation Files

The Sponsor’s Investigator file will include all relevant documents that are filed in the Investigator file and additional internal information (e.g. internal communication Sponsor-CRO). The CRO file will contain all study related documents including all internal and external communication.
All data about X-rays will be kept for at least 30 years after completion of the study.

4.16.3. Essential Documents for the Conduct of a Clinical Trial

The Investigator file will be provided to the Investigator at the Study Initiation Visit. It is required by law that the Investigator keeps this file updated and in good condition during the entire study.

The Investigator file contains the essential documents for the conduct of a clinical trial:

- Emergency contact numbers
- Patient enrolment log and screening failure log, if applicable
- Patient identification register
- Subject identification code list after unblinding (if applicable)
- Signed register of monitoring visits
- Report of an audit (if any)
- Signed protocol
- Protocol signature sheet
- Signed protocol amendment(s), or signed amendment signature sheet(s) - if applicable
- Initiation visit report
- Trial close out visit report
- Signed trial agreement(s)
- Signed financial agreement(s), if applicable (may be filed separately from Investigator file by Investigator)
- Confidentiality agreement(s)
- Physician's information (Declaration of Helsinki)
- "Statement of Investigator" (FDA/Sponsor), if applicable
- Financial disclosure form, if applicable
- Site authorization list
- Curricula vitae of the main Investigator (in English), co-Investigator
- IRB approvals covering the following documents: protocol, amendment(s), patient information(s), informed consent form(s), advertisements, etc.
- Interim or annual reports to IRB (if applicable)
- List of members and qualifications of IRB + working procedures
- Approved patient information (as distributed, i.e., all approved versions)
- Approved informed consent form, final version and all previous versions (as distributed, blank)
- Informed consent form signed by the subject
4.17. Archiving

The Investigator shall maintain the Investigator file, which contains the trial documents as specified in “Essential Documents for the Conduct of a Clinical Trial” mentioned above and as required by the applicable regulatory requirement(s).

The Investigator should take measures to prevent accidental or premature destruction of these documents.

Essential documents shall be retained for 15 years in the study site and with the Sponsor after completion of the study. Under no circumstances shall the Investigator relocate or dispose any trial documents before having obtained written approval of VertiFlex®. This also applies if the archiving period of 15 years has come to an end.

Any difficulty in storing original documents must be discussed with the Clinical Research Associate as soon as possible.

5. PERFORMANCE EVALUATION AND MEASUREMENTS

5.1. Primary Variables of Performance

The identical Month 24 CCS endpoint used in the IDE study will be used to compare PAS results to IDE study results and to update the Bayesian posterior probabilities of non-inferiority and superiority relative to IDE study control device X-STOP® (Objective 1). For Objective 2, the Month 24 CCS will be slightly modified to note that implant-related complications are applicable to the Superion® group only. This is because the decompression group receives no device.

Month 24 success for this comparison will require:

- No re-operations, revisions, removals or supplemental fixation at the index level(s)
Clinically significant improvement in outcomes compared to baseline, as determined by meeting the following for at least two of three domains of the 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 major implant or procedure-related complications
  - no device component fracture, deformation or disassembly
  - no dislodgement, migration, or deformation
  - no new or persistent worsened neurological deficit,
  - no spinous process fracture remaining unhealed at Month 24
  - no deep infection at the operative site requiring hospitalization, surgical drainage, or IV antibiotics
  - no death, or other permanent device attributed disability

- no spinal cord stimulators or rhizotomies;
- no post-operative epidural steroid injections, or nerve block procedures performed to treat spinal stenosis at the index level(s).

The Month 24 CCS for Objective 2 (comparison of Superion® to decompression surgery) will be modified to note that implant-related issues are applicable to the Superion® group only.

The Month 36 CCS will be slightly modified to account for failures occurring between 24 and 36 months and to assess changes in clinical status from baseline to month 36. However, a different approach will be used for lumbar epidural injections in order to avoid calling transient symptom management a device failure unless there is subsequent re-operation or unless patient status is compromised as reflected in an ODI improvement from baseline that is less than 15%. Therefore, for Month 36 CCS, only lumbar injections occurring within 12 months of the Month 36 visit will indicate Month 36 CCS failure. This is because a lumbar injection within 12 months of the Month 36 visit can confound the Month 36 assessment.

5.2. ZCQ

Improvement in the Zurich Claudication Questionnaire is the primary clinical status indicator among non-failures. The ZCQ is a self-reported outcome instrument to measure treatment outcomes in patients with lumbar spinal stenosis. The ZCQ quantifies severity of symptoms, physical function characteristics, and patient’s satisfaction after treatment. In order to be considered a ZCQ success, the patient must meet the following for at least two of the three domains of the 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.

5.3. Secondary Variables of Performance

Secondary evaluation criteria include:
• VertiFlex® Patient Satisfaction Survey (percent of patients scoring ≤ 2.5 on a 4-point scale)
• Oswestry Disability Index (ODI) compared to baseline at 24 and 36 months
• ODI improvement of 15 points compared to baseline at 24 and 36 months
• VAS (Low Back and Leg) compared to baseline at 24 and 36 months
• Low Back/Leg Pain VAS improvement of 20mm (on the 100 mm scale) compared to baseline after 24 and 36 months
• SF-12 generic health status compared to baseline at 24 and 36 months
• Maintenance of distraction defined by ≤ 4mm of measurable decrease in the posterior disc space height on successive radiographs obtained at 3 months and 24/36 months post-operatively
• The CCS will be modified to examine the effect narcotics use (opioids and/or opiates) has on treatment success rates. When comparing Superion® to surgical decompression, this modified Month 24/36 CCS will include:
  - No use of narcotics (opioids or opiates) at month 24/36.

