VertiFlex® Superion® Interspinous Spacer

PMA No. P140004

Executive Summary

This Executive Summary presents an abstract of the clinical trial conducted to support FDA approval of the **VertiFlex® Superion® Interspinous Spacer** PreMarket Approval (PMA) application, No. P140004. The Superion® implant is designed for the treatment of symptoms of neurogenic intermittent claudication secondary to moderate lumbar spinal stenosis.

For a complete Summary of Safety and Effectiveness Data (SSED) derived from the clinical trial supporting FDA approval of the Superion® PMA, please refer to the SSED posted on the FDA website at http://www.accessdata.fda.gov/cdrh_docs/pdf14/P140004b.pdf.

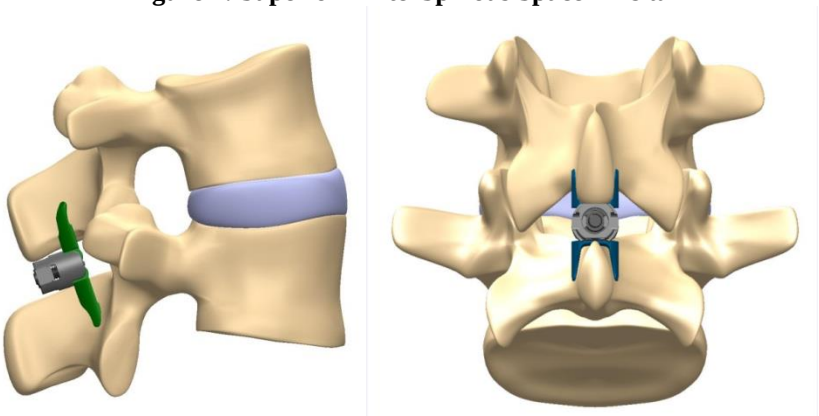
1. SUMMARY

The Superion® Interspinous Spacer (Superion® ISS) is a spinal implant designed to treat symptoms of intermittent neurogenic claudication secondary to moderate degenerative lumbar spinal stenosis, and is implanted by minimally-invasive methods through a cannula. The implant provides indirect decompression of spinal nerves, and functions as a spinal extension-blocker to prevent compression of neural elements in extension. The Superion® ISS was designed to treat a similar patient population as the FDA approved X-STOP® Interspinous Process Device (IPD®).

1.1 Device Description

The Superion® ISS is available in five (5) sizes, from 8mm to 16mm, in 2mm increments, to accommodate a range of spinal anatomy, and is composed entirely of Titanium 6Al-4V alloy conforming to ASTM Standard Specification F136, *Standard Specification for Wrought Titanium-6 Aluminum-4 Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications*. **Figure 1** depicts the implant in its final position after placement between the spinous processes.

Figure 1: Superion® InterSpinous Spacer *in situ*



Lateral View **A/P View**

The Superion® ISS can generally be described in two (2) "states": Undeployed (closed), and deployed (open). The implant is supplied in the undeployed state, and it is in this form that it is passed through a delivery cannula placed at midline, to the implantation site. Once delivered to, and located in, the interspinous space between the spinous processes at the selected level, the Superion® ISS is deployed to open the superior and inferior cam lobes. In doing so, these cam lobes rotate 90° from the implant axis to engage the lateral aspects of the superior and inferior spinous processes posterior to the lamina. **Figure 2** provides views of the implant as it transitions from the closed to open (or deployed) configuration.

Figure 2: Superion® ISS in Closed and Extended (Deployed) Position

The device may be implanted under general, or local (e.g., conscious sedation) anesthesia. The patient is placed prone with the spine in a flexed position. A percutaneous or mini-open approach is used for incision and placement of the cannula via sequential dilation, to allow cannula positioning in the interspinous space. Once the cannula is in place, a sizing tool is employed to determine the proper device size. The Superion® ISS is then inserted through the cannula and deployed under fluoroscopic guidance between adjacent vertebral spinous processes at the level to be treated. The insertion instrumentation is then removed, leaving the implant in place. The rigid implant serves thereafter to maintain the desired distraction between the spinous processes while still preserving motion. This maintains the intervertebral space and prevents narrowing of the canal by limiting extension at that level. Where a second, contiguous level is also symptomatic, the same procedure is used to place a Superion® ISS at that level.

1.2 Indications for Use

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

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

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

1.3 Contraindications

The Superion® Interspinous Spacer is contraindicated in patients with:

- an allergy to titanium or titanium alloy;
- spinal anatomy or disease that would prevent implantation of the device or cause the device to be unstable in situ, such as:
- significant instability of the lumbar spine, e.g., isthmic spondylolisthesis or degenerative spondylolisthesis greater than grade 1.0 (on a scale of 1 to 4);
- an ankylosed segment at the affected level(s);
- acute fracture of the spinous process, *pars interarticularis*, or laminae fracture (unilateral or bilateral);
- significant scoliosis (Cobb angle >10 degrees);
- *Cauda equina* syndrome defined as neural compression causing neurogenic bladder or bowel dysfunction;
- diagnosis of severe osteoporosis, defined as bone mineral density (from DEXA scan or equivalent method) in the spine or hip that is more than 2.5 S.D. below the mean of adult normals in the presence of one or more fragility fractures;
- active systemic infection, or infection localized to the site of implantation.

1.4 Clinical Study Design

The Superion® clinical trial was an FDA-approved study conducted under Investigational Device Exemption (IDE) number G070118. The trial was a prospective, randomized, multi-center, concurrently-controlled clinical study conducted to compare the Superion® ISS to an FDA-approved control, the X-STOP® IPD® device. A Bayesian statistical plan was employed to demonstrate non-inferiority. A total of 470 patients were enrolled in the study. 51 patients were post-consent screen failures prior to treatment. From the remaining 419 patients who met eligibility criteria, 28 non-randomized patients were assigned to a Superion® "training" cohort, while 391 patients were assigned to the randomized Intent-to-Treat (mITT) cohort. Of these patients, 190 were randomized to the Superion® arm, and 201 to the X-STOP® arm. Patients had follow up examinations at discharge, 6 weeks, 3 months, 6 months, 12 months, 18 months, and 24 months, with annual follow-up visits thereafter. Follow-up of patients will continue to 60 months as an FDA condition of approval.

1.4.1 Inclusion/Exclusion Criteria

The inclusion and exclusion criteria were designed to target a patient population having moderate degenerative stenosis, using criteria that would (a) include patients having sufficiently advanced stenosis (i.e., those who no longer benefit from conservative care) to require surgical treatment for spinal stenosis, while (b) excluding those patients with severe spinal stenosis likely to require more extensive intervention.

1.4.2 Patient Demographics

Baseline demographic information is presented in **Table 1** and **Table 2**.

Table 1: Baseline and Demographic Variables - Superion® and X-STOP® mITT Analysis Set

	Superion®					X-STOP®					p[1]	Effect
Demographics	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**		**Size**
Age at surgery (yrs)	190	66.9	9.4	47.0	88.0	201	66.2	10.2	46.0	89.0	0.291	0.06
Height (inches)	190	67.2	4.2	57.1	76.0	201	67.9	3.8	59.1	77.2	0.088	-0.19
Weight (lbs)	190	189.7	36.5	89.1	288.8	201	195.8	36.9	114.9	284.4	0.105	-0.17
BMI (k/m^2)	190	29.5	4.6	16.4	40.0	201	29.7	4.6	19.8	39.5	0.667	-0.05
Baseline Functional Status	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**		
Oswestry (ODI)	190	39.1	13.4	8.9	74.0	201	39.9	11.6	6.7	80.0	0.477	-0.06
Zurich Claudication Qx Severity	190	3.33	0.64	1.6	5.0	201	3.37	0.61	2.0	5.0	0.489	-0.07
Zurich Claudication Qx Physical	190	2.63	0.43	1.6	3.6	201	2.72	0.43	1.8	3.8	0.033	-0.22
SF-12 PCS (Physical)	189	29.4	8.1	12.1	52.4	201	28.5	6.9	12.7	55.0	0.285	0.11
SF-12 MCS (Mental Health)	189	50.0	12.7	15.6	73.7	201	48.9	12.2	19.6	73.8	0.381	0.09
VAS Back pain	190	55.4	27.9	0.0	93.0	201	55.1	27.4	0.0	100.0	0.809	0.01
VAS Leg pain (right leg)	190	55.0	31.3	0.0	100.0	201	52.9	32.5	0.0	100.0	0.533	0.07
VAS Leg pain (left leg)	190	49.6	31.8	0.0	100.0	201	50.8	31.7	0.0	100.0	0.758	-0.04

Notes: [1] Wilcoxon rank sum tests for interval variables and ordinal variables.

