DEPARTMENT OF HEALTH AND HUMAN SERVICES **PMA REVIEW MEMORANDUM**

Division of General and Restorative Devices
Orthopedic Devices Branch, HFZ-410

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

Date: **July 13, 2004**
To: **File**
From: **Medical Officer**
Subject: **X-Stop Interspinous Process Distraction System**
Sponsor: **St. Francis Medical Technologies, Inc.**

CLINICAL SUMMARY P040001

Clinical Background/Rationale for the device:

Lumbar Stenosis

Lumbar stenosis is a condition of the spine with multiple etiologies that creates a clinical syndrome characterized by back, buttock or leg pain with characteristic provocative or palliative features caused by narrowing of the spinal canal or neural foramina producing nerve compression, and ischemia. Central stenosis involves compression of the spinal cord and thecal sac, while lateral stenosis involves compression of the nerve root medially or laterally by facet hypertrophy. Tumor and infectious masses can also be the cause of stenosis of the spine. Symptoms usually occur after late middle age affecting men more often than women. Etiologies of stenosis can be congenital or acquired, (the most common type), often due to degenerative enlarged facet joints, or degenerative spondylolisthesis. Soft tissue (ligamentum flavum or disc) can contribute to thecal sac compression (up to 40%). Often degeneration is not limited to one level but encompasses more than one level in the spine. It is not uncommon at all to have lumbar stenosis that primarily affects only one or two levels. In some cases there may be an amount of degeneration at multiple (or all) levels, but often the canal stenosis is severe in only one two adjoining levels and good symptomatic relief can be achieved by decompressing only the levels where there is significant canal stenosis and nerve root compression. If multiple levels are involved, one cannot easily differentiate which are causing symptoms, and thus all levels where the stenosis is causing root compression are usually decompressed.

Symptoms include insidious onset of leg and back pain and paresthesias with ambulation and extension of the spine, relieved by lying supine or with flexion of the spine. Patients complain of pain numbness or giving way, with radicular pain being uncommon. Neurogenic claudication occurs in less than half of patients with stenosis. Ordinarily abnormal neurologic signs or positive tension signs are seen in less than ½ of the patients unless induced by provocative testing or ambulation until claudication symptoms occur. The natural history of degenerative stenosis is not well characterized. Some authors conclude that severe progression is unlikely while others state that clinical improvement occurs in approximately 1/3 to ½ of the patients with stenosis associated with or without degenerative spondylolisthesis.

Treatment for stenosis involves initial rest, abdominal exercises, pelvic tilt and flexion exercises, NSAIDS and weight reduction. Epidural Steroids may be helpful for short

term relief but have not shown long term efficacy in sparse controlled studies. Surgical decompression with and without fusion is indicated when patients with positive imaging studies experience unacceptable impaired quality of life due to symptoms. There are multiple variations of procedures that decompress and then, if necessary, restabilize the spine following decompression.

Frequently, patients with lumbar spinal stenosis have multiple co-existing medical conditions that may make them unsuitable risky candidates for lengthy surgical procedures and general anesthesia. This device proposes to fill in the continuum between conservative care and invasive surgical procedures to decompress the spinal cord or nerve roots, with a minimally invasive procedure which can be done as an outpatient under local anesthesia.

The Device

The device that is the subject of this PMA is the X-Stop™, an interspinous process distraction device. The device is implanted between the spinous processes in order to block lumbar extension, following distraction of the interspinous space by the patient's position on the operating room table and dilation of the soft tissue by the surgeon. The device is manufactured from Ti6Al-4V ELI titanium alloy and consists of two components: a spacer and two wings. The spacer is comprised of a tissue expander, a fixed wing and oval spacer. The wing consists of an adjustable wing and locking screw. The device is implanted with the patient in the right lateral decubitus, spine flexed position, under local anesthesia with IV sedation, through a small 1-2 inch midline incision posteriorly over the spinous processes. After the spacer is implanted under the supraspinous ligament and through the interspinous ligament, the wing assembly is attached. The width is adjusted and the set screw tightened with a torque limiting screwdriver.

There have been 4 versions of the design of the device. The first was a one piece device with an H shape and one elongated arm and implanted in 1 patient. The second was a multi-piece square spacer design implanted in the remaining 9 pilot study patients and the third a multi-piece design with an oval spacer. The fourth version welded the components of the multi-piece design so they would not disassemble. The first two versions were implanted in the pilot study patients only. The third and fourth versions were implanted in the patients in the pivotal studies

Intended Use

The sponsor states: "The X-Stop™, an interspinous process implant system, is intended to be used in patients with symptomatic lumbar stenosis at one or two levels who have failed at least six months of conservative treatment."

Clinical Study Overview

Studies to support safety and effectiveness were completed in two phases: a pilot phase and two pivotal phases.

The review that follows summarizes the clinical safety and effectiveness data from the three clinical studies which are submitted to support the device use in humans. This review focuses on the final pivotal superiority study which evaluates the final version of the device and encompasses the data provided that is intended to support the safety and effectiveness of the device the sponsor intends to market. This study was a prospective, randomized, controlled, multicenter clinical investigation of the fourth version of X-stop™ device involving 191 patients at 9 investigational sites implanted via a minimal posterior approach or enrolled in the control group. The control group was a group of patients who had continued non-operative therapy which included the use of bed rest, controlled physical activity, physiotherapy, anti-inflammatory drugs, lumbar corset and a varied number of epidural steroids. Patients were 50 years or older, had a radiographic and clinical diagnosis of one or two level lumbar spinal stenosis with leg, buttock, groin pain with/without back pain that can be relieved by flexion , and completed 6 months of conservative therapy. Details of the protocol and analysis follow under the discussion of the clinical studies. Patients were considered failures if their symptoms required treatment by laminectomy and decompression. In addition to the primary analysis of pain and function, analysis of the successful X-stop and control patients was compared to a non-randomized group of study failures who went on to have laminectomies.

Summary of Results

Outcomes for patients receiving the investigational device are compared to outcomes for patients receiving a non operative, conservative care control.

For the primary effectiveness endpoint: overall success, the 24-month overall success rate for the X-Stop group was 45.7% (42/92) and for the Control group 4.9% (4/81). Of note the results for the site where the device was invented had a higher effectiveness success outcome (85%) as compared to the other investigational sites (≤50%) The effectiveness outcome was compared to the results for laminectomy in the literature and the patients in this study who underwent laminectomy. For the secondary effectiveness endpoint: back and leg pain, at 24 months, *mean* back and leg pain scores were significantly less frequent and less severe in the X-stop group as compared to the control group while sitting, standing or walking. When looking at actual *mean* improvement, the X-stop group had significantly greater improvement than the control group in frequency and severity of back pain while standing and walking, while there was no significant difference in improvement scores for back pain while sitting.

The safety of the profile of the device is not remarkable. Device related events are minor and few in number, including secondary surgeries (laminectomy or removal with or without fusion), spinous process fractures, migration, death and local wound events. However the incidence of what the sponsor calls "systemic" events particularly the musculoskeletal and accidental events are much higher in those patients receiving the X-STOP implant. It is not clear if these events are related to prior co-morbid conditions, lumbar stenosis symptoms unrecognized preoperatively or progressive symptoms as a result of biomechanical changes in the spine due to implantation of the distraction device.

Panel Issues

There are several issues that the panel will be asked to focus on in their discussion which are the subject of the panel questions. These are summarized below and detailed in the review that follows, and will be the basis of FDA's questions to the panel.

Long Term effectiveness information

In the case of this device, a decision as to the safety and effectiveness of this device is based solely on 24 month data and information on the patient outcomes after 24 months is not available. This information becomes important when looking at pain relief and return to function. Even though the goal of the study was accomplished showing a significant, statistical difference between the investigational and control groups, more patients report improvement at 12 months than at 24 months. Contrary to what has been observed in spinal fusion studies, in this study, a percentage of patients whose symptoms improved at 6 and 12 months show a trend of regression of pain and function symptoms toward baseline levels. Because follow-up on patients stopped immediately after the last patient reached the 24 month evaluation point, it is not clear how long the effect of treatment is maintained.

Defining the population

The outcomes of this study were worse than expected based on the sponsors literature review and pre-study calculations. The sponsor projected very low success rates based on the literature; 60% for the investigational group and 37.5% for the placebo/control . The overall success for the intent to treat population is 47.5% and 4.9% for the investigational and control groups respectively, much lower than that expected from literature review. Based on the low effectiveness in both groups, including a slightly worse rate of outcome for those patients with longer symptom duration in both the X-stop and control groups, did the enrollment criteria and patient demographics discern the comparable patients, and did the study define the population in the continuum of lumbar spinal stenosis patients who would most benefit from the device or did this population of stenosis patients all require some type of surgical /reconstructive/decompressive intervention at the time of entry into the study.