5.4. Reoperations

Reoperations, revisions, removals and supplemental fixation are defined as follows:

• 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 configurations are removed with or without replacement.

• A reoperation is any surgical procedure at the involved level(s) that does not remove, modify, or add any components to the system. Note: a surgery to alleviate post-operative superficial wound problems will not be considered a treatment failure.

• A supplemental fixation is a spinal 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) at the index level(s).

5.5. Epidural Steroid Injections

Any patient receiving an epidural steroid injection at the index on or before the Month 24 is considered a CCS failure. Patients receiving an epidural steroid injection within or before their Month 36 interval will be evaluated by the CEC to determine if the injection potentially impacts clinical outcomes at Month 36.

A different approach seems advisable for the Month 36 CCS endpoint to be used in this ‘real conditions of use’ study. This is to avoid calling transient symptom management a device failure unless there is subsequent re-operation or unless patient status is compromised as reflected in an ODI improvement from baseline that is less than 15%. Therefore, for Month 36 CCS, only lumbar injections occurring within 12 months of the Month 36 visit will indicate Month 36 CCS failure. This is because a lumbar injection within 12 months of the Month 36 visit can confound the Month 36 assessment.
Note: non-steroidal injections are not considered treatment failures.

5.6. **Major Implant or Procedure-Related Complications**

In the investigational cohort: presence of a major implant-related complication is defined as:

- device component fracture, deformation or disassembly
- dislodgement, migration, or deformation
- other permanent device attributed disability

The major implant-related complications are not applicable to the decompression alone groups since no implant is present.

The following may be attributable to the implant or the procedures:

- new or persistent worsened neurological deficit,
- Fracture of the vertebral anatomy (e.g., spinous process fracture) remaining unhealed at Month 24
- deep infection at the operative site requiring hospitalization, surgical drainage, or IV antibiotics
- death

5.7. **ODI**

ODI will be evaluated using the following criteria:

- ODI score compared to baseline at 24 and 36 months.
- Change in ODI after 24 and 36 months compared to baseline as a continuous variable in terms of achieving a 15 point improvement.

5.8. **VAS**

VAS will be evaluated using the following criteria:

- VAS back and leg pain score compared to baseline at 24 and 36 months.
- Change in Visual Analog Scale (VAS) for low back pain (on the 100 mm scale) after 24 and 36 months compared to baseline as a continuous variable and in terms of achieving a 20 point improvement.
- Change in right leg pain, left leg pain, and worst leg pain using a Visual Analog Scale (VAS) 100 mm scale after 24 and 36 months compared to baseline as a continuous variable and in terms of achieving a 20 point improvement.

5.9. **SF-12**

SF-12 will be evaluated using the following criteria:

- SF-12 score compared to baseline at 24 and 36 months.

5.10. **Distraction**

Maintenence of distraction will be evaluated with distraction defined by ≤ 4mm of measurable decrease in the posterior disc space height on successive radiographs obtained at 3 months and 24/36 month post-operatively.
5.11. Migration
Assessment of significant migration of the implant or complete expulsion (significant is defined > 5 mm) will be assessed from X-ray images (point of reference is the tip of the U-portion implant identified on the corresponding X-ray image). Baseline images will be made before discharge of the patient. Further images will be made after 3 months and after 24 months, and annually thereafter. All X-ray images from all centers will be evaluated centrally by two independent, blinded radiologists. In the case of a disagreement, a third independent, blinded radiologist will adjudicate the findings.

5.12. Spinous Process Fracture
Spinous process fractures will be assessed from X-ray. All X-rays from all centers will be evaluated centrally by two independent, blinded radiologists. In the case of a disagreement, a third independent, blinded radiologist will adjudicate the findings. Presence of Spinous process fractures will not be considered a treatment failure.

CT imaging will be captured at 24 months for subjects with a confirmed or suspected spinous process fracture and at 36 months for subjects with a confirmed spinous process fracture. CT imaging will utilize lateral views to observe spinous process fractures. CT imaging will be used to investigate the incidence of spinous process fractures in both Superion® and decompression patients.

5.13. Neurological Status
Neurological status will be assessed before and after surgery. Further assessments will be made during every patient visit.

5.14. Other Endpoints
Other endpoints will include length of hospital stay, operative time, estimated blood loss, worst status and time to return to work or normal activities of daily living (ADL), type of anesthesia, and rehabilitation utilization (concomitant treatments).

6. STUDY CRITERIA FOR SAFETY
Adverse events and SAEs and implant and procedure-related complications (e.g., breaking of implants) will be documented. Specific AEs will be summarized according to incidence (per patient) and counts of AE overtime. Safety endpoints will also include:

- Assessment of revisions and additional stabilizations
- Assessment of epidurals
- Assessment of narcotics usage

All AEs as well as SAEs (related and not related, including incidents) will be mentioned in the final report of the study. The same will be done for device related complications.

6.1. Adverse Events
At each visit all adverse events, whether voluntarily reported by the patient or observed by the investigators, will be recorded in the appropriate CRF. It has to be stated at least:

- Description of sign or symptom,
• Date of start and date of end of the adverse event,
• Maximum intensity (mild, moderate, severe),
• Frequency (once/intermitting/continuous),
• Action taken
• Relation to study device or surgery (definite, probable, possible, unlikely, unclear),
• Subject outcome

An AE is any undesirable clinical occurrence in a subject whether or not it is related to the Superion® device or the surgery. Any condition at baseline that is recorded as a preexisting condition is not an AE unless it worsens in intensity or duration. The collection of AEs will begin in the operating room when the incision(s) is made that starts the implant procedure. All AEs that occur through completion of the final follow-up visit, whether observed by the investigator or by the subject, and whether or not thought to be device related, will be reported in detail on the appropriate eCRF and followed to resolution.