Table 2: Baseline and Demographic Variables - Superion® and X-STOP® Control mITT Analysis Sets

	Superion®		X-STOP®		p[1]
	n	%	n	%	
Number of subjects	190		201		
Males	110	57.9	129	64.2	0.214
Females	80	42.1	72	35.8	
Race	n	%	n	%	
White	177	93.2	196	97.5	0.020
Asian	0	0.0	1	0.5	
African American	8	4.2	1	0.5	
American Indian or Alaska Native	0	0.0	0	0.0	
Native Hawaiian or Other Pacific Islander	0	0.0	1	0.5	
Other	5	2.6	2	1.0	
Ethnicity	n	%	n	%	
Hispanic or Latino	5	2.6	11	5.5	0.204
Not Hispanic or Latino	185	97.4	190	94.5	
Use of nicotine products	n	%	n	%	
No	89	46.8	101	50.2	0.809
Current Use	24	12.6	24	11.9	.
Previous Use	77	40.5	76	37.8	.

Note: [1] Fisher's exact test (2-sided).

There were no differences in all but one baseline demographic parameter.

1.4.3 Patient Accountability

At the time of database lock for PMA submission (July 7, 2014), 94.6% (183 Superion® and 187 X-STOP® IPD®) of patients enrolled in the study were available for analysis at the study completion (24-month post-operative visit). The Superion® ISS cohort had a follow-up rate of 97.3% and the X-STOP® IPD® cohort had a follow-up rate of 94.9% through 24 months. Further, for patients theoretically due for 36 month follow-up at that time, the Superion® cohort had a follow-up rate of 90.2% and the X-STOP® cohort had a follow-up rate of 91.4%.

1.4.4 Primary and Secondary Endpoint Design

The primary endpoint of the investigation included effectiveness, safety, and risk-benefit criteria. Individual patient success required that a patient meet all of the following criteria at 24 months follow-up:

- Clinically significant improvement in outcomes compared to baseline, as determined by meeting the criterion for at least two of three domains of ZCQ
  - ≥ 0.5 point improvement in physical function
  - ≥ 0.5 point improvement in symptom severity
  - Score of ≤ 2.5 points on patient satisfaction domain
- No re-operations, removals, revisions, or supplemental fixation at the index level(s)
- No major implant or procedure related complications
  - No dislodgement, migration, or deformation
  - New or persistent worsened neurological deficit at the index level
  - Spinous process fractures
  - Deep infection, death, or other permanent device attributed disability
- No clinically significant confounding treatments:
  - No epidural injections or nerve block procedures at index level, spinal cord stimulators or rhizotomies

In addition, secondary outcomes included clinically significant decreases in leg pain and back pain (measured by ≥20mm decrease in Visual Analog Scale [VAS]), maintenance or improvement of SF-12, and clinically significant decrease (defined as ≥15 point decrease vs. baseline) in Oswestry Disability Index (ODI). Radiographic assessments were also performed for both groups by an independent radiographic core laboratory to determine qualitative and qualitative radiographic measures.

2. CLINICAL TRIAL OUTCOMES

2.1 Primary Endpoint Components

The percentage of subjects achieving success in each of the individual components of the composite primary endpoint at the 24 month follow-up are presented in **Table 3**:

Table 3: Primary Endpoint Component Success – 24 Months

Component Success Through 24 Months	Component Success	
	Superion®	X-STOP®
Clinical Success in any 2 of 3 ZCQ Domains	81.7%	87.2%
No Re-operations or Revisions	80.0%	86.6%
No Confounding Additional Treatments	86.3%	82.6%
No Major Related Complications	86.8%	83.1%

Importantly, success in these primary endpoint components remained durable at the 36 month follow-up, as shown in **Table 4**:

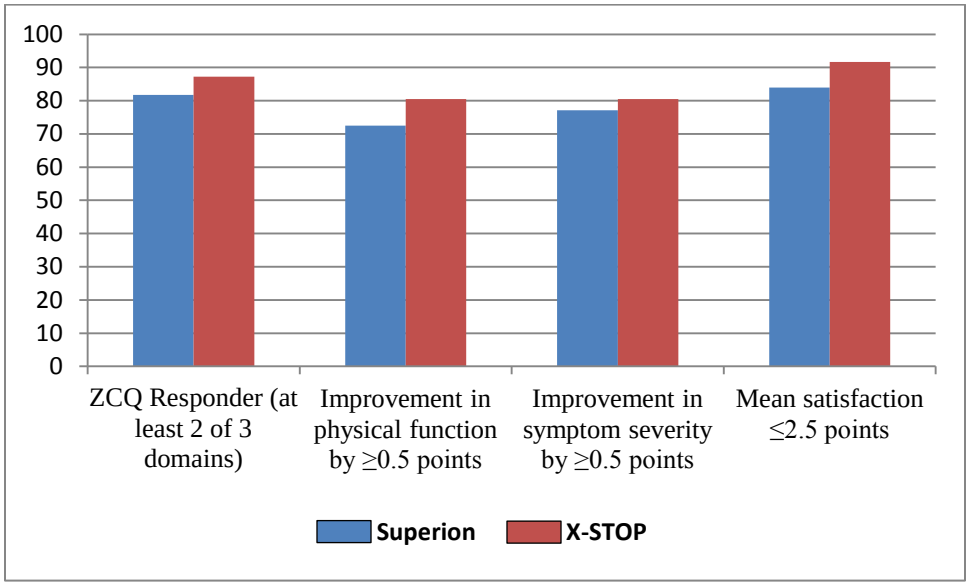
Table 4: Primary Endpoint Component Success – 36 Months

Component Success Through 36 Months	Component Success	
	Superion®	X-STOP®
Clinical Success in any 2 of 3 ZCQ Domains	87.7%	84.0%
No Re-operations or Revisions	81.2%	79.7%
No Confounding Additional Treatments	87.0%	79.7%
No Major Related Complications	90.6%	85.1%