Choosing Levels of treatment

The use of this device at one or two levels may be different with regard to patient populations, postoperative outcomes and what the long term impact of the device implantation on spinal mechanics is. The majority of patients in both groups had multiple co-existing variables noted on radiographs. These include a thickened ligamentum flavum, narrowed lateral recess, hypertrophied facets, central canal narrowing by 50% and spondylolisthesis. In both groups there was more than one level involved. The sponsor's subgroup analysis noted that the patients with 2-level implantation had a slightly better outcome in all aspects of the effectiveness evaluations, with more single level patients undergoing laminectomy than those with two levels implanted. Adverse event occurrence in 2-level treated patients was also less frequent than those with single level treatment. Cadaveric biomechanical studies showed that the dimensions of spinal foramen and the spinal canal were larger in X-stop implanted levels than without the X-stop. However, these results were observed only at the implanted

level, but not at adjacent spinal levels (Module 2, Attachments 4-30, Binder). Given these demographics, outcome results and the results of the cadaveric biomechanical studies, is it appropriate to treat just one level in cases where the ligamentum flavum is thickened, degenerative changes are noted at multiple levels and the spinal canal is decreased by 50% at more than one level?

Effect on Spinal Biomechanics

Is there concern about the effect on adjacent levels, since the preclinical testing did not examine the effect of the device on the biomechanics of the spine other than at the implanted level. Has the preclinical testing fully addressed the biomechanical effect on the adjacent spinal levels and other areas of the spine in the case where more than one X-stop is implanted?

Concomitant Treatments: Epidural injections and laminectomy

The protocol did not define what criteria were to be used in either group to proceed to laminectomy or whether,in the control group, to administer additional epidural injections. Since it was up to surgeons to decide when the subsequent epidural injections were to take place and decisions were not applied in a standard fashion across all the sites or groups, just as there is a bias by defining laminectomy as a failure of treatment, there is a potential bias in deciding what subsequent treatment the patients should get for the study. In addition, some patients in the investigational (X-stop) group got the control (epidural injection for pain) rather than proceeding to laminectomy. What effect does this have on the effectiveness outcomes of this study?

Radiographic evidence of Effectiveness

Radiographic measurements of each level treated were made on plain AP and lateral views to determine spinous process distance, anterior and posterior disc height angulation, foraminal height and percentage of spondylolisthesis. There were no significant differences between the X-Stop and control groups in any of the *mean* radiographic measurements made at either the 12 or 24 months follow-up visits. Measuring the maintenance of distraction was measured by the distance between the spinous process. Of 113 levels treated, a decrease greater than 4 mm was measured in 5 levels at 24 months as compared to 6 weeks; 50 levels remained radiographically the same as baseline, and the remainder (63 levels) showed some change (loss of distraction) of 1 mm or more; with 59% of the remaining levels (37 levels) showing $\geq$ 2 mm of apparent loss of height from baseline at 6 weeks. In the absence of flexion extension radiographic evaluations, in light of the claim that this device limits a specific amount of extension of the spine what is the best way to interpret the radiographic measurements as they relate to device effectiveness?

Clinical measurement of effectiveness

When evaluating the outcomes of treatment in the lumbar stenosis population, is there evidence that 0.5 points decrease on each of the Zurich Claudication Questionnaire domains (symptom severity domain and physical function) is clinically significant or predicts short/long term effectiveness of the device?

Biomechanical effect and safety profile

When looking at adverse events deemed "not related to the implant" in the pivotal trial, those who had the X-stop implanted had a higher incidence of lower back disorders, lower extremity disorders, hip disorder, upper back disorder, neurological and neuropathological disorders. Although a possible explanation is that once the stenosis associated pain was relieved, other comorbid conditions responsible for pain were unmasked and came to the forefront, the changes in the spinal dynamics and biomechanical function that occur with the limitation of extension may also be responsible for referred pain that is noted in the X-stop group. This investigational study does not evaluate whether these or an additional explanation is the cause.

Pain and Function Outcome results for X-stop and control failures who received laminectomies

In the additional analysis, the sponsor provides a comparison between the successful X-Stop patients and the patients who were failures in both the X-Stop and Control groups and went on to have laminectomies. Symptom severity, physical function and satisfaction data was collected from the failures who had laminectomies up to a mean of 1.2 years. Comparison of a randomized and a non-randomized group, and a comparison of successes to failures is not a valid comparison. In addition, the patients who failed initial treatment may have been in worse physical condition may have been more likely to require a laminectomy. It is difficult to discern the clinically meaningful implication of such a comparison.

Differences in outcomes between sites

When evaluating the outcomes at different sites there is a significant difference in outcome between the patients treated at Site 01 (85% success) and all the other centers (less than 50% success). This suggests some learning curve for the implantation technique or improved ability to properly select patients who would benefit from the device. .

Overall Final Effectiveness Risk/Benefit Analysis

In relation to the risk of surgical intervention and non resolution/short term deterioration of symptoms, has this study provided evidence that this device a viable alternative to either a conservative treatment approach, or a more invasive intervention, thereby delaying a potentially successful intervention?

SUMMARY OF THE CLINICAL STUDIES

Pilot study (Appendix A)

The pilot study consisted of 10 patients with lumbar stenosis who received the first generation of the device between May 1997 and April 1998. Patients were evaluated preoperatively at 6 months and 12 months using the Zurich Claudication Questionnaire. Of these, 2 patients (20%) were failures (One had device related complication and in one, symptoms recurred). Both of these patients had the X-stop device removed and laminectomy performed. The remaining 8 patients (80%) showed some level of

improvement in their symptom severity score. The sponsor reports that radiographs at 12 months showed no sign of device breakage, slippage, subsidence or angulation of the vertebrae.

Patients in this study ranged in age from 64-89 with an average of 72.4 years. There were 7 women and 3 men. Eight patients had one level diagnosis at L4-5 and 2 patients had 2 level disease. The estimated blood loss ranged from 10-60cc with an average of 24cc. No information is provided detailing other complications associated with the study.

Pivotal Study- Part I- Unwelded Implant (Appendix B)

The clinical study using the third version of the device was initiated in February 2000, but had to be stopped three months later on May 9, 2000 because a radiograph at 6 weeks showed disassembly of the device. Twenty-two patients in 6 sites had this version of the device implanted before it was modified by laser welding to prevent disassembly of the implant.

These patients and the concurrent 20 control patients are reported separately from the second pivotal trial using the newer design. Of these 42 patients, there were 3 patient deaths in the implant group, 2 of whom died after the 3 year post operative point.

Pivotal Study Part I Accountability at 24 months

	24 months	
	Inv	Con
Theoretical	22	20
Deaths, [1]	1	0
Failures[2],	4	5
Expected	17	15
Evaluated	17	14
% Follow-up	100%	93.3%
Lost	0	1

[1]There were a total of 3 deaths for the investigational group. 2 occurred after the 2 year study period.
[2] The sponsor has counted one patient twice in the control group for 2 modes of failure.

Demographics:

The patients in the implant group were on average older, taller and heavier, but not to statistical significance. Mean operative time was about 50 minutes with 24 cc blood loss on average.

Efficacy

Based on the success criterion of 0.5% improvement on the ZCQ, the overall success for the patients receiving the implant was 47% and for the control was 5.3%. It is not clear whether a number of patients received epidural steroid or pain injections, or any other concommitant care in the control group. There is a large difference between the surgical group and the control group in regard to successful efficacy results. It appears the sponsor may have pooled in the effectiveness data report those patients who had a second surgical treatment together with those that had disassembly.. Based on the accounting 21 patients should have been evaluated at 24 months. Of these, 6 had failure of the implant

and cannot be considered successful. There was one death. Therefore Table 4 ZCQ scores at 24 months is not accurate. The overall success may be closer to 30% (4/14 patients with overall success.)

Radiographic evaluation

One patient in the implant group had a decrease in the distraction postoperatively at one year. It is not clear whether this was due to implant failure or bony failure/subsidence. Radiologists were asked to report the presence of metallosis. This is ordinarily an intraoperative diagnosis and can rarely be seen on radiograph. By the sponsors explanation the term "metallosis" was adopted because the X STOP is comprised of only titanium alloy. Metallosis in the protocol refers to the secondary osteolysis as a result of metal particles being released by the implant, as adopted from the hip arthroplasty literature, where it well-described that polyethylene and/or metal alloy particles can cause osteolysis of the femur and acetabulum. Osteolysis was not identified radiographically in any patient during the study and, based on the mechanical fatigue testing performed on the X STOP, is unlikely to occur for any short duration of implantation.

Adverse events

- ?? Control group
  - One patient had a dural tear/spinal fluid leak during an epidural injection
- ?? Implant group
  - No intraoperative complications were reported
  - 6 patients had implant disassembly, 5 of these occurred in the postoperative period, 1 occurred at 36 months (the sponsor does not detailed how soon after surgery the disassembly occurred. This device failed in 6 patients in a 3 year period for a revision rate of 6/22 = 27% The sponsor provides outcomes after secondary surgery for these patients which is not supportive of the effectiveness of the device.
  - The sponsor has not clearly delineated which patients were failures. In the accounting table they note 4 failures however, 6 devices disassembled .
  - Based on the accounting on page 1, Appendix B, 21 patients should have been evaluated at 24 months. Of these, 6 had failure of the implant and cannot be considered successful(#0112,0207,0502,0601,and 0701).
  - The sponsor has determined 3 patients #0406, 0601, and 0701 in whom the implant disassembled, to be effectiveness successes. This does not make sense as the device failed.
  - Device related adverse events reported include disassembly(6), removal(4) replacement of device (2), laminectomy(2), stenosis pain (2)
  - When looking at adverse events deemed *not related* to the implant, those who had the X-stop implanted had a higher incidence of lower back disorders, lower extremity disorders, hip disorder upper, back disorder, neurological and neuropathological disorders. These adverse events associated with the musculoskeletal system may be related to the effectiveness of the device and may be potentially due to the change in spinal biomechanics that may occur with the device.