The description of the AE will include the date and time of onset, severity, causal relationship to the investigational device, or procedure, the results of any diagnostic procedures or laboratory tests, any treatment required, and the outcome of the event. In addition to the AE categories listed below, AEs will be listed as “Early,” within 30 days of surgery, or “Late,” more than 30 days after surgery. The investigator will follow each subject who experiences an AE until the event resolves. In the unusual circumstance that an AE has not resolved by the time of the subject’s completion of the study, an explanation will be entered on the appropriate CRF.

6.2. Assessment of Severity (AE/SAE):
• Mild: The AE is transient and easily tolerated by the subject.
• Moderate: The AE causes the subject discomfort and interrupts the subject’s normal activities.
• Severe: The AE causes considerable interference with the subject’s usual activities and may be incapacitating or life-threatening.

NOTE: The term “severe” is a measure of intensity while the term “serious” is assigned based on the regulatory criteria discussed below.

Serious Adverse Event (SAE):
• Led to death;
• Resulted in life threatening illness or injury;
• Resulted in subject hospitalization or prolongation or existing hospitalization;
• Resulted in subject disability or permanent damage or required intervention to prevent permanent impairment / damage.

All Serious Adverse Events, whether related to the device or not, must be reported to VertiFlex® or its representative within 24 hours of learning of the occurrence.

6.3. Relationship to Implant or Procedure
The investigator will evaluate the relationship of the adverse event to the Superion® device and the procedure according to the following definitions. The term “implant-related,” as it pertains to adverse
events, means that the event was or may have been attributable to a medical device, or that a device was or may have been a factor in an event, including those occurring as a result of malfunction, poor manufacture, inadequate labeling, or improper design. The same is true for “procedure-related”.

- **Definite**: The adverse event is clearly related to the investigational agent(s) or research intervention: the adverse event has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known pattern of response, or is otherwise logically related to the investigational product, and no alternative cause is present.

- **Probable**: The adverse event is likely related to the investigational agent(s) or intervention: the adverse event has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known or suspected pattern of response, or is otherwise logically related to the investigational product, but an alternative cause may be present.

- **Possible**: The adverse event may be related to the investigational agent(s) or intervention: the adverse event has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a suspected pattern of response, or is otherwise logically related to the investigational product, but an alternative cause is present.

- **Unlikely**: The adverse event is doubtfully related to the investigational agent(s) or intervention: the adverse event has a temporal or other relationship to the administration of the investigational agent(s) or research intervention, but follows no known or suspected pattern of response, and an alternative cause is present.

- **Not Related**: The adverse event is clearly NOT related to the investigational agent(s) or intervention: the adverse event has no temporal or other relationship to the administration of the investigational product or research intervention, follows no known or suspected pattern of response, and an alternative cause is present.

### 6.4. Unanticipated Adverse Device Effect (UADE)

A UADE is defined as “any serious adverse effect on health or safety or 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 investigational plan or application, or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of subject.” AEs that might reasonably occur because of placement or attempted placement of the product or during follow-up were identified through a risk analysis. The risk analysis lists clinical risks to the subject associated with study participation.

If VertiFlex® determines that a UADE of a device presents an unreasonable risk to study subjects, VertiFlex® / physician will:

- Terminate the investigation, or the parts of the investigation presenting that risk, within 5 working days after VertiFlex® makes an “unreasonable risk” determination or within 15 working days after VertiFlex® first received notice of the UADE;

- Immediately investigate and evaluate the adverse effect (21 C.F.R. § 812.46(b)(1) and (2));

- Report the results of the investigation to all reviewing IRBs and to all participating investigators within 10 working days after VertiFlex® first receives notice of the UADE (21 C.F.R. § 812.150(b)(1));

- Resume the study, if appropriate, as specified by the IRB; and
6.5. Event Reporting

The FDA’s medical device reporting requirements regulations state the following requirements for event reporting:

MDR Mandatory Reporting Requirements:

Manufacturers: are required to report to FDA when they learn one of their devices may have caused or contributed to a death or serious injury. Manufacturers must also report to FDA when they become aware that one of their devices has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction happened again. Deaths, serious injuries and malfunctions must be reported to FDA within 30 calendar days from the manufacturer becoming aware of an event. Use FDA form 3500A

Events that require remedial action to prevent an unreasonable risk of substantial harm to the public health and other types of events within 5 work days from becoming aware of an event. Use FDA Form 3500A

User Facilities: User Facilities (e.g., hospitals, nursing homes) are required to report a suspected medical device-related death to both the FDA and the manufacturer. User facilities should report a medical device-related serious injury only to the manufacturer. If the medical device manufacturer is unknown, the user facility should report the serious injury to FDA. A user facility is not required by the MDR regulation to report a malfunction, but can use the voluntary MedWatch program to advise FDA of problems with medical devices. Health-care professionals within a user-facility should familiarize themselves with their institution’s procedures for reporting adverse events to the FDA. See "Medical Device Reporting for User Facilities1", a guidance document issued by FDA.

In this trial all SAEs reported by the investigators will be evaluated but only MDRs will be reported to the FDA by the sponsor.

6.6. Reporting/Documentation of Adverse Events

6.6.1. Adverse Events

New AEs will only be documented for each patient until the last study related patient visit.

The investigator will assess and record any AE in detail on the adverse event form included in the case report forms (CRFs).

Investigators will actively check for and report potential implant-related and procedure-related Adverse Events for all study patients in the time period between the first device application/surgical procedure and the end of the clinical phase of the trial at the site.