2.1.1 Zurich Claudication Questionnaire (ZCQ)

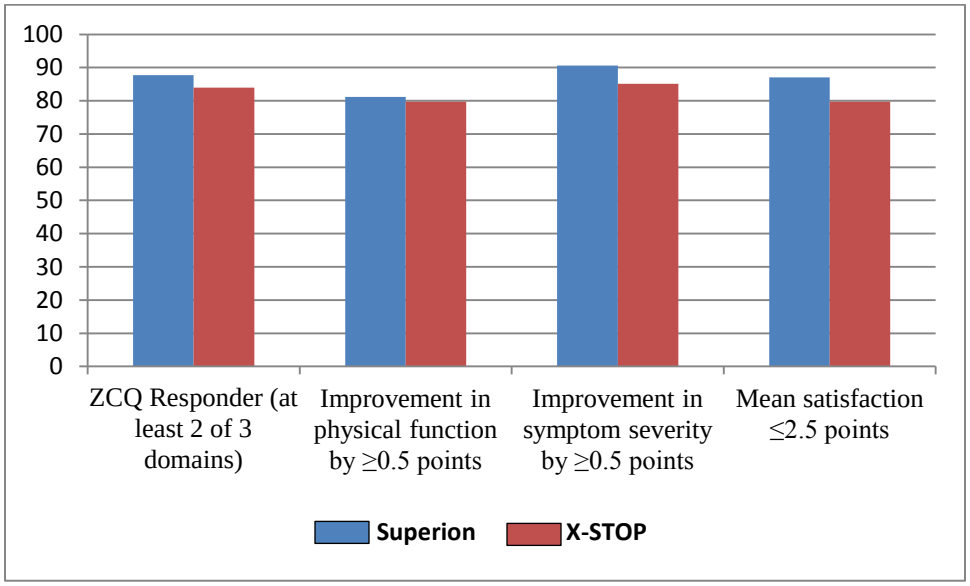
The Zurich Claudication Questionnaire (ZCQ) is a validated outcome measure for evaluating pain, function, and patient satisfaction in lumbar stenosis patients suffering from neurogenic intermittent claudication. The percentage of subjects in each arm whose scores reflect a clinically meaningful improvement over baseline at 24 months are shown below in **Figure 3**, and establish that, in a large majority of subjects, both the Superion® and X-STOP® devices provided significant improvement in pain and function, and a high degree of patient satisfaction with the procedure.

Figure 3: Success in ZCQ domains at 24 months



Notably, these outcomes proved durable through longer follow-up through 36 months, as shown in **Figure 4**:

Figure 4: Success in ZCQ domains at 36 months



2.1.2 Reoperations, Revisions, and Supplemental Fixations

In the modified intent-to-treat patient population (mITT), there were a total of 49 reoperations or revisions in the Superion® group (49/190, 25.8%) compared with 44 reoperations or revisions in the X-STOP® group (44/201, 21.9%, p = 0.365) through the last available follow-up, which included time points past 24 months for many patients, as shown in **Table 5**.

Through 24 months (as part of the primary endpoint), there were a total of 38 reoperations or revisions in the Superion® group (38/190, 20.0%) compared with 29 reoperations or revisions in the X-STOP® group (29/201, 14.4%, p = 0.179). Reoperations and revisions in patients prior to day 730 of treatment were considered to be failures in the primary endpoint although, as noted above, there was an increased number of reoperations and revisions in the X-STOP® arm, *vs*. the Superion® arm, at time points after 2 years.

Table 5: Reoperation and Revision Events – Intent-to-Treat (mITT) Population

Reoperation or Revision Type	Treatment Group	Event Time Course (months)								Total (events)	Reasons
		<1.5	1.5-3	3-6	6-12	12-24	24-36	36-48	48-60		
Decompression and Device Removal	Superion®	-	3	4	8	4	7	-	-	26	20 leg and/or low back pain, 2 bone-related fracture, 2 neurological decline, 1 device deployment issue, 1 facet cyst
Device Removal and Fusion	Superion®	1	-	-	4	5	2	1	-	13	9 leg and/or low back pain, 2 bone-related fracture, 1 neurological decline, 1 unknown
Device Removal	Superion®	-	-	-	1	-	-	-	-	1	1 leg and/or low back pain
Fusion (no device removal)	Superion®	-	-	-	1	1	1	-	-	3	2 leg and/or low back pain, 1 synovial cyst
Supplemental Decompression	Superion®	-	-	2	1	1	-	-	-	4	3 leg and/or low back pain, 1 synovial cyst
I&D and Device Removal	Superion®	1	-	-	-	-	-	-	-	1	1 dural tear
Intraoperative Failure	Superion®	1							-	1	1 dural tear
Decompression and Device Removal	X-STOP®	1	1	3	3	8	4	2	1	23	18 leg and/or low back pain, 3 device dislodgement, 1 neurological decline, 1 herniated disc
Device Removal and Fusion	X-STOP®	-	-	-	1	5	5	2	-	13	12 leg and/or low back pain, 1 bone-related fracture
Device Removal	X-STOP®	-	-	-	1	-	1	-	-	2	1 leg and/or low back pain, 1 bone-related fracture
Device Replacement	X-STOP®	-	1	-	1	-	-	-	-	2	2 leg and/or low back pain
Intraoperative Failure	X-STOP®	2	-	-	-	-	-	-	-	2	2 bone-related fracture
Irrigation and Debridement	X-STOP®	2	-	-	-	-	-	-	-	2	2 deep infection

The primary reason for reoperation or revision in both Superion® and X-STOP® patients was related to progression of, or failure to adequately relieve, the symptoms of spinal stenosis. One could consider these "treatment failures," as would be expected to be observed with any therapy. The subsequent surgical procedures following device removal performed in the Superion® clinical trial were consistent with consensus clinical standards. In particular, for subjects without grade I spondylolisthesis, surgical decompression was performed. For patients with grade I spondylolisthesis, surgical decompression with fusion was performed.

2.1.3 Neurological Outcomes

Neurologic success was defined by the presence of no new or worsening neurologic deficit with respect to motor or sensory function. The rate of neurologic failures was similar for both Superion® and X-STOP® groups. The Superion® patient population had seven (7) patients (3.7%) that had new or worsening persistent motor or sensory neurologic assessments at 24 months, while the X-STOP® population had five (5) failures (2.5%) of these criteria.

2.1.4 Additional Treatments (Epidural Injections, Rhizotomies, and Spinal Cord Stimulators)

Following index surgery, 25 of the 190 (13.2%) Superion® mITT subjects received an epidural steroid injection or nerve block at the level(s) of surgery prior to Month 24. In contrast, 33 of the 201 (16.4%) X-STOP® mITT subjects received an epidural steroid injection or nerve block at the level(s) of surgery prior to Month 24 (p=0.395). All patients who received such injections or nerve blocks at the level(s) of surgery prior to Month 24 and were considered study failures.

Following index surgery, none of the 190 (0.0%) Superion® mITT subjects received a rhizotomy at the level(s) of surgery prior to Month 24. One (1) of the 201 (0.5%) X-STOP® mITT subjects received a rhizotomy and was therefore considered a study failure (p = 1.000). No subject in either group received a spinal cord stimulator at the level(s) of surgery prior to Month 24.

2.1.5 Radiographic Observations

The incidence of radiographic observations is shown in **Table 6**.

Table 6: Subjects with Radiographic Observations in the Superion® IDE

Radiographic Observation	Superion® (n=190)		X-STOP® (n=201)	
	n	%	n	%
Spinous Process Fracture (any time)	31	16.3%	17	8.5%
Spinous Process Fracture (non-healed at 24 months)	21	11.1%	10	5.0%
Device Migration (>5mm)	0	0.0%	16	8.0%
Device Dislodgement	0	0.0%	20	10.0%
Any Radiographic Observation (any time)	31	16.3%	34*	16.9%
Any Radiographic Observation (24 months)	21	11.1%	28	13.9%

*Significant overlap was present in X-STOP® subjects having spinous process fractures, device migration, and device dislodgement.

The rate of spinous process fractures at 24 months for both groups was 11.1% and 5.0% for Superion® and X-STOP® patients, respectively. The rate of migrations and dislodgements was 0% in the Superion® group, but 11.9% in the X-STOP® group. In many cases these fractures and device movements were asymptomatic, and had no discernible effect upon the patient or their daily life through 24 months. It was observed that in some cases of dislodgement and migration in the X-STOP® arm clinical sequelae after the event were observed. As discussed below, those patients that had an X-STOP® migrate or dislodge showed an increase in VAS back pain scores (i.e., worsening pain) through 24 months, and in many cases had worse pain and function (ZCQ) scores at 24 months compared to those in whom the device did not migrate or dislodge.