SECONDARY SURGICAL INTERVENTIONS												
Type of Adverse Event/Complication	**Surgery/ Discharge**		**6 Weeks**		**6 Months**		**12 Months**		**24 Months**		**Total # Events**	
Treatment Group (U = Un-welded; C = Control)	**U**	**C**	**U**	**C**	**U**	**C**	**U**	**C**	**U**	**C**	**U**	**C**
# of Patients at Each Follow-up Interval	**22**	**20**	**22**	**20**	**22**	**20**	**22**	**19**	**22**	**19**	**22**	**20**
Laminectomy*				1	1	1		1	1	2	2	5
Device removed without replacement					2		1		1		4	
Device removed and replaced			1				1				2	
TOTAL	**0**	**0**	**1**	**1**	**3**	**1**	**2**	**1**	**2**	**2**	**8**	**5**

*Both X STOP patients had device(s) removed at time of laminectomy; one control patient (#0402) had two laminectomy surgeries

Pivotal Trial 2- Welded Implant

INVESTIGATIONAL PLAN FOR THE PIVOTAL STUDIES

The sponsor provided the data from the prospective, randomized, controlled, multicenter clinical investigations of the fourth version of X-stop™ device, (the welded implant,) implanted via a minimal posterior approach. The control group was a group of patients who had continued non-operative therapy which included the use of bed rest, controlled physical activity, physiotherapy, anti-inflammatory drugs, lumbar corset and epidural steroids.

Inclusion/Exclusion Criteria

Inclusion

?50 years old.
Lumbar spinal stenosis.
Completed 6 months of conservative therapy (e.g., P.T., bracing, traction, systemic or injected medications).
Leg, buttock, groin pain with/without back pain that can be relieved by flexion (e.g., sitting in a chair).
Qualifies for surgery at a single or double level L_1 through L_5 (L_6).
Has a score of 2.5 on the Physical Function Scale in the Zurich Claudication Questionnaire.
Signed Informed Consent

Physically/mentally willing and able to comply.
Lives nearby or willing to comply with postoperative evaluations
Sits for 50 minutes without pain

Able to walk 50 feet or more
Had narrowing of the lumbar spinal canal, nerve root canal/intervertebral foramen at 1 or 2 levels using CT scans/MRI where the area of spinal canal is < 50% compared to segments above and below

Exclusion

Multiple surgeries of the lumbar spine.
Previous back surgery at the affected level.
Axial back pain only with no leg, buttock, or groin pain.

Fixed motor deficit.

Spondylolisthesis >Grade I

Cauda equina syndrome or neurogenic bowel/bladder dysfunction.
Severe arterial insufficiency of the legs., peripheral vascular disease
Significant scoliosis. (Cobb > 25^o)
Pregnancy, planning to become pregnant

Sustained pathologic fractures of the vertebra or multiple fractures of the vertebra or hip.
Physically or mentally compromised.
Systemic disease that would affect the subject's welfare or overall outcome of the study. Angina, RA, DM or other systemic disease

Immune suppression or receiving steroids in excess of usual doses.
Active systemic disease, such as AIDS, HIV, or

active infection.
Obesity (BMI >40kg/m^2).
H/O narcotic abuse.
involved in another investigational spinal study
Allergy to any component of the device. Ti
Not able to sit for 50 minutes
Not able to walk more than 50 feet
Unremitting pain in any spinal position
Severe symptomatic lumbar stenosis at > 2 levels
Significant peripheral neuropathy by NCVT (peroneal and sural nerves)
Acute denervation 2^o to radiculopathy as shown by EMG
Osteoporosis of the spine or hip(DEXA and NOF def) <2.5 SD below mean
Paget's dz at involved segment or mets
Immunologically suppressed, received steroids >1 mo in past 12 mos.

Of note: patients with malignancies were not excluded. Three of the 8 patients who died in this study had diagnosis of malignancy. Patients who use alcohol and or tobacco were not excluded.

Evaluations

The protocol specifies that subjects will be evaluated preoperatively, and postoperatively at 6 weeks, 6 months, and 12 months.

Baseline demographic and medical information will be documented at the preoperative evaluation, including:

HPI: (date of onset, duration, treatments, medications, litigation status, working status),
Past Medical History (prior surgeries), Physical Exam
Neurological assessment: sensory, motor, DTR, SLR, rSLR, ROM)
Radiographic evaluation (will include either MRI, CT, or myelogram).
Zurich Claudication Questionnaire
SF-36 Quality of Life Questionnaire

The radiographic review was completed by an independent radiologist.
CT or MRI were obtained and plain radiographs to document baseline:

- ?? Involved level
- ?? Status of the ligamentum flavum, lateral recess, foramina, facets
- ?? Comparison of spinal canals
- ?? Percentage of spondylolisthesis
- ?? Curvature of the spine
- ?? Angulation of the vertebrae
- ?? Anterior and posterior disc height
- ?? Distance between spinous processes
- ?? Foraminal height

The following measurements were taken on the AP and lateral radiographs (Volume 1, Appendix L)

?? Percent Slip (Spondylolisthesis)
?? Curvature (Coronal Cobb Angle) of the Spine [test for exclusion criterion]
?? Anterior Angulation (Sagittal Cobb Angle) of the Spine [vertebrae above and below implanted level(s)]
?? Anterior Angulation (Sagittal Cobb Angle) of the Spine [L1 to L5]
?? Curvature (Coronal Cobb Angle) of the Spine [for Case Report Form R]
?? Anterior and Posterior Disc Height Measurements [at the implanted levels]
?? Distance Between the Spinous Processes
?? Distraction of the Intervertebral Foramina

Study Endpoints

The primary efficacy endpoints are:
Patient success rates

1. Physical function measured by ZCQ at 24 months
2. Symptom Severity measures by ZCQ at 24 months
3. Patient satisfaction as measured by ZCQ at 24 months
4. Maintenance of the distraction as measured by radiographs

The Secondary Efficacy Endpoints are:

1. SF-36 General Health Index
2. Use of analgesic agents (narcotic, non-narcotic, and frequency)
3. Time to laminectomy
4. Leg and Back Pain: severity(none, mild, moderate, severe, 0-3) and frequency(none, minimal, moderate, severe) measured

Primary Safety Endpoints

1. No additional surgery
2. No dislodgement of the device
3. Absence of device related complications

Secondary Safety Variables include:
Complications (implant fracture, collapse, failure, migration, spinous process fracture, pain at implant site, pain other, death, infection, neurologic deficit, bleeding, dural tear, dural leak, epigastric bleeding and all others)

Success/Failure Criteria

The primary clinical and radiographic endpoints in the pivotal study are the endpoints used in the definition of individual patient success.

1. Improvement in Physical Function measured as a decrease of 0.5 points on the ZCQ at 24 months,
2. Improvement in Symptom Severity measured as a decrease of 0.5 points on the ZCQ at 24 months
3. A report of satisfied or very satisfied on the Satisfaction domain of the ZCQ and the device in proper position at 24 months , a score of < 2.5
4. Did not require additional surgery for lumbar stenosis
5. Distraction must be maintained at 24 months (X-Stop group only)
6. Implant must be positioned properly at 24 months (X-Stop group only)
7. Absence of device related complications (X-Stop group only)

A patient in the implant group must satisfy all the above to be a success; in the control group a patient must satisfy the first 4 to be considered a success.

Note: The authors of the ZCQ estimated after validity analysis that 0.3-0.5 point change was significant. Although this value may be statistically significant, it is not clear that 0.5 points on the Zurich Claudication Questionnaire is clinically meaningful or comparable to other assessment scales such as the Oswestry Disability Index.

Study success criterion

The X-Stop™ group has a higher success rate than the control group with the difference statistically significant ($p<0.05$ two-sided).

Statistical predictions *For complete statistical analysis see statisticians report.*

Based on the literature, the sponsor predicted a success rate of the control as 37.5% and for the investigational group 60%. A detailed comparison of outcomes of the control patients compared to outcomes reported in the literature is included in Appendix I in the PMA (Vol 1, pp 168-170).

CLINICAL DATA FOR THE WELDED X-STOP™ PIVOTAL TRIAL

Study Description

The study was conducted at 9 investigational sites by 11 surgeons in a total of 229 enrolled and randomized patients. These Investigators and co-investigators and devices used are listed in Volume 1,Appendix D, p.155. There were 2 surgeons who implanted the majority of the devices, and 5 of the investigators implanted the device in 10 or more patients. Each was a trained neurosurgeon or orthopaedic surgeon. The study was initiated on June 6, 2000 and the last patient was treated on July 23, 2001. The date of database closure was December 19, 2003 Therefore all patients have reached their 24 month follow-up postoperative anniversary. The sponsor states that due to the rapid rate of subject enrollment, there was no significant overlap between the due date of the last enrolled patient's 24 month follow-up visit and the due date of the first patients' annual follow-up visits per the requirement stated above. Therefore, the Sponsor did not require annual follow-up visits beyond the 24 month time point.