Investigators will also report to the CRA all serious Adverse Events that are related to the use of the device (see Section 6.6.2 for contact information). The CRA will forward this report to the sponsor. The sponsor will then make an evaluation if he agrees that the unexpected and serious AE was in fact implant-related. It is the reporting responsibility of the Investigator to notify the responsible IRB of Adverse Events which are classified by the sponsor as serious and related, unless otherwise required and documented by the IRB.
All AEs must be recorded and followed up until the event is either resolved or adequately explained, even after the patient has completed the clinical investigation.

6.6.2. Serious Adverse Events

In case of Serious Adverse Events, the Investigator has to notify the CRO (or the monitor) as soon as possible, but at least within one working day after becoming known to the Investigator.

New SAEs will only be documented for each patient until the last study related patient visit.

MDRs have to be reported within 30 working days. In case of acute risk the incident has to be reported immediately.

In case of an SAE, the investigator must in addition to filling out the adverse event form in the CRF complete a special form “Serious Adverse Event Form”.

**SAE contact numbers:**

VertiFlex: VertiFlex®
1351 Calle Avanzado, Suite 100
San Clemente, CA 92673
Phone: (949) 940-1400
Fax: (949) 940-1450

CRO: TBD

The first report of a Serious Adverse Event may be made by telephone or facsimile (FAX). The Investigator must provide the minimal information: i.e., trial number, subject's initials and date of birth, period of application, nature of the Adverse Event and Investigator's attribution.

This report of a Serious Adverse Event by telephone must always be confirmed by a written, more detailed report (or the completely filled out SAE report form). For this the Investigator will use the SAE form in his/her Investigator file, or the Sponsor contact person will provide the Investigator with the Serious Adverse Event Form, to be completed and signed by him/her.

7. STATISTICAL ANALYSIS

7.1. Objectives

The first objective of this “real conditions of use study” is to compare Superion® device performance in the PAS population to Superion® device performance observed in the IDE study. Patients will be enrolled at sites that were not involved in the IDE study. The likelihood of PAS patients achieving Month 24 CCS will be compared to the same likelihood as observed in the IDE study population. In the IDE study, 95 of 183 patients (51.9%, 95% Bayesian credible interval 44.6% to 58.8%) achieved Month 24 CCS.

Objective 2 is to test the hypothesis that Superion® is superior to surgical decompression in terms of the same Month 24 composite clinical success (CCS) used in the IDE Study. The primary superiority test will involve determining the Bayesian posterior probability that the likelihood of achieving Month 24 CCS is larger for patients implanted with the Superion® device compared to patients undergoing decompression. It is hypothesized that Superion® will be superior to decompression in terms of the proportion patients expected to achieve Month 24 CCS. Symbolically this is Ho:
**CCS_{Superion} – CCS_{decomp} ≤ 0 vs Ha: CCS_{Superion} – CCS_{decomp} > 0.** Ho will be rejected in favor of Ha if the Bayesian posterior probability of superiority exceeds the Objective 2 posterior probability study success criterion.

The third objective is to test the hypothesis that Superion® is superior to surgical decompression in terms of Month 36 composite clinical success (CCS). The Month 36 endpoint will be slightly modified so that only epidural lumbar injections occurring within 12 months of the Month 36 endpoint will be counted as a Month 36 CCS failure.

### 7.1.1. Superion® PAS vs. Superion® IDE

This is a post approval, real conditions of use study, designed to evaluated device performance in the hands of ‘non-IDE’ surgeons. Therefore, device performance in the real conditions of use population must be evaluated with reference to the IDE device performance in some sense or another. In principle, IDE results should be the very best way to justify a Bayesian informative prior for a post approval study. But, this presents a problem since the goal of the study is to compare PAS results to IDE results. To address this problem, a frequentist approach will be used for Objective 1 only. The IDE results were still used to justify formulation of an appropriate null and alternative. The key results from the IDE study are that 95 of 185 (51.9%) patients implanted with Superionex® achieve the primary Month 24 composite clinical success criterion. The 95% Bayesian credible interval is 44.6% to 58.8%. This implies that the Bayesian posterior probability that the true Month 24 CCS is larger than 58.8% is equal to 0.975. The lower bound of this credible interval justifies the following frequentist hypothesis setup. We assume the same non-inferiority margin of 0.10 is used as previously specified and again note that in the IDE sample, the proportion of patients achieving Month 24 CCS was 0.519. Therefore, Objective 1 will be met by testing the following hypotheses using a chi-square test with a 1-sided alpha=0.05.

\[
\text{Ho: Month 24 CCS (real conditions of use) } \leq 0.519 - 0.10 = 0.419 \text{ (inferior)} \\
\text{Ha: Month 24 CCS (real conditions of use) } > 0.519 - 0.10 = 0.419 \text{ (not inferior)}
\]

If there is no performance degradation in the hands of non-IDE surgeons, then the Bayesian probability is 0.975 that the true Month 24 CCS rate is at least as large 0.446. This provides substantial confidence at the design stage that a finding of non-inferiority will not be due to a type 1 error and thus justifies the use of a 1-sided alpha=0.05.

### 7.1.2. Superion® vs Decompression Alone at Month 24

### 7.1.3. Superion® vs Decompression Alone at Month 36
7.2. Development of Bayesian Prior Distributions

7.3. Predictive Probability Sample Size Re-Estimation

7.4. Analysis of Secondary Effectiveness Endpoints

7.5. Analysis of Safety

7.5.1. Adverse Events

All adverse events (AE) will be listed according to ICH guidelines. Additional tables presenting a survey of the incidence rates by treatment groups will be drawn up for the following classifications and items:

- Premature Termination, Serious Adverse Events and Causal Relationship
- Separate Presentation of Serious Adverse Events

7.5.2. Review Committee

Since this trial will be performed as an open trial, a blinded review of data is not possible. Therefore, a blinded review protocol will not be written.