While the incidence of spinous process fractures was higher in the Superion® group, the overall rate of radiographic observation was similar in both treatment groups (16.3% of Superion® vs. 16.9% of X-STOP®, p=0.690).

2.2 Secondary Endpoints

Patients in the Superion® group exhibited a similar success proportion at 24 months in all secondary endpoints when compared to the X-STOP® group (**Table 7**). Importantly, several of these secondary endpoints, such as pain measured by VAS, are arguably valid indicators of the device's effectiveness in relieving the neurogenic claudication symptoms that prompted patients to seek treatment.

Table 7: Secondary Endpoints at 24 Month Follow-Up in Superion® Clinical Trial

Outcome Measure	Superion® %	X-STOP® %	p-value[1]
ODI: ≥15 point decrease	63.4%	66.9%	0.606
VAS Back: ≥20mm decrease	67.2%	68.4%	0.895
VAS Leg (Worse): ≥20mm decrease	75.6%	77.4%	0.772
SF-12 Physical Function: Maintenance or Improvement	80.5%	89.5%	0.055
SF-12 Mental Health: Maintenance or Improvement	60.2%	66.9%	0.303

[1]Fisher's Exact Test

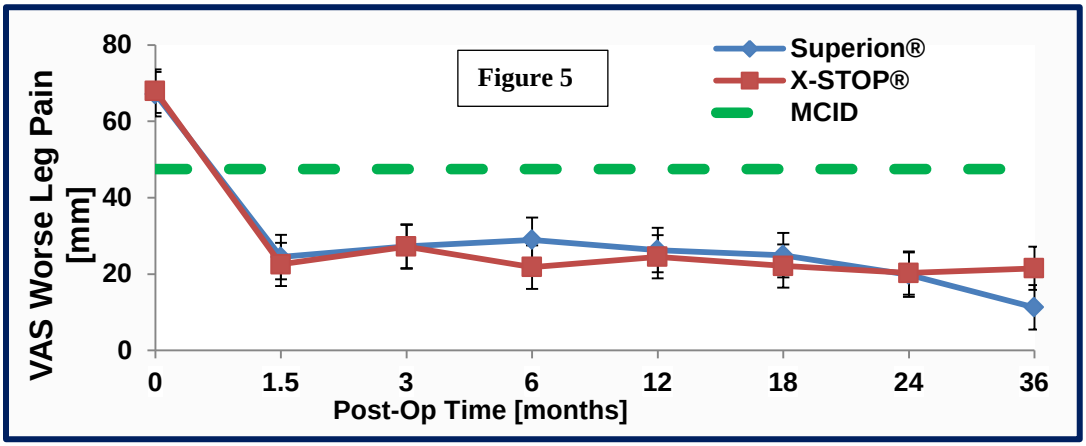
Here also, Superion® efficacy, as measured by secondary outcome metrics, remains durable at 36 months as shown in **Table 8**.

Table 8: Secondary Endpoints at 36 Month Follow-Up in Superion® Clinical Trial

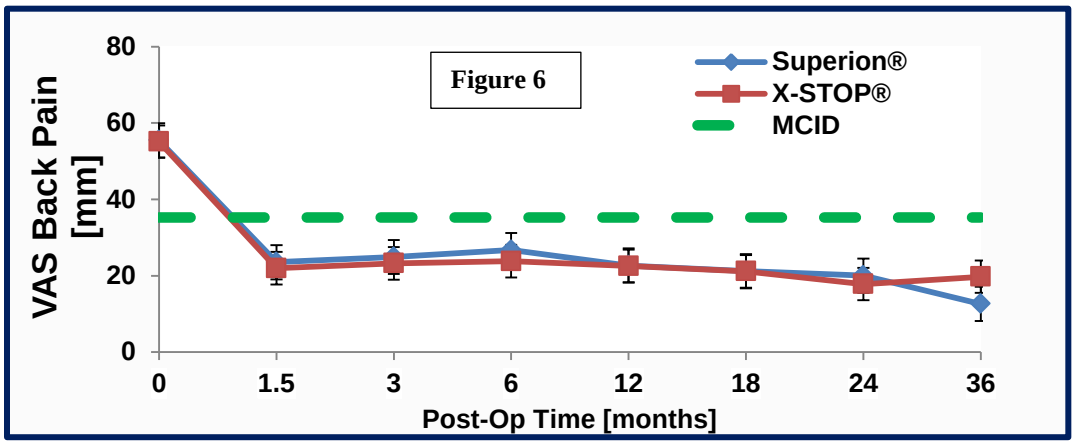
Outcome Measure	Superion® %	X-STOP® %	p-value[1]
ODI: ≥15 point decrease	69.5%	71.4%	0.863
VAS Back: ≥20mm decrease	76.8%	69.7%	0.369
VAS Leg (Worse): ≥20mm decrease	84.1%	69.7%	0.037
SF-12 Physical Function: Maintenance or Improvement	89.0%	86.8%	0.808
SF-12 Mental Health: Maintenance or Improvement	63.4%	60.5%	0.745

[1]Fisher's Exact Test

The time course of VAS – Leg Pain scores for each arm is indicated below in **Figure 5**, where mean scores for each arm are plotted through 36 months. The minimum clinically important difference (MCID) of 20 point improvement vs. baseline is also indicated. Relief of leg pain (shown here as the values corresponding to the worst of the two legs) was apparent at the first follow-up visit, and durable over the course of follow-up.



The time course of VAS – Back Pain scores for each arm are indicated below in **Figure 6**, where mean scores for each arm are plotted through 36 months. The minimal clinically important difference (MCID) of 20 point improvement vs. baseline is also indicated. Relief of back pain was apparent at the first follow-up visit, and durable over the course of follow-up.



2.3 Exploratory Analyses

Additional exploratory analyses were performed to demonstrate the poolability of several baseline patient cohorts and implantation procedures are presented in **Tables 9** and **10**. Baseline differences in covariates di not have an impact on the clinical success of patients in either group.

Table 9: Superion® IDE Composite Success Stratified by Demographic – Related Subgroups

	Superion®	X-STOP®	p-value
Age			
<67 Years	50.0% (44/88)	54.5% (54/99)	0.560
≥67 Years	53.7% (51/95)	44.3% (39/88)	0.237
BMI			
<29.5	55.9% (57/102)	46.7% (42/90)	0.247
≥29.5	46.9% (38/81)	52.6% (51/97)	0.547
Presence of Orthopedic Comorbidities			
Yes	50.9% (59/116)	48.8% (63/129)	0.799
No	53.7% (36/67)	51.7% (30/58)	0.859
Nicotine Use			
Yes	46.9% (45/96)	52.2% (47/90)	0.557
No	57.5% (50/87)	47.4% (46/97)	0.186

Table 10: Superion® IDE Composite Success Stratified by Indication – Related Subgroups

	Superion®	X-STOP®	p-value
Levels Treated			
1-level	55.2% (53/90)	48.4% (46/95)	0.386
2-level	48.3% (42/87)	51.1% (47/92)	0.766
Spondylolisthesis			
Grade 1 Spondylolisthesis	57.4% (39/68)	56.0% (42/75)	0.691
No Spondylolisthesis	48.7% (56/115)	45.5% (51/112)	1.000
Stenosis Type			
Central Only	53.1% (34/64)	44.8% (26/58)	0.691
Lateral Only	31.3% (5/16)	46.7% (7/15)	0.473
Mixed	54.4% (56/103)	52.6% (60/114)	0.892
Surgical Approach (Superion® Only)			
Mini-Open	51.1% (46/90)	-	-
Percutaneous	52.8% (47/89)	-	-

2.4 Adverse Events

The safety profile of the Superion® device is similar to that of the X-STOP® device when considering adverse event incidence.