Patients were selected based on the presence of clinical signs and symptoms of intermittent neurogenic Claudication, confirmed by radiographic evidence of lumbar spinal stenosis. (see inclusion/exclusion criteria above)

The protocol did not define what criteria were to be used in either group to proceed to laminectomy or whether in the control group to administer additional epidural injections. Since it was up to surgeons to decide when the subsequent epidural injections were to take place, there is a potential bias in deciding what subsequent treatment the patients should get for the study. In addition, some patients in the investigational (X-stop) group got the control (epidural injection for pain) rather than proceeding to laminectomy. These decisions were left to the investigator and were apparently not applied in a standard fashion across all the sites or groups. In amendment 3, the sponsor provided an explanation of what principles, though not specifically written in the protocol were applied to determine the appropriate course of treatment following the initial injection:

- ?? If the initial injection resulted in relief of symptoms for a satisfactory period of time and the patient was willing to undergo a repeat injection, then a repeat injection was performed upon return or worsening of symptoms beyond a level tolerable to the patient. Relief of symptoms for a month was generally considered a satisfactory response to warrant another injection if the patient agreed.
- ?? A partial response to the epidural steroid injection with residual symptoms could warrant a repeat injection if the patient remained symptomatic at least 2 to 3 weeks after the first injection.
- ?? Patients were generally limited to a series of 3 injections, 1 to 3 months apart, or 4 injections in a 12 month period.
- ?? If inadequate or no relief of symptoms was obtained following the initial injection, repeat injections were not given.
- ?? If conservative treatment and epidural steroid injections resulted in unsatisfactory relief of symptoms and the investigator felt no other options were available to the patient, laminectomy surgery was offered to the patient.

The study protocol did not specify these criteria, but allowed for investigators to follow these standard medical practices. Although the sponsor does point out the lack of consensus in the literature, for a clinical trial, all the patients should be treated equally according to a pre-described protocol, to avoid any confounding factors that would confuse the study outcomes. The decision to leave the frequency and timing of repeat injections to the discretion of the investigator, It appears that the patients were not all treated the same within a group or between groups when deciding who had symptoms requiring surgical decompression. For example, the X-stop patient with progressing pain (1022) who required serial nerve root injections, was not operated on, however the patient 0706 was, but not until 66 days following injection despite progressive neurologic deficit pain and loss of sexual function less than 2 weeks after epidural injection. In addition, in the X-stop group, eight patients had pain injections after the implantation of the device, while patients in the control treatment group had varying numbers of epidural injections; 32 patients had only one injection while some had more than 4 injections There is still not good evidence that success in those patients in the X stop group receiving an injection after the implantation of the device could be discerned between temporary relief from the injection or from decompression by the device.

Patient Populations

A total of 229 patients were enrolled and randomized into the study. Of these, 38 (16.6%; 14 investigational, 24 control) patients withdrew or were excluded prior to receiving treatment leaving 100 patients receiving the X-stop ™ and 91 Control patients to complete the randomization portion of the study.[these patients are defined in Table 4 and section 6.2 , page 26.] Fifteen additional patients were considered "discontinued" leaving a total of 176 patients in the "evaluable" population according to the sponsor.

Of the original 191 treated patients, 146 patients (76%) completed follow-up at 24 months without secondary surgical intervention. Thirty patients had a subsequent

laminectomy because of continuing symptoms prior to the 24 month evaluation; 6 in the X-stop group and 24 in the control group. The following table summarizes patient follow-up.

Patient Accounting (Vol. 1 Tables 5 & 6 , page 28, Vol 7, Table 1)

	Preop		Intraop		6 Weeks		6 months		12 months		24 months	
	Inv	**Con**	**Inv**	**Con**	**Inv**	**Con**	**Inv**	**Con**	**Inv**	**Con**	**Inv**	**Con**
Theoretical	114	115	100	91	100	91	100	91	100	91	100	91
Deaths, (cumulative)			1	0	1	0	1 (2)	1 (1)	(2)	1(2)	2 (4)	2 (4)
Failures[2], (cumulative)			1	1	1	2	3	13	5	17	(7)	25
Expected[3]			99	91	98	89	95	77	93	72	89	63
Evaluated*			99	91	94	70	88	64	88	69	88	58
Lost	14*	24*	0	0	4	19	7	13	5	3	1	5
Actual % Follow-up*	88%	79%			96%	**78.7 %**	92.6 %	**83%**	95%	96%	98.8 %	92%

1 Theoretical = Patients enrolled in the study

2 For example, device removals, replacement, laminectomy

3 Expected = Theoretical – (Deaths + Failures)

* This number includes those patients who were evaluated outside the prescribed follow-up windows

** These patients were enrolled but not treated

At 24 months, the goal of 85% follow-up was obtained for the patients who were treated. However the patients available for determining efficacy of the treatment was less, particularly in the control group (approximately 60%). In addition, this table accounts for all patients not those that had data available for efficacy determination.

Patients enrolled but not treated

Thirty-eight patients (14 investigational, 24 control) enrolled and randomized in this trial did not receive treatment. Of these, only 2 were excluded due to the study inclusion criteria. The majority of the remainder "voluntarily withdrew from the study (8 and 19 patients respectively). This reduces the number of patients in the study by 15%in the investigational group and 26% in the control group.

Discontinued patients

Of the 191 patients treated after enrollment, 15 patients were discontinued leaving 176 according to the sponsor as being considered "evaluable" in the sponsor's analysis at 24 months for effectiveness. The discontinued patients included patients who died, patients in whom the X-stop was removed, a patient in whom an epidural injection was aborted and 6 patients (one X-stop treated) who withdrew from the study. Three of the control patients had exacerbations of medical problems that preceded their withdrawal. One got better and one could not tolerate treatment. Two additional patients in the X-stop group withdrew from the study but completed the SF-36 and ZCQ at 24 months.

The sponsors provide the patient status (success or failure) at the time of withdrawal in Amendment 3.

Protocol Deviations

Protocol deviations occurred both at enrollment, and after treatment was initiated. There were 7 patients who were protocol deviations at enrollment, 4 in the control, and 3 in the X-stop group. Three X-stop and one control patients did not meet the inclusion criteria.

One X-stop and two control patient did not meet the intended use with stenosis at a level outside the intended use(L5-S1). Five of these were treatment failures, One X-stop patient was a treatment success, and one patient was lost to follow-up at 6 weeks. On table 8.8, the sponsor states that there were 3/5 patients in the X-stop group who were successes while none of the epidural patients were a success. This is inconsistent with what is noted in the executive summary in Volume 1. In addition, Table 1.4 (Vol 7 p. 1640) lists 7 X-stop and 6 Control patients in this category. In table 1.4, success is inconsistently defined, however 3 of the X stop protocol deviation patients were reported as failures, 1 success and 3 of the control protocol deviations were considered failures, (1 additional died) at 24 months. Again this does not correspond to the statement in the executive summary.

Eight patients were treated with one or more epidural or nerve root blocks injections post operatively. Six of these patients were considered failures at 24 months. All of these patients cannot be compared to those who followed the protocol. Since they required additional treatment they should be considered failures. Again these patients should not be included in the final comparative analysis.

Data Accounting

The effectiveness data available for review for the X-STOP and Control treatment groups were 92 and 81 patients. The following tables list the data accountability for the primary and secondary effectiveness endpoints for the two groups.

Data Accounting Primary endpoints

	Preop		**6 Weeks**		**6 months**		**12 months**		**24 months**	
Enrolled	100	91	100	91	100	91	100	91	100	91
ZQC symptom severity	100	91	94	70	88	64	88	69	86	56
ZCQ physical function	100	91	94	69	88	63	87	68	86	56
ZCQ satisfaction	-	-	94	71	91	77	93	85	93	78
No additional surgery	-	-		-		-		-		-
Maintenance of distraction		-	95-98	-	82-88	-	88-89		84/100	-
No dislodgement of device		-	95-98	-	85-88	-	88-89	-	84/100	-
Absence of device related AE	100	91	100	91	100	91	100	91	100	91
Overall Success	-	-	-	-	-	-	-	-	92	81

The sponsor states that there were 93 patients with 2 year data in the X-Stop group and 81 patients with 2 year data in the control group.

Data Accounting Secondary Endpoints

	Preop		6 Weeks		24 months	
	X-stop	Control	X-stop	Control	X-stop	Control
Enrolled	**100**	**91**	**100**	**91**	**100**	**91**
Back Pain	100	90	98	72	84	54
Leg pain	100	90	98	72	84	54
SF-36 PCS	100	90	91	68	82	53
SF-36 MCS	100	90	91	68	82	53
Radiographic	100	90	84	0	82	49
ROM	100	90	98	72	83	54
Leg pain present	100	90	98	72	84	54
Clinical evaluations	100	90	98	72	83/84	54
Medications/ work status/ post op therapy	100	90	98	72	83	54

Demographics

The two treatment groups were very similar demographically, and there were no statistically significant ($p < 0.05$) differences for any of the demographic covariates.

Description of the Study Populations		
	X-STOP	**CONTROL**
Number of patients	**100**	**91**
Men / Women	57/43	46/45
Age, year (mean)	50-94 (70)	50-88 (69.1)
Height (in)	56-74 (67.3)	56-75 (66.3)
Weight (lbs)	105-265 (177.1)	98-293 (180.2)
Duration of symptoms 6-12 mo	20	15
1-2 years	18	16
> 2 years	57	55

Keep in mind that patients in this study had already failed conservative treatment including epidural injections and had symptoms for more than 2 years prior to entering the study and in the control group, patients were offered further treatment that had already proven to be ineffective. There were no statistically significant differences in co-morbid characteristics between groups ($p<0.05$).