The assignments to the safety set and to the full analysis set are pre-specified in this protocol because of the open trial character of this study. Only a decision concerning the per-protocol population for the supporting analyses will be made by the committee.

7.6. Software for Data Analyses

Validated clinical data will be provided by the data management CRO to the statistical CRO. Further data processing, constructing of indices, evaluation of theoretical and expected due status, statistical screening, etc. will be conducted using SAS version 9.2 or higher. Statistical procedures, which are not implemented in the standard SAS modules BASE, STAT and GRAPH, will be implemented using the SAS language.

7.7. Missing Data

We will use Bayesian multiple imputation when determining posterior probabilities and this technique will be used to address missing values for the Bayesian analyses in support of Objectives 2 and 3. For Objective 1, a tipping point sensitivity analysis will be performed in order to assess the impact of missing data on the results of the chi-square test. P-values for Object 1 non-inferiority will be recomputed for all possible combinations of Month 24 CCS successes and failures in the Superion® real conditions of use analysis set. The sensitivity of the primary Objective 1 statistical conclusion to assumptions concerning missing data will be fully described. For Objective 2 and 3, although the Bayesian multiple imputation will be considered primary, corresponding two-group tipping point analyses will performed with results graphically represented on an x-y axis grid and the percentage of total combinations in which the statistical conclusion changes will be tallied.

For Objectives 2 and 3, a validated Bayesian multiple imputation (MI) algorithm will be used to impute the expected status at month 24 for patients who have not completed follow-up and have not been denoted “terminal” failures. Terminal failures are patients that experience an event that makes them a Month 24 CCS failure at the time of the event, for example a reoperation at the index level. The imputation algorithm uses a beta-binomial distribution to model the transition probabilities from the outcome at month j to that at month 24, separately for the investigational and control device. Specifically, the probability of a success for a subject in treatment group t (1= Superion® following surgical decompression, 2=surgical decompression

...
alone), with last follow-up value \( j \) (baseline, 3, 6, 12, or 18 months) and last follow-up value \( r \) (1=failure, 2=success) can be described using a beta distribution: \( \Pi_{t,j,r} \sim \beta( a_{t,j,r} + S_{t,j,r}, b_{t,j,r} + F_{t,j,r} ) \), where the probability of success is denoted \( \Pi_{t,j,r} \), \( S_{t,j,r} \) represents the number of 24 month successes and \( F_{t,j,r} \) the number of 24 month failures on treatment \( t \) that had follow-up status \( r \) at follow-up time \( j \). Finally, \( a_{t,j,r} \) and \( b_{t,j,r} \) represent the prior distributions used to inform the imputation. In the determination of final posterior probabilities, \( a_{t,j,r} \) and \( b_{t,j,r} \) will be set to 1 and 1 implying a uniform prior from 0 to 1. When applying multiple imputation to the computation of Bayesian predictive probabilities for use in sample size re-estimation, mildly informative priors based on data relevant to the Sponsor will be employed. These priors will be specified in the forthcoming iSAP. Whether the prior is informative or non-informative, it will be updated using the results from patients already evaluable for Month 24 CCS.

To impute the subject specific outcomes at month 24, a value \((\pi_i)\) is chosen randomly from the specific beta distribution, and success (=1) or failure (=0) is chosen randomly from a binomial distribution with \( n=1 \) and \( p=\pi_i \). This process is applied to all patients missing data at month 24. After all patients have been imputed, the total number of successes \((S)\) and failures \((F)\) at month 24 are calculated. The probability of treatment success is then defined using the beta distribution with non-informative prior \((a=1, b=1)\), i.e. \( \beta(1 + S, 1 + F) \), separately for the investigational and control devices. Once these beta distributions are defined, the final posterior distribution is determined by calculating \( \pi_{\text{Superion}} - \pi_{\text{decompression}} \) from repeated random draws from the respective investigational and control beta-distributions. The posterior probability of superiority is then calculated as the number of simulations in which \( \pi_{\text{Superion}} > \pi_{\text{decompression}} \). An analogous approach will be used to address missing data for the Objective 3, Month 36 comparison. In this way, patients with missing endpoint data are included in the analyses with multiple imputations informed by each patient’s most recent endpoint status.

7.8. Statistical Analysis Plan

Additional details, including summaries of Bayesian simulations will be provided in a separate Statistical Analysis Plan (SAP).

8. DATA MANAGEMENT

8.1. Description of Procedures

All data in this study will be entered into an Electronic Data Collection System managed by the CRO for this study. Once data on the eCRFs are considered complete (no missing fields) and accurate via monitoring and queries (see Study Management), and have been reviewed by the investigator, data will be reviewed by a data management contractor. The unique study database will be maintained and updated throughout the course of the study following predefined methodologies. This official database will serve as a reference for all data inquiries.

8.2. Data Cleaning

In the scope of the data management the data will be checked for completeness and plausibility. Open questions and missing values will be clarified using Data Correction Forms. Furthermore electronic cleaning procedures will be applied to further identify and resolve data inconsistencies. The data manager will check all discrepancies and will initiate the printout of the corresponding DCFs (queries). These forms have to be answered and signed by the Investigator.
After the data cleaning has been finished, the data will be regarded as "clean" if they show no conspicuous features with respect to criteria coordinated with the Sponsor or if all still remaining conspicuous facts can be explained.

9. **ETHICAL AND LEGAL ASPECTS**

9.1. **Institutional Review Board (IRB)**

This trial can only be undertaken after full approval has been obtained through the IRB. The approval(s) must cover the protocol and addenda, if applicable, as well as the current Patient Information and Informed Consent Form as well as the product brochure and manufacturer information (if applicable).