Table 11 summarizes adverse events in the trial that occurred perioperatively or post-operatively, and those that were related to the device or procedure. No device-, or procedure-related deaths were reported in either group.

Table 11: Comparison of Summary Adverse Event Rates – Superion® and X-STOP®

	Superion® (I) (N=190)		X-STOP® (C) (N=201)		I vs. C		
	n	%	n	%	Diff	LB	UB
Any adverse event (per patient)	180	94.7	184	91.5	-3.2	-13.1	6.8
Any device related AE	22	11.6	15	7.5	-4.1	-14.0	5.8
Any procedure related AE	27	14.2	32	15.9	1.7	-8.2	11.6
Any serious AE	88	46.3	92	45.8	-0.5	-10.5	9.4
Serious AE that is either device or procedure related	16	8.4	19	9.5	1.0	-8.9	10.9
Deaths	6	3.2	5	2.5	-0.7	-10.6	9.3

Notes:
[1] Exact 95% confidence interval for the group difference.

Specific adverse events where the difference between Superion® and X-STOP® were more than 2% are indicated in **Table 12**.

Table 12: Specific Adverse Events in Superion® IDE

	Superion® (N=190)			X-STOP® (N=201)			I vs C
Adverse Event Type	No. of Events	No. of Pts.	% of Pts.	No. of Events	No. of Pts.	% of Pts.	p-value
Back pain	56	50	26.3	71	66	32.8	0.184
Cardiovascular	25	20	10.5	20	16	8.0	0.389
Device Migration	1	1	0.5	8	7	3.5	0.068
Device Subsidence	4	4	2.1	0	0	0.0	0.055
Dizziness	5	5	2.6	0	0	0.0	0.026
Genitourinary	25	22	11.6	17	17	8.5	0.317
Leg pain	41	37	19.5	54	47	23.4	0.389
Musculoskeletal	108	78	41.1	100	70	34.8	0.212
Neurological disorder	27	22	11.6	13	13	6.5	0.110
Other, specify	15	14	7.4	10	5	2.5	0.033
Pain - buttock or groin	23	21	11.1	13	13	6.5	0.150
Skin and Subcutaneous Tissue	2	2	1.1	10	8	4.0	0.106
Soft tissue damage	1	1	0.5	7	7	3.5	0.068
Spinous process fracture	24	22	11.6	14	13	6.5	0.110

There were no trends or statistical differences within any of the device-related or surgery-related categories of adverse events. Pain-related adverse events were distributed differently between the Superion® and X-STOP® groups. X-STOP® patients were more likely to have back pain or leg pain adverse events, while Superion® patients were more likely to have buttock or groin adverse events. In addition, X-STOP® patients were more likely to have events related to device migration, skin and subcutaneous tissue, and soft tissue damage. Superion® patients were more likely to have an adverse event related to spinous process fracture and neurological disorder. Overall, the adverse event rates between the Superion® and X-STOP® patients were similar, despite minor differences in type of events.

2.5 Study Summary

The Superion® IDE demonstrated reasonable assurance of safety and effectiveness through valid scientific evidence collected by means of a scientific study design, rigorous study conduct, and high level of patient accountability, and to establish non-inferiority of the device to the FDA-approved control device. Overall, the patients in both treatment groups demonstrated an immediate improvement in their stenosis symptoms, which was maintained in both groups through 24 months, and in the Superion® group through 36 months, as measured by ZCQ. In addition, there were similar safety profiles of both treatment groups.

3. COMPARISON OF STUDY RESULTS TO PRIOR STUDIES

For patients with moderate stenosis a number of treatments are available, depending on other concomitant pathologies present in the patient's spine. Each of these treatments has a different risk-benefit profile, and these risk-benefit profiles, along with the concomitant spinal pathologies, must be taken into consideration when comparing different treatment options.

3.1 Comparison to Direct Decompression

Direct decompression of the spine is utilized in many surgical procedures to treat moderate to severe lumbar spinal stenosis. A direct decompression surgery removes the osseous and soft tissues impinging upon the spinal nerve roots and column, thereby relieving a patient's spinal stenosis symptoms. Additional posterior stabilization in the form of posterolateral fusion with hardware (e.g., pedicle screw systems) or the coflex® Interlaminar Technology is often utilized in conjunction with a direct decompression, as the removal of bony tissue to relieve the patient's symptoms can create mechanical instability in the affected motion segment.

3.1.1 Perioperative Outcomes and Adverse Events

The major benefit of indirect decompression compared to surgical decompression with or without stabilization is the minimally-invasive nature of the procedure which lends itself to shorter surgeries and lower rates of perioperative adverse events, such as infection. These benefits can be quantified by comparing perioperative outcomes between studies of indirect decompression and decompression with or without posterior stabilization.

The coflex® IDE clinical trial utilized direct decompression for both treatment arms, followed by stabilization with coflex® or posterolateral fusion. A comparison of the Superion® trial results to the results from the coflex® trial[1] (for moderate to severe spinal stenosis with back pain) highlights the differences in perioperative outcomes (**Table 13**). Even though these devices are indicated for different patient populations, the blood loss and operative time data provide incremental benefit to the risk-benefit profile for indirect decompression.

Table 13: Perioperative Results from Superion® IDE and coflex® IDE (mean ± SD)

Operative Detail	Superion® IDE		coflex® IDE[1]	
	Superion®	X-STOP®	Decompression + coflex®	Decompression + Fusion
	(n=190)	(n=200)	(n=215)	(n=107)
Blood Loss (cc)	13.5 ± 15.9	38.7 ± 43.8	109.7 ± 120.0	348.6 ± 281.8
Hospital Length of Stay (days)	1.80 ± 1.5	1.90 ± 1.5	1.90 ± 1.08	3.19 ± 1.61
Operative Time (min)	56.3 ± 26.8	47.2 ± 18.8	98.0 ± 41.1	153.2 ± 55.5

As shown in the perioperative results from both Superion® and coflex® studies, indirect decompression surgeries with both Superion® and X-STOP® entailed significantly less blood loss and operative time than surgical decompression and stabilization with coflex® or fusion. While the severity of stenosis and baseline patient demographics in these two studies are different, the results demonstrate the differences in operative time and patient morbidity (based on estimated blood loss) between indirect decompression and decompression with stabilization using coflex® or posterolateral fusion.

In addition, the coflex® trial cited wound problems in 14.0% of decompression + coflex® patients (with irrigation and debridement required for 1.9% of decompression + coflex® patients), while the Superion® IDE cited infection in only 2.6% of Superion® patients (with irrigation and debridement required for 0.5% of Superion® patients and 1.0% of X-STOP® patients).

Other published studies demonstrate higher complication rates associated with direct decompression procedures compared to those demonstrated with interspinous spacers. A recently published retrospective study[2] comparing X-STOP® to a demographic-matched control of surgical decompression saw higher complication rates within 30 days of index surgery for surgical decompression (9.2%) compared to X-STOP® (3.4%), and an increase in mean index hospitalization for surgical decompression (2.49 days) compared with X-STOP® (1.58 days). Given that hospitalization and complication rates between the Superion® and X-STOP® devices were similar in the IDE trial, comparable comparisons can be extended to the Superion® device.Perioperative complication rates reported in the literature for direct decompression range from 10% to 29.6%[3,4,5], with greater complications associated when a fusion procedure is utilized for adjunctive stabilization[6]. These perioperative complications include infection, dural tear, hematoma, seroma, inflammatory reaction, pulmonary edema, urinary retention, and mechanical complications. A recent review of spinal devices in the Medicare population reported higher complication rates in decompression surgeries compared to interspinous spacers[7] (**Table 14**).