Comorbidity		
	X-STOP	**Control**
Patients	100	91
Worker's Compensation: Yes	4	2
Preop Work Status: Working	33	27
Preop Work Status: Not Working	67	64
# due to back symptoms	7	11

The majority of patients in both groups (about 60%) were retired and not working. Smoking and alcohol use was not evaluated in the covariate analysis.

Preoperative Patient Characteristics

The sponsor states that there were no statistically significant ($p < 0.05$) differences between the treatment groups related to the preoperative medical conditions. The two groups were closely matched in most preoperative evaluations and by medical history showing that randomization was effective based on the demographic variables analyzed.

The majority of patients in both groups had multiple coexisting variables noted on radiographs. These include a thickened ligamentum flavum, narrowed lateral recess, hypertrophied facets, central canal narrowing (Over 90% in both groups) and all patients had spinal canal smaller by 50%, and spondylolisthesis. In both groups, there was more than one level involved (30% in the X-stop and 10% in the control). This brings up the question whether it is a appropriate to treat just one level in cases where the ligamentum flavum is thickened and the spinal canal is decreased by 50% with more than one level involved.

Approximately 3% of the population had prior surgery, but about ¾ of the population had used medications for pain. **The X-Stop group had a higher percentage of epidural injection treatments as compared to the control group which reached statistical significance**. Details of prior treatments in both groups of patients are found in Vol. 1, page 36, Table 14.

As per the inclusion criteria, all except one patient had leg pain; over 50% had bilateral leg pain. Few of the patients had a bowel or bladder symptoms or motor deficit, but most had reduced reflexes and a sensory deficit (Volume 1, Table 17, p.37) There was no statistical difference in co-morbidities between the two treatment groups. Cardiovascular, musculoskeletal, endocrine and respiratory disorders were the most frequent categories of co-morbidities.

Baseline Evaluations

Baseline Evaluations		
	X-STOP	**Control**
Patients	100	91
ZCQ Symptom Severity	3.14	3.10
ZCQ Physical Function	2.48	2.48
SF-36 PCS	27.8	28.9
SF-36 MCS	51.5	50.6
Back Pain Score (mean) frequency/severity		
Sitting	0.5/0.49	0.69/67
Standing	1.79/1.74	1.99/1.93
Walking	1.85/1.78	2.11/2.14
Leg Pain Score (mean) frequency/severity		
Sitting	0.39/0.38	0.36/0.37
Standing	2.34/2.27	2.24/2.24
Walking	2.58/2.53	2.57/2.59

ROM		
Flexion	78.9	77.4
Extension	11.9	14.7
Lateral	19.9	21.6
Rotation	22.1	23.0

There was no statistically significant differences in baseline scores between the two groups, except for back and leg pain. In every case, the X-stop group had less *mean* back pain when sitting, standing and walking in both frequency and severity than the control group. However, in every case, the X-stop group had less mean leg pain when sitting, standing and walking in both frequency and severity than the control group. The severity of back pain while walking was significantly different between the two groups.

In both groups, almost all patients had leg and back pain relieved in flexion.

RESULTS

Treatments

A number of patients received conscious IV sedation in addition to local anesthesia and/or general anesthesia.

	X-Stop
Anesthesia General anesthesia only	1
Local anesthesia only	30
Conscious IV sedation only	46
Local anesthesia + conscious IV sedation	21
Local anesthesia + general anesthesia	1
Local anesthesia + general anesthesia + conscious IV sedation	1
TOTAL	**100**
Mean Operative Time (min)	53.6
Mean EBL (ml)	46.4
LOS (<1days)	96
1 day	3
3 days	1
Levels treated	
1 level	64
2 levels	36
Treatment Levels:	
L_{2-3}	3
L_{3-4}	43
L_{4-5}	89
L_5-S_1	1

The majority of patients (80) were given narcotics at discharge,7 patients were discharged with NSAIDs (1), antibiotics (16) or no medications (6). The single level operative time (51 min) and blood loss (40cc) were less than those of the two level (58 minutes, 58 cc) All X STOP patients enrolled in the Pivotal Trial received pretreatment intravenous (IV) antibiotics prior to implantation.

Control Patient Treatments

Number of Epidural Injections Given to Patients in Control Group

# of Injections per Patient	Number of Patients		Total # of Injections	# Surgeries Performed*	Mean # of Days to Surgery (Range)
	(n/N)	%			
Initial Treatment (1 injection only)	91/91	100.0%	91	10	189 (56-541)
Following Initial Treatment					
1	22/91	24.2%	22	9	264 (103 – 507)
2	21/91	23.1%	42	3	386 (123 – 465)
3	8/91	8.8%	24	0	N/A
4 or more	8/91	8.8%	37	2	631 (586 – 676)
Total			**216**	**24**	

* Number of patients who ultimately underwent laminectomy surgery.

Twenty-two patients in the control group received 1 additional injection following the initial treatment, 9 of whom went on to a laminectomy. The mean time to surgery in this group was 264 days. With increasing numbers of injections per patient, the average time to surgery increased, to 631 days for patients who received 4 or more injections.

Those patients who responded positively to initial injections received additional injections when symptoms warranted treatment, thereby extending the course of their conservative therapy. Patients who did not obtain adequate symptom relief from injections received fewer total injections and proceeded to laminectomy surgery more rapidly.

Of the 91 patients, 59 patients had $\geq$2 injections; however 32 patients had only one injection. Second injections were left to the discretion of the investigator. The protocol does not stipulate what criteria qualified patients for additional injections. This practice may have introduced some potential bias in the decision for progressing to laminectomy treatment.

Effectiveness Evaluation Overview

	6 weeks		6 months		12 months		24 months	
	X-STOP	**Control**	**X-STOP**	**Control**	**X-STOP**	**Control**	**X-STOP**	**Control**
Number patients per accounting	**99**	**91**	95	77	93	72	**83**	**54**
Zurich Claudication Questionnaire*								
Symptom Severity	84/95	37/72	75/91	38/77	76/93	38/86	73/93	26/81
Physical	80/95	32/71	74/91	31/76	76/92	36/85	68/93	30/81
Patient Satisfaction	84/94	37/71	70/91	32/77	72/93	34/85	68/93	28/78
Overall ZCQ success	50/94	8/71	52/91	7/76	57/92	10/86	45/93	4/81
Maintained Distraction							80/84	n/a
Overall Success w/distraction	50/94	8/71	52/91	7/76	57/92	10/86	42/92	4/81
Leg pain present	51/98	69/72	50/88	55/63	37/89	59/65	30/84	46/54
Painful rotation	11/98	23/71	5/87	23/62	7/89	20/65	8/83	13/54
Reflexes abnormal	61/98	45/72	55/88	41/63	60/89	38/65	56/83	36/54
SLR pain	6/98	16/72	4/88	14/63	2/89	21/65	5/83	18/54
Sensory Deficit	15/98	16/72	18/88	13/63	12/89	12/65	16/84	12/54
Muscle Strength impaired	1/98	3/72	2/88	0	3/89	2/65	3/84	3/54
Babinski reflex present	10/98	8/72	7/88	8/63	7/89	7/65	7/84	7/54
SF-36								
SF-36 PCS	39.5	31.1	40.1	31.9	41.1	32.6	38.6	31.2
SF-36 MCS	55.6	51.1	54.7	50.4	54.8	49.9	54.3	32.5
Range of Motion (mean)								
Flexion	78.9	77.4	82.6	78.4	82.3	76.3	82	78.3
Extension	11.9	14.7	18	16.4	18	15.9	17.2	18.1
Lateral	19.9	21.6	23.2	22.8	22	21	22.7	21.6
Rotation	22.1	23.0	27.8	28.4	26.3	25.6	27.2	25.5

* The denominator includes all patients seen at each follow-up + those patients defined as treatment failures including those who had partial data that indicated failure in any assessments. Missing data included those with partial data that was not considered a failure, and these patients do not appear in the numerator or denominator of these results. (Thus, the denominators do not match with the accountability tables.)

Primary Effectiveness Endpoint

Zurich Claudication Questionnaire: Symptom Severity and Physical Function

The sponsor states that a greater percentage of patients experienced a clinically significant improvement in symptom severity and physical function. By the sponsor's calculations, there are 56 and 53 successful patients in the X-Stop group and only 15 and 12 successful patients respectively in the control group for this endpoint. At 24 months, the mean absolute values for symptom severity are similar for the X-stop group (2.14) and the control group (2.84) ,but somewhat different for physical function (1.7 and 2.25 respectively). Patient satisfaction was reduced over time in both groups but more so in the control group (1.70 and 2.53 respectively). A larger percentage of patients were successful in both groups at early time points (until 12 months) and by 24 months the

number of patients who were successful had decreased by about 15% in the symptom severity score and about 10% in the function score for the X-stop, although the control group did not change much from the 6 week time point in function. This is not explained by the number of patients who had laminectomies or device removals. In addition, it is not clear why in the control group the "N" increases. All of these factors affect the rates as reported.