During the trial the following documents will be sent to the IEC/IRB for their review:

- Changes to the product brochure and manufacturer information
- Reports of all Adverse Events that are rated serious and associated with the investigational device.
- All protocol amendments and revised Patient Information and Informed Consent Form (if any).

For protocol amendments, which increase subject risk, the amendment and applicable Patient Information and Informed Consent Form revisions must promptly be submitted to the IEC/IRB for review and approval prior to implementation of the change(s).

Reports on, and reviews of the trial and its progress will be submitted to the IEC/IRB by the Investigator at intervals stipulated in their guidelines.

At the end of the trial, the Investigator will notify the IEC/IRB about the trial completion.

9.2. **Good Clinical Practice**

This trial will be conducted in accordance with the current ICH-GCP-guidelines as specified for medical devices in ISO 14155.

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

9.3. **Informed Consent Form**

Prior to entry in the trial, the investigator must explain to potential subjects or their legal representatives the trial and the implications of participation. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not impact on the care the subject will receive for the treatment of his/her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that competent authorities may access their records and authorized Sponsor’s persons without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF) the subject or legally acceptable representative is authorizing such access.
The subject or legally acceptable representative will be given sufficient time to read the informed consent form and to ask additional questions. After this explanation and before entry to the trial, consent should be appropriately recorded by means of either the subject's or his/her legal representative's dated signature or the signature of an independent witness who certifies the subject's consent in writing. After having obtained the consent, a copy of the Informed Consent must be given to the subject.

In case the subject or legally acceptable representative is unable to read, an impartial witness must attest the written informed consent.

Subjects who are unable to comprehend the information provided can only be enrolled after obtaining written consent of a legally acceptable representative.

9.4. Liability and Insurance

The sponsor has product liability coverage. Because the Superion® device is a commercially available implant, this liability coverage is sufficient.

9.5. Acknowledgement/Approval of the Protocol

The Superion® device is already PMA approved. Due to the additional investigations for patients, this trial has to be submitted to the FDA for approval.

9.6. Financial Disclosure

All the involved persons (main investigators, co-investigators, study staff involved) have to sign an Investigator Financial Disclosure Questionnaire and declare that they work strictly according these declarations.

9.7. Confidentiality

All the involved main investigators have to confirm that they handle the information which is available in the handed over documents (Protocol, etc.) strictly in confidence.

10. ADMINISTRATIVE PROCEDURES

10.1. Responsibility of the Sponsor

The Sponsor will ensure that the Investigator is:

- An appropriately qualified practitioner legally entitled to practice.
- Trained and experienced in the field of application of the device under consideration.
- Familiar with the background to - and the requirements of - the clinical investigation.

The Sponsor:

- Is in charge of the organization and the financing of the clinical trial. The mandate of any CRO within the trial organization is clearly defined by a separate contract. The overall responsibility for the trial remains with the Sponsor.
- Is responsible to contract a product liability insurance accordance with the legal requirements.
• Has to safeguard that the trial is not started before an approval of the responsible ethical committees are available.

• Will safeguard that appropriate information and/or training is given to the clinical Investigators in the use of the device in accordance with the Clinical Investigation Plan.

• Will judge (together with the Investigator) all Serious Adverse Events without delay and take all necessary steps to protect the subjects taking part in the clinical investigation.

• Is responsible that the regulatory authorities will be notified of incidents in accordance with the legal requirements (MDRs).

• Is in charge of a continuously evaluation and documentation of all SAEs and other safety relevant information. If necessary, interventions for the safety of the study patients have to be arranged.

• Is responsible for the quality of the devices tested. This covers production, packaging, labeling, testing, release and documentation of all investigated devices.

• Reserves the right to demand the exclusion of a patient from the clinical investigation in the case of severe protocol deviations or violations.

• Authorizes CRO to exclude Investigators from the clinical investigation because of severe protocol violations or because of fraud and misconduct.

• Is also entitled to terminate the clinical investigation prematurely due to continued protocol violations or because of technical or other shortcomings. If this should become necessary the Sponsor and the Investigator will wind up the proceedings after consideration and consultation, taking into account the protection of the patients’ interests.

• Will arrange that remuneration agreements between Sponsor and Investigators will be laid down in separate contracts.

10.2. Responsibility and Qualification of the Investigator

• The Investigator has to make themselves thoroughly familiar with the properties of the investigational device, which is described in the product brochure and manufacturer information.

• The investigators ensures that there is sufficient time to carry out the clinical investigation, that adequate staffing and facilities are available for the complete duration of the clinical investigation, and that the planned number of patients can be recruited within the proposed period of time.

• The investigator submits the Sponsor a current curriculum vitae for documentation purposes or submission to an IRB.

• The investigator confirms in writing that he has read and understood the protocol, that he will work in compliance with the protocol, Good Clinical Practice and the regulatory requirements, that he will accept the function of the CRA and the inspections, that he is independent of the Sponsor, and that he will come to an agreement with the Sponsor about publication.
• Together with the administration (in case the study site is based in a hospital) the investigator signs a contract with the Sponsor, which specified the duties and rights and his remuneration. Also, a signed a financial disclosure questionnaire is required.

• The investigator fully informs all the staff who is involved in carrying out the clinical investigation or looking after the patients about all relevant aspects of the trial. It must be documented in writing if clinical investigation tasks are delegated.

• The investigator will explain all aspects of the clinical investigation to the patient in a comprehensible manner, as mentioned in the written Patient Information, and will inform the patient as soon as possible of any new particulars that could influence the patient's willingness to participate in the clinical investigation. The Investigator has to confirm that he has informed the patient in this way with his signature on the Informed Consent Form.