Table 14: Complication Rates Associated with Lumbar Spinal Stenosis Surgery, from Deyo et al. (2013)

	Interspinous Process Spacer	Interspinous Process Spacer + Decompression	Decompression Alone	Fusion
N for measures that include mortality	3,965	1,644	76,520	16,955
N for safety & utilization measures	3,912	1,617	75,310	16,623
Wound complications @ 30 days	30 (0.8%)	21 (1.3%)	1,343 (1.8%)	548 (3.3%)
Cardiopulmonary or stroke complications @ 30 days	39 (1.0%)	21 (1.3%)	1,192 (1.6%)	473 (2.9%)
Death w/in 30 days	7 (0.18%)	7 (0.43%)	240 (0.31%)	102 (0.60%)
Life-threatening complications (either of prior two rows)	45 (1.2%)	25 (1.6%)	1,351 (1.8%)	553 (3.3%)
All-cause rehospitalization within 30 days	175 (4.5%)	92 (5.7%)	4,985 (6.6%)	1,568 (9.4%)

3.1.2 Clinical Outcomes

While there have been no large scale randomized clinical studies comparing interspinous devices to direct decompression for the treatment of moderate stenosis, clinical outcome measurements presented in published clinical studies can be compared to the results from the Superion® trial to compare the effectiveness of these devices versus direct decompression. While these studies did not utilize a robust composite endpoint (as was utilized in the Superion® study), comparison of individual clinical outcomes is possible. Studies of direct decompression using the same ZCQ success criteria as the Superion® clinical trial are presented in **Table 15**.

[1]US Food and Drug Administration. Summary of Safety and Effectiveness Data – coflex® Interlaminar Technology. P110008. October 2012. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110008b.pdf.
[2]Patil CG, Sarmiento JM, Ugiliweneza B, Mukherjee D, Nuno M, Liu JC, Walia S, Lad SP, Boakye M. Interspinous device versus laminectomy for lumbar spinal stenosis: a comparative effectiveness study. Spine J. 2014; 14:1484-92
[3]Fokter SK, and Yerby SA: Patient –based outcomes for the operative treatment of degenerative lumbar spinal stenosis. Eur Spine J, 2006. 15:1661-1669.
[4]Ciol MA, et al.: An Assessment of Surgery for Spinal Stenosis: Time Trends, Geographic Variations, Complications, and Reoprations. J Am Geriatric Soc, 1996. 44(3): 1-10.
[5]Atlas SJ, et al.: The Maine Lumbar Spine Study, Part III: 1-Year Outcomes of Surgical and Nonsurgical Management of Lumbar Spinal Stenosis. Spine, 1996. 21(15)1: 1787-1794.
[6]Deyo RA, et al.: Morbidity and mortality in association with procedures on the lumbar spine. The influence of age, diagnosis, and procedure. J Bone Joint Surg Am, 1992. 74-A(4): 536-543.
[7]Deyo RA, et al.: Interspinous Spacers Compared With Decompression or Fusion for Lumbar Stenosis. Complications and Repeat Operations in the Medicare Population. Spine, 2013. 38(10): 865-872

These results demonstrate higher rates of perioperative complications associated with surgical decompression, with or without stabilization, compared to indirect decompression procedures such as Superion® and X-STOP®.

While direct comparison of these results with the Superion® trial are difficult due to differences in reporting, the results nonetheless align with the lower levels of wound-related complications shown in the Superion® trial compared with the results from the coflex® trial (which utilized decompression plus coflex® or posterolateral fusion).

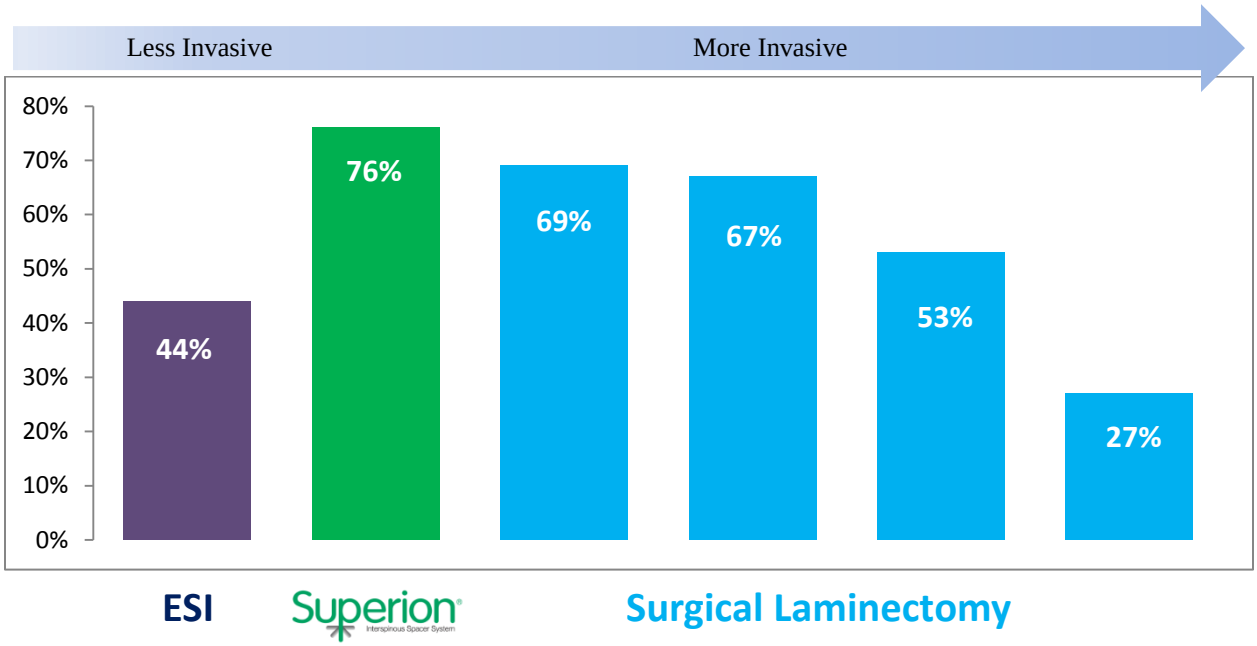
Table 15: Comparison of ZCQ Results of Decompression Studies to Superion® IDE

Article	n	Treatment	Time point	ZCQ Success (2 of 3)
Superion® IDE, Superion®	131	Superion®	24 months	81.7%
Superion® IDE, X-STOP®	133	X-STOP®	24 months	87.2%
Superion® IDE, Superion® (non-censored for injections)*	144	Superion®	24 months	80.6%
Superion® IDE, X-STOP® (non-censored for injections)*	156	X-STOP®	24 months	84.0%
Fokter et al., 2006[3]	58	Decompression	27 months (mean)	63.8%
Moojen et al., 2013[8]	79	Decompression	12 months	69%

*Subjects with epidural steroid or nerve root blocks are excluded from assessments of clinical outcome measurements due to the masking effects these procedures may have on the clinical outcome measurements. For direct comparison to results from the literature, subjects with injections are included in this assessment.

In comparison to these ZCQ results, both treatment arms in the Superion® trial achieved a higher rate of ZCQ success compared with patients undergoing decompression alone. In addition, leg pain improvement following laminectomy without posterior stabilization has been reported in 27-67% of subjects at 2 years[9,10,11], while 75.6% of Superion® subjects reported clinically significant leg pain improvement (>20mm VAS decrease vs. baseline) at 2 years. These data indicate that Superion® may perform at least similarly to direct decompression at 2 years postoperatively.