In the Physical Function domain, the absolute success rate change in the X STOP group was lower at all time points except for the 24-month time point where the absolute success rates were 10.4% and 4.9% in the X STOP and control groups, respectively. The relative change in the X STOP group was lower than in the control group at each time point including the 24-month time point

The Absolute and Relative Change Success Rates for the X STOP and Control Groups – Physical Function

Interval	X-stop				Control			
	N	% Success	ABS ?*	REL ?*	N	% Success	ABS ?*	REL ?*
6 wk	95	67.4%	-	-	71	19.7%	-	-
6 mo	91	62.6%	4.7%	7.0%	76	11.8%	7.9%	39.9%
12 mo	92	67.4%	0.0%	0.0%	85	18.8%	0.9%	4.5%
24 mo	93	57.0%	10.4%	15.4%	81	14.8%	4.9%	24.9%

The terms ABS ? and REL ? represent the absolute and relative success rate change scores from the 6-week time point respectively

Zurich Claudication Questionnaire: Patient Satisfaction

The patients who were satisfied with the result decreased in both groups over time but the number of patients who were satisfied with the result decreased by a factor of 2 in the X-stop group by 24 months even though the numbers of satisfied patients were greater in the X-stop group overall. These results suggest that in about 15% of patients the treatment by X-stop offered only temporary relief, and /or the population who should receive this device was not adequately defined.

Overall success based on the ZCQ is significantly greater in the X-stop group. It appears that the X-stop is effective to about a year and then begins to decline in efficacy toward baseline.

The *mean* improvement for the X-stop group was greater than the *mean* improvement in the control group in the symptom severity and physical function scores. The mean improvement was 0.99 and 0.76 for the X-stop and 0.17 and 0.08 for the control group respectively. The number of patients in the X-stop evaluated were also higher than the number of patients evaluated in the control group. By the sponsors calculation the improvement in symptom severity was almost 25% and in physical function was 19%. In the control group there was a 4.3% improvement in symptom severity and 2% in physical function.

Clinical Evaluations

There was a significant difference in the patients with leg pain between the remaining X-stop and control patients who did not go on to have laminectomy, with the 30/84 patients

in the X-stop and 46/54 control patients at 24 months having leg pain still present. Although this is statistically significant, based on the treatment variability for the control group, the clinical significance of this is not clear.

At 24 months and compared to preoperative values, there was a significant difference between the X-stop and control groups with respect to the SLR and femoral stretch test.(Patients in both groups showed improvement from preoperative status: Pre operative SLR 21/100 compared to 4/84 patients in the X-Stop group had a positive SLR, while in the control group 20/90 at enrollment and 10/ 54 had a positive SLR.

There were no significant differences in the mean range of motion, reflexes, or pulses evaluations at 24 months postoperatively between the X-stop and control groups.

Missing data

At 24 months, 1 X-Stop patient and 5 control patients did not have follow-up data and are unaccounted for according to the sponsor.

Primary Effectiveness Endpoint: Distraction

Radiographs including plain AP and lateral radiographs were performed at each follow-up visit. Dynamic (Flexion/Extension) radiographs were not performed. An independent radiologist made measurements to determine disc height, increase in angulation or curvature, change in spondylolisthesis, and maintenance of distraction on the plain radiographs. Measuring the maintenance of distraction was measured by the distance between the spinous process. Failure to maintain distraction was defined as a measurable loss of 4mm distraction at 24 months. Patients with implants at two levels were required to have maintenance of distraction at both levels to be considered a treatment success. There were 2 patients who were failures by this definition. One patient refused to have follow-up radiographs at 24 months and was not included in the 24 month data calculations. The sponsor states that 95.6% of the patients maintained distraction (less than 4 mm of loss of height).

Of 113 levels treated, a decrease greater than 4 mm was measured in 5 levels at 24 months as compared to 6 weeks; 50 levels remained radiographically the same as baseline, and the remainder (63 levels) showed some change (loss of distraction) of 1 mm or more; with 59% of the remaining levels (37 levels) showing $\geq$ 2 mm of apparent loss of height from baseline at 6 weeks. (volume 1, Table 51, page 91)

On table 8. Volume 7, page 1505, 80/84 patients were noted to have successful maintenance of distraction in the X-stop group. This leaves by the accounting 16 patients without distraction results. (There were 4 deaths and 7 failures by 24 months. 100-11=89. This leaves 5 patients unaccounted for in this parameter.

There were no significant differences between the X-Stop and control groups in the *mean* values of any radiographic measurements made at either the 12 or 24 months follow-up visits.

Primary Effectiveness Endpoint: Overall Success

The 24-month overall success rate for the X-Stop group was 45.7% (42/92) and for the Control group 4.9% (4/81). This was compared to the results for laminectomy in the literature and the patients in this study who underwent laminectomy.

Secondary Effectiveness Results

Secondary Effectiveness Endpoint: Back and Leg pain

At 24 months mean back and leg pain scores were significantly less frequent and less severe in the X-stop group as compared to the control group while sitting, standing or walking. When looking at actual mean improvement the X-stop group had significantly greater improvement than the control group in frequency and severity of back pain while standing and walking, while there was no significant difference in improvement scores for back pain while sitting. The X-stop group had a significantly greater improvement than the control group in the frequency and severity of leg pain while sitting, standing or walking at 24 months. It appears that treatment with the X stop has the most effect on leg pain when standing and walking as compared to the relief of back pain (i.e. for claudication)

Improvement in Leg and Back Pain at the 24 Month Follow-up Compared to Baseline

Variable		X STOP		Control		p-value*
		n/N	%	n/N	%	
Back pain when sitting	Frequency	20/89	22.5%	9/63	14.3%	0.295
	Severity	20/89	22.5%	11/63	17.5%	0.542
Back pain when standing	Frequency	45/89	50.6%	17/63	27.0%	0.004*
	Severity	46/89	51.7%	21/63	33.3%	0.031*
Back pain when walking	Frequency	49/89	55.1%	18/63	28.6%	0.002*
	Severity	50/89	56.2%	21/63	33.3%	0.008*
Leg pain when sitting	Frequency	18/89	20.2%	7/63	11.1%	0.183
	Severity	18/89	20.2%	8/63	12.7%	0.277
Leg pain when standing	Frequency	71/89	79.8%	17/63	27.0%	<0.001*
	Severity	73/89	82.0%	24/63	38.1%	<0.001*
Leg pain when walking	Frequency	72/89	80.9%	23/63	36.5%	<0.001*
	Severity	74/89	83.1%	27/63	42.9%	<0.001*

* indicating a level of significance < 0.05; p-values determined using the Fisher exact test

Secondary Effectiveness Endpoint: Analgesic Use

There was apparently some difficulty in collecting this data according to the sponsor, so its reliability may not be valid. Analgesic use, both narcotic and non-narcotic, was decreased in both treatment groups. Although the use of narcotics was significantly less in th X-stop group at the 6 week and 12 month visit, there was no significant statistical difference between the two groups at 6 or 24 months. This is consistent with the pain scores noted.

Secondary Effectiveness Endpoint: Radiographic Endpoints

Measurements of each level treated were made to determine spinous process distance, anterior and posterior disc height angulation, foraminal height and percentage of spondylolisthesis. There were no significant differences between the X-STOP and control groups in the mean values of any radiographic measurements made at either the 12 or 24 months follow-up visits. (table 52: Mean radiographic Measurements Volume 1, page 91)

One fracture and heterotopic bone formation was noted in another patient by radiographic review. The implant was noted to be malpositioned in 2 patients, with one implant noted to be dislodged after a fall from a chair.

Secondary Effectiveness Endpoint: SF-36.
In each of the physical domains the X-stop group had a significantly higher values, However, there was improvement in both the physical and mental component summary in both treatment groups over the course of the study. There are no statistical differences in the mental summary scores between the groups. When comparing improvement over baseline at 24 months, the X-stop patients improved significantly over baseline in all domains except general health. In the control group there was no statistically significant improvement in any domain. (Vol.1, Table 38, page 55)

Sample Radiographs (Amendment 4)
Of note, the sponsor provided sample radiographs both in hard copy and scanned on a CD ROM, which is included in the panel packs. Review of each radiograph is not relevant as they are only samples of a series of radiographs in patients considered overall successes and overall failures. What is pertinent is the observation that the radiographs are of a quality that may make it difficult to perform the measurements required in the trial. Many of the samples are coned down views which may make evaluation of spinal angulation (Cobb angle) and alignment difficult. Others show severe degenerative disease, or osteopenia which may impede evaluations of disc height and measurement of foramen height to determine distraction of the intervertebral foramina.

Other Analyses

Pooling Across Investigational Sites (Vol. 1,Table 36, p. 53)
When evaluating success by site, there is a wide divergence of results, particularly the fact that there is an 85% success rate for the X-stop (St. Mary's Medical Center) at one site when the majority of other sites had a less than or equal to 50% success rate. Similarly the success rate of the control group is greater at two sites (E. Cooper Reg Medical Center, St. Mary's Medical Center) while it is zero at all the other 6 sites. While the differences were not statistically significant, the difference suggests there is a learning curve for the device, differences in patient expectations, evaluations or other covariates influenced the outcome. There is a stark difference between a 27% success (GBMC) and an 85% (St. Mary's) success rate in the different sites.