• The investigator will give the patient ample opportunity to ask questions, and will allow the patient sufficient time to reach a decision regarding participation. The Investigator will give the participant the written Patient Information and a copy of the signed and dated written Informed Consent Form.

• He collects all data correctly and completely, records them in an appropriate source document transfers the necessary data to the CRFs and signs the CRFs.

• The investigator informs the Sponsor and the CRO promptly if a Serious Adverse Event occurs.

• Before trial start the Investigator will define all source documents that are used in this trial.

• The investigator must keep a confidential patient list showing the patient's name and date of birth and the patient's number, so that an unambiguous identification of each individual patient is possible.

• The trial participation of any study patient will be mentioned in the corresponding medical files for documentation and information of other physicians who are not involved in the trial but may take care of the patient.

• The Investigator is responsible for ensuring that every patient can be identified by means of the patient list for 15 years after completion or termination of the clinical investigation. The patient list and other source data must be kept for at least 15 years.

10.3. Responsibility and Qualification of the CRO

The CRO will handle study preparation, coordination, monitoring, data management and evaluation according to the contract with the Sponsor.

10.3.1. Recruitment of Centers

The recruitment of centers will be conducted by the study sponsor. Academic opinion leaders and community spine centers will be contacted. A pre-qualification visit will be conducted, solely to evaluate the potential sites’ ability to recruit the required patient population and the presence of adequate staffing to fulfill all required study-related tasks. The sponsor will document outcome of a successful pre-qualification visits in a memo to the CRO noting the site visited with contact information, that it has the capacity to perform the activities and there is mutual interest in participation. This will be done until 15 sites are recruited. Following identification of a study site, the CRO will then commence all ongoing study related activities for the
duration of the trial such qualification and initiation visits, IRB submissions and annual renewals, protocol training, periodic monitoring visits, data cleaning and final study visit among other tasks. Note that surgical training on the study device which will be carried out by the study sponsor, and contract negotiations will be done with active participation of the sponsor.

10.3.2. Study Timeline

Start of Site Recruitment: January 2015
Planned End of Site Recruitment: December 2016
Completion of IRB Approvals: June 2016
Planned Start of Patient Enrollment: November 2015
Planned End of Patient Enrollment: October 2016
Planned End of Clinical Phases: Month 24: January 2019
                                      Month 36: January 2020
Planned Draft Interim Report: July 2019
Planned Draft Final Report: July 2020

It is anticipated that one to two sites will obtain IRB approval per month.

10.3.3. Assessment of Clinical Study Sites

Additional data on each of the clinical study sites will be collected to assess the representativeness and generalizability of the study results. This data includes the size of the participating clinical center (number of beds), whether or not the hospital is a teaching hospital, and the geographic location of the institution (e.g., urban, suburban, or rural).

10.3.4. Notification of the Clinical Study

Following the protocol approval in the United States, the investigation will be listed on www.clinicaltrials.gov.

10.3.5. Study Management and Monitoring

An experienced CRA(s) will be available to advise the Investigator during the clinical investigation and to perform on site monitoring.

The CRA shall check and confirm that:

- The clinical Investigator(s) is (are) informed of the investigational status of the device and the requirements necessary to verify the performance of the device;
- The compliance with the Clinical Investigation Plan is maintained by periodic communications;
- Any deviation from the protocol is discussed with the clinical Investigator(s) and reported to and agreed with the Sponsor;
• Sufficient suitable staff and facilities are available at any trial site at any time to conduct the clinical investigation effectively and guarantee the safety of the study patients;
• All essential documents and contracts are signed by the appropriate persons;
• Any Investigator meets the patient recruitment targets or not;
• SAEs are recorded reported to the Sponsor;
• The device is being used according to the documented instructions, and if modifications appear to be needed, either to the device or to the Clinical Investigation Plan, this is reported to the Sponsor;
• The trial documentation file is updated;
• An adequate supply of the device is maintained at the clinical investigation site;
• A correctly filled in Informed Consent has been obtained of each patient before any trial related action has been performed;
• Withdrawal and/or non-compliance by the subject is being documented;
• The data in the case report form conforms with that in the source documents;
• Any reason for the termination of the clinical investigation has been documented.

The CRA must handle the patients’ personal medical data confidentially, to which he/she has access to during inspection of inspecting the medical records and other source data.

The relevant monitoring guidelines must to be followed.

10.3.6. Pre-Study Visit

During the Pre Study Visit Project Manager or Medical Director will verify the qualification of all involved persons whether according to their ability to conduct this trial.

Therefore the following points need to be verified:

• Does the Investigator have the possibility to recruit the amount of requested subjects according to the protocol?
• Are the trial-involved persons trained enough to cope with the device according to the manufactures guidelines?
• Are the trial-involved persons trained enough concerning the content of the protocol?
• Has the main-Investigator sufficient experience in conducting an international clinical trial?
• Are the trial-involved persons willing to work in compliance with the protocol?

10.3.7. Study Initiation Visit

During the Study Initiation Visit it is the responsibility of the CRA to secure that the following documents are present in the trial documentation file:

• Written FDA approval,
• Written IRB approval,
• Members of the IRB and qualifications,
• Signed trial agreement(s),
• Signed financial agreement(s),
• Signed Clinical Investigation Plan,
• Signed Amendment(s), if applicable,
• Confidentiality Agreement(s), if applicable,
• "Statement of Investigator" (FDA/Sponsor), if applicable,
• Financial Disclosure,
• Signature Authorization Log,
• Curricula vitae of the main Investigator, co-Investigator and study staff,
• Written Informed Consent Form,
• Patient information sheet.

A Study Initiation Visit Report will be provided to the Investigator as a follow up to the Trial Initiation meeting.