Comparing the results of the Superion® trial to those presented in published clinical literature (**Figure 7**) establishes that the Superion® device provides comparable clinical outcomes. Examining improvement in leg pain (a signal symptom associated with neurogenic claudication secondary to lumbar spinal stenosis), the improvement seen among Superion® trial patients compares favorably to both epidural steroid injections and surgical laminectomy when measured using the Visual Analog Scale (VAS):



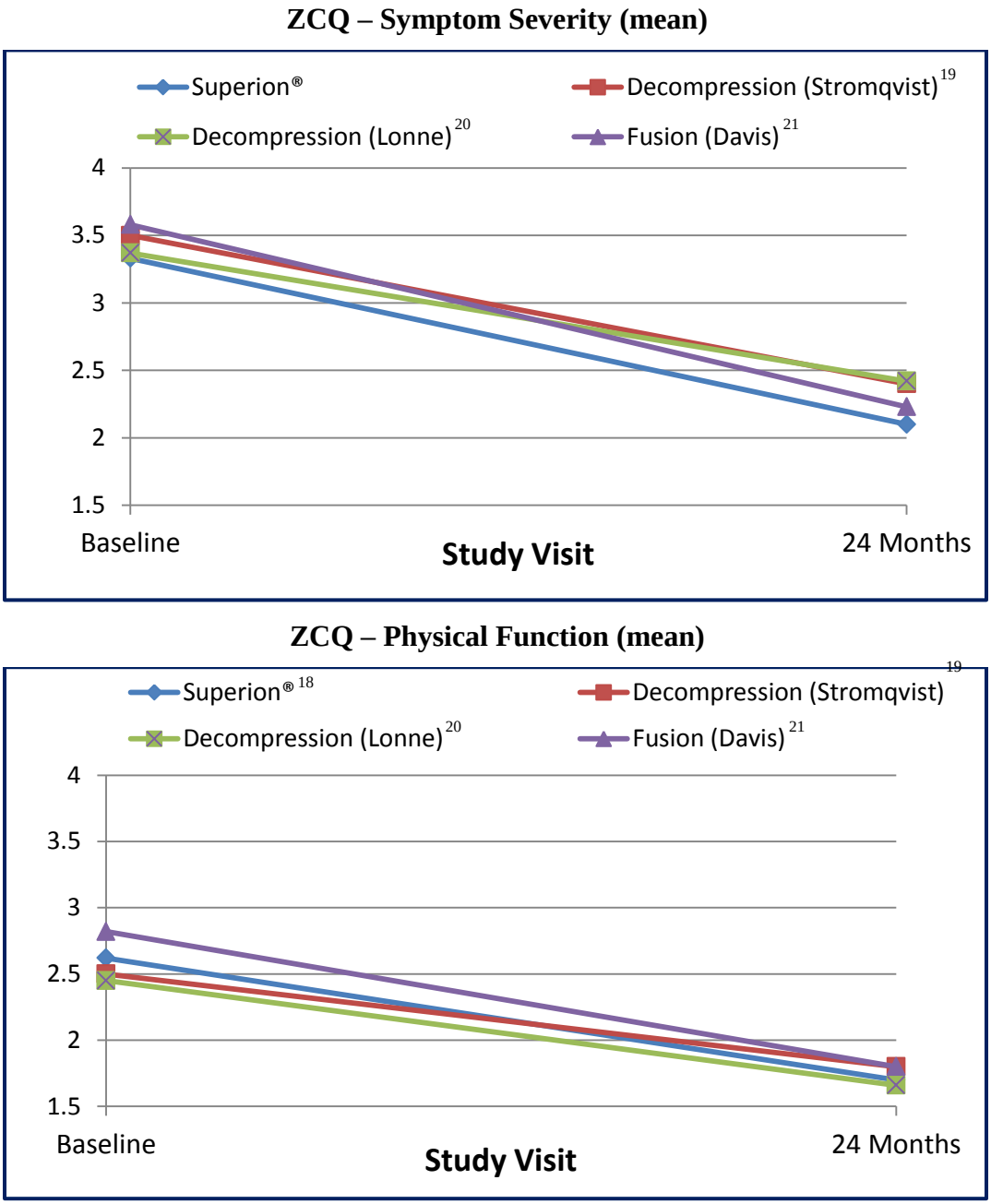
Author (Journal)	n		n	Author (Journal)	n
Manchikanti[12] (Pain Physician 2012)	**50**	**Superion® Trial Results**	**131**	**Davis[13] (Spine 2013)**	**86**
				Stromqvist[11] (Spine 2013)	**50**
				Malmivvaara[10] (Spine 2007)	**42**
				Haro[9] (Spine 2008)	**50**

Figure 7: Comparison to Published Rates – Relief of Leg Pain (VAS)

Examining published outcomes of treatment for lumbar spinal stenosis, as measured by the Zurich Claudication Questionnaire (ZCQ), provides data for comparing the Superion® device to both decompression and fusion surgery. As shown in **Figure 8**, below, improvements in both the Physical Function and Symptom Severity domains of the ZCQ among patients treated with the Superion® device are similar to those seen among patients following decompression surgery, as well as fusion surgery.

[3]Fokter SK, Yerby SA. Patient-based outcomes for the operative treatment of degenerative lumbar spinal stenosis. Eur Spine J. 2006 Nov;15(11):1661-9.
[8]Moojen WA1, Arts MP, Jacobs WC, et al. Interspinous process device versus standard conventional surgical decompression for lumbar spinal stenosis: randomized controlled trial. BMJ. 2013 Nov 14;347:f6415.
[9]Haro H, Maekawa S, Hamada Y.: Prospective analysis of clinical evaluation and self-assessment by patients after decompression surgery for degenerative lumbar canal stenosis. Spine J. Mar-Apr 2008;8(2):380-384
[10]Malmivaara A, Slatis P, Heliovaara M, et al.: Surgical or nonoperative treatment for lumbar spinal stenosis? A randomized controlled trial. Spine (Phila Pa 1976). Jan 1 2007;32(1):1-8.
[11]Stromqvist BH, Berg S, Gerdhem P, et al.: X-STOP Versus Decompressive Surgery for Lumbar Neurogenic Intermittent Claudication: Randomized Controlled Trial With 2-Year Follow-up. Spine (Phila Pa 1976). Aug 1 2013;38(17):1436-1442.
[12]Manchikanti L, et al.: Results of 2-Year Follow-Up of a Randomized, Double-Blind, Controlled Trial of Fluoroscopic Caudal Epidural Injections in Central Spinal Stenosis. Pain Physician 2012. 15:371-374.
[13]Davis et al., Spine 2013.

Figure 8: Comparison to Published ZCQ Outcomes



[19]Stromqvist BH, Berg S, Gerdhem P, et al.: X-STOP Versus Decompressive Surgery for Lumbar Neurogenic Intermittent Claudication: Randomized Controlled Trial With 2-Year Follow-up. Spine (Phila Pa 1976). Aug 1 2013;38(17):1436-1442. [n=50]

[20]Lonne G, et al.: Comparing Cost-effectiveness of X-STOP With Minimally Invasive Decompression in Lumbar Spinal Stenosis. Spine, 2015. 40(8):514-520. [n= 41]

[21]Fusion: Davis et al., Spine 2013 [n=86]

3.1.3 Summary

Comparison of the results from the Superion® trial to other studies in the literature suggests that the Superion® ISS may provide similar rates of clinical success to other treatment options, but with a minimally-invasive surgical procedure and fewer perioperative complications. Further, the spinal anatomy is not altered significantly by the implantation procedure thereby offering the possibility of reducing the complexity of future surgical options in the event that reoperation becomes necessary to address return of symptoms as degenerative changes in the spine advance.

4 CONCLUSIONS

4.1 Device Design

Placement of the Superion® ISS between two adjacent spinous processes is intended to limit compression of the neural elements at the treated level by blocking extension motion of the affected spinal segment. This principal of "extension-blocking" is fundamental to the manner by which interspinous spacers such as the Superion® ISS achieve their intended effect. This mechanism of action is a function of the size of the implant placed, and maintenance of the device's position between the spinous processes.