Success rates by covariate analysis
When looking at patients who have had prior epidural injections which failed, 26/58 patients (44.8%) were successful with X-stop placement, while 16/34 (47.1) were not. In the control group, there was only 1 patient who had had failed prior epidural injections had success with subsequent treatment. For those who have no prior epidural injections only 3/48 (6.3%) were successful. These findings suggest that epidural injections may not have been appropriate treatment for the patients enrolled in this study, bringing into question whether the enrollment criteria defined the population who should get this device**.**

Comparing X-stop success with success rates of the failed patients after laminectomy

Comparison of the effectiveness results between the X-stop patients and those patients with laminectomy is provided in Volume 7, table 20.4 and Amendment 3 Attachment 5 [Tables 20.1-20.4]).. Six patients who received the X STOP did not achieve satisfactory relief of symptoms and had a decompressive laminectomy performed. Two patients who received an un-welded implant also went on to a laminectomy. Twenty-six control patients in the Pivotal Clinical Trial elected to undergo a laminectomy because of ongoing stenosis symptoms (including 2 patients who underwent laminectomies after their 24 month follow-up visits), and 5 control patients treated in the un-welded implant study went on to a laminectomy. Finally, one X STOP and six control patients enrolled in the Pivotal Clinical Trial were not treated and elected to have a laminectomy instead. Thus a total of 46 patients from both the Pivotal Clinical Trial and un-welded implant study elected to undergo a laminectomy. Outcomes for 36 of these patients are available.

It is not proper method to compare the success rates of the patients in the treatment group(also a randomized population) with the rates of patients who failed treatment in both groups (also a non-randomized population) The comparison of a group of successfully treated patients with a group of failures is not comparing like patients and in the group that progressed to laminectomy may already have had worse symptomatic manifestation of spinal stenosis upon entering the study.

Financial Interests of the Investigators

Two of the investigators had a financial interest in the device. The site at which these investigators operated had higher success rates than other institutions. See the statistician's discussion of site related outcomes for a full discussion.

Subgroup Analysis

Over the course of the study, 64 patients received the X STOP device at one level and 36 patients received the implant at two levels. A subgroup analysis for the X STOP patients who had one-level and two-level implantations is provided below. A significantly greater proportion of patients with two-level implantation were successes in the Physical Function domain compared to patients with one-level implantation.

Success Rates for Primary Endpoints at 24 Month Follow-up in the X STOP Group – One Level vs. Two Level Implantation

Endpoint	One-Level X STOP Implantation		Two-Level X STOP Implantation		p-value
	n/N	%	n/N	%	
Individual ZCQ Domain					
?? Symptom Severity	36/58	62.1%	20/31	64.5%	1.000
?? Physical Function	29/58	50.0%	24/31	77.4%	0.014*
?? Patient Satisfaction	41/58	70.7%	27/31	87.1%	0.116
Overall ZCQ Success	27/58	46.6%	18/31	58.1%	0.375
Overall Study Success (all enrolled patients)	26/64	40.6%	16/36	44.4%	0.833

* indicating a level of significance < 0.05; p-values determined using the Fisher exact test

Patients who had longer pre enrollment symptom duration had a slightly worse outcome than those who had a shorter duration of symptoms though not statistically significant for the patients with longer symptom duration in both groups

The following table summarizes outcome data for X STOP and control patients who had stenosis symptoms for 2 years or less, compared to X STOP patients who had stenosis symptoms for more than 2 years prior to study entry.

Success Rates for Primary Endpoints at the 24 Month Follow-up in Patients with Symptom Duration = 2 Years vs. > 2 Years – X STOP vs. Control Group

Patient Population and Endpoint	X STOP		Control		p-value
	n/N	%	n/N	%	
Symptom Duration = 2yrs duration					
Individual ZCQ Domain					
?? Symptom Severity	22/37	59.5%	7/23	30.4%	0.036*
?? Physical Function	23/37	62.2%	4/23	17.4%	0.001*
?? Patient Satisfaction	29/37	78.4%	11/23	47.8%	0.024*
Overall ZCQ Success	19/37	51.4%	2/23	8.7%	0.001*
Overall Study Success (all enrolled patients)	19/43	44.2%	2/36	5.6%	< 0.001*
Symptom Duration > 2 yrs duration					
Individual ZCQ Domain					
?? Symptom Severity	34/52	65.4%	8/40	20.0%	<0.001*
?? Physical Function	30/52	57.7%	8/40	20.0%	<0.001*
?? Patient Satisfaction	39/52	75.0%	17/40	42.5%	0.002*
Overall ZCQ Success	26/52	50.0%	2/40	5.0%	<0.001*
Overall Study Success (all enrolled patients)	23/57	40.4%	2/55	3.6%	< 0.001*

* indicating a level of significance < 0.05; p-values determined using the Fisher exact test

Effectiveness Conclusions

The sponsor states that a statistically significant proportion of the X-Stop patients achieved improvement in symptom severity and physical function as compared to the control group. This statement though statistically true requires some discussion.

First one must look at the control group. Comparing an operative group to a non operative group is subject to bias and expectation differences for patients which includes a placebo effect. Choosing a control, one in which the treatment has already failed, will allow easy demonstration of greater effectiveness by the treated patient group. Laminectomy in the population with claudication varies in success between 65-85%, but generally has a good result due to decompression. In this study, symptom relief was only 60% for pain and function and symptom relief and satisfaction waned from 6 months to 2 years as was previously noted in the is review. Approximately 15% of those with initial relief had return, worsening or increase of symptoms, though better than baseline, by 24 months.

This population enrolling in this study is a group of patients who, in majority, had failed 2 or more years of conservative therapy and the controls got more of the therapy that was ineffective. When one looks at the results, it is clear that the control therapy was ineffective after another 2 years. Patients with single level treatment and those with longer duration of symptoms preoperatively had a worse clinical outcome.

24-Month Effectiveness Results (Per sponsor's calculations)		
Primary Endpoints	**X-STOP**	**CONTROL**
Symptom Severity	60.2 %	18.5 %
Physical function	57 %	14.8 %
Satisfaction	73.1 %	35.9 %
Overall Success	45.7 %	4.9 %

Predictive analysis

The sponsor has done an analysis of the covariates in order to discern those variables that may be associated with an unfavorable or favorable outcome.

According to the analysis favorable outcome was predictive with a positive femoral stretch test. Whether this is clinically useful is not clear. Patients with co-morbid conditions and higher blood loss were negatively correlated with out comes. This finding is not uncommon with a surgical intervention. Worse baseline scores on the ZCQ physical function score were predictive of a positive outcome. Patients who were employed, had involvement at L4 -L5 or had used narcotics for pain prior to enrollment were weakly correlated with a positive outcome. Patients with worse symptoms and scores in the SF-36 and had greater range of motion preoperatively were weakly correlated with a positive outcome. Those who were older and had back pain were weakly correlated with a worse outcome. No conclusions can be accurately drawn from these weak associations. The usefulness of this analysis in selecting appropriate patients for treatment is not clear.

Gender, symptom duration and number of operated levels were not predictors of outcome in this analysis. This finding does not follow what is generally known for this spinal diagnosis. .

In the secondary endpoint analysis, mean improvement scores over baseline were significantly better in the X-stop group for the SF-36 except for general health, while there were no statistically significant improvement in the mean scores in any SF-36 domain in the control group. In the X-Stop group, there was mean improvement scores in the frequency and severity of back and leg pain while sitting, standing or walking were significantly better in the X-stop group except for back pain while sitting. In comparison there was no significant improvement in the mean scores in the control group in the frequency and severity of back and leg pain while sitting, standing, or walking.

Although the overall results show that the X-stop group achieved better results than the control group, there were several trends that deserve attention. In the X-stop treated group, a trend of immediate relief in the first six months for pain and function was observed, but this relief was not sustained in all patients and over time, the mean scores and number of patients with improvement decreased with out a great decrease in the

numbers of patients that was seen in the control group. In approximately 15% of patients treated by X-stop who showed improvement in pain scores, treatment offered only temporary pain relief by 24 months. In approximately 10% of patients treated by X-stop who showed initial improvement in function scores, this improvement was not sustained through 24 months.

Safety Evaluation

Adverse events were determined by the investigators as to the relationship of the event to the device. Adverse events that were related to the device or device implantation are described as implant related or operative site related. Adverse events related to the patients disease, occurred in the perioperative period or were associated with epidural injections were described as LSS disease, surgery or treatment related. Adverse events were designated as systemic if they had no relation ship to the implant or procedures.

Adverse Event Rates

Implant related adverse events

As a result of the implant related events, the sponsor has modified inclusion/exclusion, and surgical techniques and labeling for the device.

Three implant related events (3%) were described by the sponsor. These include dislodgement of the device following a fall from a chair 11 days after surgery, which required removal; spinous process fracture, noted on follow-up radiograph at 6 months. Because it was felt that the device was initially not stable after placement due to facet hypertrophy, the surgical technique and device labeling were modified.
The second patient had an asymptomatic spinous process fracture noted at the 6 month visit radiograph, not seen on the 6 week radiograph. Because healing was noted at subsequent radiographs, no other intervention occurred. This patient did meet the success criteria at 24 months.
The third patient had a double level implantation and at the 6 week visit, the investigator noted that the intraoperative radiographs show that the implant had been positioned too far posteriorly. This patient did not meet the success criteria at 24 months.

Deaths

There were 4 deaths in each treatment group. No death was linked to the specific treatment the patient received according to the sponsor. However, in one X-stop patient, (0508) death occurred 2 days after surgery due to pulmonary edema and FDA believes it should be considered procedure related. Other deaths in the X-Stop group occurred at 4 months, and 1.5 years post operatively. In the control group, deaths occurred in two patients 1.5 years after enrollment but associated with additional surgery. Two other patients in the control group died at 5 months and 2 years after treatment.