During the initiation visit it must be ensured that the main investigator, co-investigator and all study staff are sufficiently trained in correct conducting the trial in accordance to the Clinical Investigation Plan GCPs. Furthermore, the trial documentation file (Investigator file) and the CRF should be reviewed with the site.

10.3.8. Routine Monitoring Visits

The Clinical Research Associate (CRA) will perform all Monitoring Visits. To this purpose he/she has to check the points mentioned under “Study Management and Monitoring” and prepare a formal Monitoring Visit Report.

The monitoring frequency will be one visit between 4 and 6 weeks. The frequency of monitoring will depend on the recruitment status of each center. In order to avoid monitoring backlog the frequency might be increased.

10.3.9. Study Termination Visit

During the study termination visit all monitoring activities in the study center have to be finalized. The study file of the Investigator has to be checked and prepared for archiving, final questions have to be solved, study related devices and materials have to be collected, and final study-related documents have to be obtained. Therefore, the CRA will perform the following main activities:

• Resolve all outstanding issues,
• Verify that the Subject Identification Register is complete and filed in the Investigator file (Investigator file),
• Verify that all Informed Consent Forms and the updated subject log are completed and filed in the Investigator file.
• Ensure that all devices supplies are returned,
• Ensure that all randomization codes are returned, if applicable,
• Determine if equipment provided for the trial will be left at the investigational site, returned, or transferred elsewhere,
• Arrange the return/disposition of other unused trial supplies, e.g. unused laboratory materials,
• Ensure that any follow-up information on Adverse Events is obtained and has been recorded appropriately,
• Ensure that any documents maintained separately from the Investigator file during the trial are filed in the Investigator file
• Review the Investigator file and ensure that it is complete, amend if necessary,
• Ensure that all forms are completed correctly and collect copies according to the filing instructions,
• Ensure that all remaining CRFs, other data collection tools, and Data Correction Forms (DCF) are completed and collected,
• Verify that all Investigator copies of completed CRFs, other data collection tools, and DCFs are together and prepared for storage,
• Obtain completed Investigator Financial Disclosure Forms from the Investigator and the co-Investigator(s),
• Prepare and sign-off the Site Closure Report.

11. TRIAL CLOSURE CONSIDERATIONS

The decision to close an investigational site upon trial completion will be made by the Project Manager or the Sponsor after intense discussion with the CRA. The Investigator must be informed by the CRA or the Project Manager about the considerations made to close his site. He has to be given the opportunity to comment on the arguments presented by the Sponsor in order to avoid the closure of the site.

If the Sponsor still wants to close the site, the site closure visit should be scheduled soon after completion of source document verification of the last case report form (CRF) and after the last queries have been solved. The Investigator should be present. The site should not be closed before the data cleaning process has been finalized and no further queries are expected.

An investigational site is considered ‘closed’ when all required documents and trial supplies have been collected and a site close out visit has been performed. Site closure may also be initiated at any time by the Investigator, the IEC/IRB responsible for the investigational site, or the regulatory authorities.

The Sponsor reserves the right to close the investigational site or terminate the trial at any time if certain circumstances apply. Reasons for the closure of an investigational site or termination of a trial by the Sponsor may include:
• Successful completion of the trial at the center;
• The required number of subjects for the trial or multicenter-wide have been recruited;
• Failure of the Investigator to comply with the protocol or GCP guidelines;
• Safety concerns;
• Sufficient data suggesting lack of performance;
• Inadequate recruitment of subjects by the Investigator.

The reasons for premature site closure must be documented in writing.

12. DOCUMENTATION AND USE OF STUDY FINDINGS

All study related findings will be reported in comprehensive integrated study report in accordance with the ICH-Guidelines. This includes any deviations from the planned procedures if not already mentioned in an amendment to this CIP.

12.1. Use of Study Findings: Reports and Publications

Data generated from the conduct of this study will be used to support Post-Approval requirements mandated by FDA. Interim reports of study data and outcomes will be provided annually (FDA annual reporting process) with an interim report submitted 3-6 months following 24 month visit completion and final report provided within 3-6 months of study conclusion (36 month visit completion).

The study results are used for marketing reasons and for the generation of medical knowledge. The Sponsor reserves the right to use the study findings for international registration purposes.

Publication of the results of the study will follow VertiFlex® Publication and Presentation Policy. Directly after the last patient has completed the clinical investigation data cleaning will be finalized, the data base lock will be performed and arrangements will be made to prepare a final report (including a statistical report) which complies with the requirements GCP.

The Sponsor and the Principal Investigator as well as all other Investigators must approve the receipt of the final report by signature. The Investigator is under obligation to handle all clinical investigation data confidentially. Publication of clinical investigation data can take place by mutual agreement of Sponsor and Investigator. The publication of data from medical investigations in reputable scientific journals and presentation of data at congresses and conferences is basically approved. Before publication, the Sponsor has to be given sufficient time to check the manuscript (as laid down in the financial contract with the Investigator).

Legitimate interests of the Sponsor will be taken into consideration, like, for example, getting optimal patent protection/coverage, coordinating submissions to the health authorities, coordinating the clinical investigation with other investigations taking place in the same area, or protection of confidential data and information. Planned publications have to be presented to the Sponsor. Legitimate objections can be raised within 6 weeks and should be taken into consideration by the Investigator. Before any publication a mutual consent between Sponsor and Investigator should be obtained.

13. DATA QUALITY ASSURANCE (AUDITING)

Throughout every part of the clinical investigation the quality management system of CRO will apply. The protocol, CRFs, monitoring, data input, evaluation and the clinical investigation report will be audited by CRO as laid down in the contract/accepted cost estimate between the CRO and the sponsor. The SOPs of CRO are taking into consideration, if not agreed otherwise. On site audits are not planned.
14. APPENDICES

Appendix I Radiographic Protocol