The surgical technique by which the Superion® ISS is implanted uses a posterior, minimally-invasive approach, wherein the device is inserted through a narrow diameter cannula placed at midline, and which requires no surgical dissection of the spinal musculature. As such, device placement is minimally disruptive of surrounding and supporting tissues.

4.2 Clinical Study Results

4.2.1 Study Integrity

The Superion® cohort had a robust follow-up rate of 96.7% and the control X-STOP® cohort had a follow-up rate of 94.1% through 24 months, providing a very complete dataset upon which to base all clinical conclusions and to analyze the composite clinical success. In addition, 90.8% had 36 month data available. The use of Bayesian multiple imputation for the primary endpoint allowed those few patients who were lost to follow up to contribute data to the primary endpoint analysis. Lastly, the excellent follow-up rate and large number of study subjects allowed for poolability and sub-analysis of variable clinical populations, including 1- versus 2-level surgery, spondylolisthesis, different categories of stenosis, and baseline demographic differences, among others. The data clearly establish that the Superion® ISS is safe and effective when used at one or two levels.

4.2.2 Effectiveness Analyses

Based upon clinical outcome scores, implantation of the Superion® ISS provides a clear benefit for patients from at least 6 weeks post-operatively (the first post-operative study visit) though 24 months following implantation. Effectiveness, or benefit in reducing or eliminating symptoms of lumbar spinal stenosis, was measured by the primary endpoint and also by a number of secondary outcome metrics. The latter included Oswestry Disability Index (ODI), Visual Analog Scale (VAS) for both back pain and leg pain, and the SF-12 quality of life metric. Clinical data from 36 month visits indicate the treatment effect for Superion® is sustained as measured by these secondary outcomes measures.

The clinical benefits of the Superion® ISS are seen in a majority of patients, particularly in the relief from stenosis symptoms (as demonstrated by ZCQ symptom severity subdomain) and in relief from leg pain (as demonstrated by VAS Leg Pain measurement), which are the predominate expressions of neurogenic claudication attributable to lumbar stenosis. The ZCQ physical function domain also improved in these patients, albeit to a lesser degree than the ZCQ symptom severity. While stenosis manifests predominately as buttock, groin, and leg pain, there are patients with associated back pain and related functional limitations. Isolated back pain is often measured by ODI and VAS Back Pain scores. These measurements also demonstrated improvement, albeit to a lesser extent and with a more delayed effect.

4.2.4 Safety Evaluations

The primary safety endpoint was the absence of re-operations, revisions, or supplemental fixation. Through 24 months (as part of the primary endpoint), there were a total of 38 reoperations or revisions in the Superion® group (38/190, 20.0%) compared with 29 reoperations or revision in the X-STOP® group (29/201, 14.4%, p = 0.179). Through the last time point, however, which includes time points past 24 months, there were a total of 49 reoperations or revisions in the Superion® group (49/190, 25.8%) compared with 44 reoperations or revisions in the X-STOP® group (44/201, 21.9%, p = 0.365). The primary reason for reoperation or revision was lack of relief, or progression, of spinal stenosis symptoms, rather than an adverse reaction to, or caused by, the device or implantation procedure.

In addition to re-operations and revisions, the safety profile of the Superion® ISS is similar to the X-STOP® device when considering adverse event incidence. In almost every category, the event rate was similar in the Superion® cohort compared to the X-STOP® cohort. There were no unanticipated adverse events in either cohort.

Serious adverse events occurred in both arms of the trial at a comparable rate, in 46.3% of Superion® patients compared with 45.8% of X-STOP® patients. In addition, X-STOP® patients exhibited a slightly higher rate of serious adverse events that were device- or procedure-related (X-STOP®: 9.5%; Superion®: 8.4%). These device- or procedure-related serious adverse events primarily occur from the day of surgery through Month 3 postoperatively.

Overall, rates of re-operation and revision were similar in both groups. Adverse event rates between the Superion® and X-STOP® patients were similar, as well as the types of adverse events. Specifically, Superion® patients had more device-related adverse events, compared with X-STOP® patients, who had more procedure-related adverse events. The data demonstrated the safety of the Superion® ISS compared to an FDA-approved device (X-STOP®) for the same intended patient population.

4.2.5 Radiographic Analysis

The clinical effects of spinous process fractures, device migration, and device displacement identified by the independent radiographic core lab were reviewed. Following surgery, 16.3% of Superion® and 8.5% X-STOP® mITT subjects exhibited a spinous process fracture, while 0% of Superion® and 11.9% of X-STOP® subjects had a device migration and/or dislodgement.

Several observations from the data are notable from these radiographic observations. The majority of spinous process fractures in both arms was detected *only* by the radiographic core lab, and was not observed by the treating clinician. The fractures themselves were not symptomatic or otherwise noticed by the patient. Further, the rate of composite clinical success in Superion® subjects in whom a fracture was detected was comparable to the rate in subjects having no fracture, as was the rate of re-operations and removals in the Superion® population having a fracture to the rate observed in the entire Superion® randomized cohort (15.1% vs. 21.1%, respectively). Finally, many of the fractures were determined to have healed, or were healing, by the 24 month visit.

These data suggest that purely radiographic observations of spinous process fracture did not elicit undue or unexpectedly high rates of adverse clinical sequelae. Further, the secondary outcomes, and specifically those indicative of pain (VAS Back and Leg), were significantly improved in both the overall Superion® cohort, and in the sub-population of Superion® patients sustaining spinous process fractures.

Additional analyses identified demographic, radiographic, and intraoperative risk factors leading to increased incidence of spinous process fracture. Importantly, these factors, which included BMI, spinous process height and shape, and device positioning, are all readily managed and mitigated by labeling and appropriate surgeon training.

4.2.6 Risk/Benefit Profile

The clinical study established that the probable benefits of the Superion® ISS outweigh the probable risks for the treatment of moderate degenerative spinal stenosis, over the 24 month time period studied, with additional benefits noted in data through 36 months. In this population, the device was shown effective in relieving the symptoms of moderate spinal stenosis in the majority of patients treated, and the effectiveness proved durable through longer-term follow-up.

The minimally invasive nature of the Superion® surgery and smaller overall device size are novel, compared to both indirect and direct decompression options. This procedure provides lower patient morbidity than open direct surgical decompression, with or without additional stabilization, while offering comparable effectiveness in relieving symptoms. This conservative surgical option offers a benefit to patients whose overall health and existing co-morbidities preclude, or put them at increased risk of complications associated with a larger decompressive surgery. Surgeries requiring decompression or decompression with fusion also carry greater risk for adverse events, and recovery time is significantly longer, generally requiring extended hospital, post-surgical care and return to activities of daily living.

In addition, the device implantation procedure imposes no alteration of the spinal anatomy, thereby preserving potential future surgical options in the event of spinal disease progression. In comparison, direct decompression surgery can introduce spinal instability and require more serious interventions, such as spinal fusion, if the initial decompression is ineffective.

Further, the Superion® ISS demonstrated safe, with re-operations and revisions primarily due to lack of pain relief, potentially attributable to continued spinal degeneration and/or symptomatology arising from untreated spinal levels. Overall, approximately 4 of 5 subjects progressed to 3 or more years post-operatively without need for additional surgery to address unrelieved or worsening symptoms, thereby avoiding such surgery and the additional risks associated therewith.

In conclusion, valid scientific evidence demonstrate the safety and effectiveness of the Superion® ISS, and that the benefits of the Superion® ISS outweigh the risks of the device when used in accordance with instructions for use, contraindications, warnings, and precautions. Further, with Medtronic's decision to remove the X-STOP device from the market, Superion® ISS is the only FDA approved device indicated for indirect decompression available to physicians today and offers a safe and effective minimally invasive technological advancement for treatment of spinal stenosis.