Intraoperative complications

There were no device related intraoperative adverse events in that surgeons were able to implant the device in all patients, no cases were abandoned and none were converted intraoperatively to laminectomy. One patient, who was supposed to have two-level

implantation, only had one level implanted because of respiratory distress during implantation.

There were 3 patients (3%) who experienced intraoperative complications. One patient was unable to tolerate the epidural injection procedure. Intraoperatively, in the X stop group, one patient each had respiratory distress, an ischemic coronary episode and technical difficulty passing the probe dilator.

In the control group, 6 adverse events occurred during epidural injection. Three events occurred at the first injection. Four occurred during injection, one post injection and one day after injection. These included a reaction resulting in pain, aborting of the procedure, an exacerbation of symptoms, two patients with paresthesias during injection which resolved, and an Myocardial Infarction 3days following the injection. One patient in the control group was unable to tolerate the epidural injections, the procedure was terminated and the patient withdrew from the study.

Device/procedure related complications

The following table lists possible device or procedure related complications (from table 11.1, Vol 7, p. 1534)

Event	X-Stop	Control
Laminectomy	**7**	**26**
Pain/Stenosis	6	26
Device removal	**7**	**0**
Epidural injection Reaction	**0**	**4**
Cardiovascular event after treatment	1	1
CHF/PE post operative death	1	0
Device Migration/dislodgement	**1**	**0**
Lung edema	1	0
Failed epidural injection	0	1
Incisional pain	1	0
Malpositioned implant	**1**	**0**
Pain & progressive neurologic deficit	0	1
Worsening pain in low back	1	0
Respiratory distress during surgery	1	0
Spinous process fracture	**1**	**0**
Surgical site hematoma	**1**	**0**
Wound dehiscence	**1**	**0**
Wound Swelling	**1**	**0**

Patients with 2-level implantation had less complications postoperatively when compared to patients with 1 level implantations.

Operative Site Related Adverse Events

Four X-stop patients had operative site adverse events including wound swelling, dehiscence, hematoma and incisional pain. Three of these required additional intervention for treatment. Although the wound was aspirated in patient #0340, no information is provided on the result.

Details of other adverse events:

Pain

One patient in each treatment group experienced worsening pain in the follow-up period. The patient treated with a series of nerve root blocks and still did not meet the criteria for success. The X-stop patient is a protocol deviation. The control patient had increasing pain, progressive neurologic deficit and loss of sexual function less than 2 weeks after epidural injection but was not treated by laminectomy until 66 days following this injection. What the sponsor terms "stenosis pain" is the complication that led 6 X-stop and 26 control patients to go on to laminectomy., however not all patients who were treatment failures went on to laminectomy. The protocol does not describe what criteria were set for progression to laminectomy in either group.

Two additional patients in the control group had laminectomy following their 24 month visits.

Neurologic Adverse Events

A total of 9 neurological events occurred in X-Stop group patients (7) compared to 2 events in Control group patients. These included headache (1), Neurological disorder (1,1) neuropathy (4) stroke (1,1) and neuropsychological disorder (5, 10) respectively.

Musculoskeletal Adverse Events

There were 67 events in 43 patients in the X-stop group and 22 events in 16 patients in the control group.

The majority of these were considered as unrelated to treatment. These included epidural injection reaction (3 control), incisional pain (1 X-stop), back (3,0), hip (11,3), lower back(17, 7), lower extremity(13,3), rib(1), upper back (4) and upper extremities (4,2), groin pain (3), wound swelling (1). The high incidence of lower extremity and back events suggests that treatment may have been incomplete for both groups, although there is a greater incidence in the X stop group. Included in these patients were some of the patients who underwent secondary procedures. Some of the increased problems are due to the increase in activity after successful resolution of symptoms. The sponsor proposes that the dwindling numbers in the control group as the study progressed contributed to the difference in the incidence of these events, however the rate of events is so significantly different, this seems unlikely.

Alternatively, it is possible that this is due to the population not completely defined had multiple co morbid and/or arthritic conditions accounting for the pain. Whether the patients and the ZCQ was able to discern the difference between the pain caused by stenosis or other etiology is not clear by the results.

Summary of Adverse Events Associated with Musculoskeletal or Nervous Systems

Type of Adverse Event/Complication		Surgery/ Discharge		6 Weeks		6 Months		12 Months		24 Months		Total	
Treatment Group (X = X STOP; C = Control)		X	C	X	C	X	C	X	C	X	C	X	C
# Pts Evaluated at Each F/U Interval Visit		100	91	94	70	88	64	88	69	88	58		
System	Code/Event												
Musculoskeletal	Lower Back			3		5	2	5	3	8	2	21	7
	Lower Extremity			1	2	6	1	6	2	3		16	5
	Upper Back					2		1		1		4	

Neurological	Neurological Disorder						1	1				1	1
	Neuropathy					2		2				4	
	Stroke								1	1		1	1
TOTAL# of Events		**0**	**0**	**4**	**2**	**15**	**4**	**15**	**6**	**12**	**2**	**47**	**14**

Systemic Adverse Events

There was a higher incidence of cardiovascular , endocrine, gastrointestinal, genitourinary, hematologic, hepatobiliary, immunological, accidental injury, respiratory disorders and infections in the X-stop group. X-stop patients were at higher risk than the controls for "systemic events" without any seeming explanation. There shouldn't be any difference given the outpatient nature and local used for most procedures. This is detailed in Table 50 (Vol. 1. page 87).

Infection Adverse Events

No events related to infection are reported except the three wound problems reported as secondary re-operations.

Vascular Adverse Events.

There was one event in one X-stop patient.

Cancer

There were 4 patients in the X-stop group and 1 patient in the control group diagnosed with cancer during the study. Patients with malignancies were not excluded from this study.

Secondary Surgical Procedures

This table summarized the time course of the secondary surgical interventions in both study groups.

SECONDARY SURGICAL INTERVENTIONS												
Type of Adverse Event/Complication* **	**Surgery/ Discharge**		**6 Weeks**		**6 Months**		**12 Months**		**24 Months**		**Total**	
Treatment Group (X = X STOP; C = Control)	**X**	**C**	**X**	**C**	**X**	**C**	**X**	**C**	**X**	**C**	**X**	**C**
# of Patients at Each Follow-up Interval	**100**	**91**	**100**	**91**	**99**	**91**	**98**	**89**	**98**	**83**	**100**	**91**
Aspiration of wound swelling			1								1	
Debridement and secondary wound closure			1								1	
Drainage of hematoma			1								1	
Implant removal without laminectomy			1*								1	
Laminectomy**			1	1	2	11	1	3	2	9	6	24
TOTAL			**5**	**1**	**2**	**11**	**1**	**3**	**2**	**9**	**10**	**24**

*This patient reportedly underwent laminectomy between 18-24 months following X STOP removal and study withdrawal.

**All X STOP patients had device(s) removed at time of laminectomy; two control patients underwent laminectomy following their 24 month follow-up visits.

*** Time intervals for this and other tables in this response are defined as follows: 6 weeks = 1-42 days; 6 months = 43-182 days; 12 months = 183-365 days; 24 months = 366 days

One patient had removal of the X-stop device which dislodged 13 days after surgery following a fall 11 days after surgery His device was removed and replaced but he did not undergo laminectomy. Six other patients failed X-stop therapy, and underwent removal followed by laminectomy. In the control group, 26 patients had laminectomy procedures. Three X-stop patients underwent minor procedures classified as re-operations for

drainage of a hematoma, aspiration of the incisional site, secondary wound closure after dehiscence. It appears that 5/6 patients who had secondary surgery had two level implants.

The following table describes 7 X STOP patients in whom the device was explanted. Five patients had one-level implantation and 2 patients had two-level implantation of the device. At the time of laminectomy surgery all devices were explanted with the exception of one patient (#1401), who withdrew from the study after the device was removed 11 days post-implantation and, reportedly, underwent laminectomy surgery approximately 18 months later.

Summary of Explanted Devices

Patient ID	X STOP Implantation		# Devices Explanted	Laminectomy	
	# Levels	Location		# Levels	Location
0213	1	L4-5	1	1	L4-5 (fusion)
0218	1	L4-5	1	2	L4-5, L5-S1 (instrumented fusion)
0320	1	L4-5	1	1	L4-5
0344	2	L3-4, L4-5	2	3	L2-3, L3-4, L4-5 (fusion)
0819	2	L3-4, L4-5	2	2	L3-4, L4-5
1009	1	L4-5	1	3	L3-4, L4-5, L5-S1 (R foraminotomy @ L5-S1)
1401	1	L4-5	1	N/A	Not performed at time of explant

The number of levels at which laminectomy was performed in those patients in both the X STOP and control groups who underwent laminectomy is summarized in the table below. Two of 6 (33%) X STOP patients had single-level laminectomy performed. Similarly, in the control group, 7 of 24 patients (29%) underwent single-level laminectomy. More patients required (approximately 2/3 of the patient who failed initial treatment) more than one level decompression than single level decompression in both study groups suggesting that those patients who failed had greater involvement than perhaps originally thought.

Number of Levels at which Laminectomy was Performed – X STOP vs. Control Patients

Laminectomy: # of Levels	# of X STOP Patients	# of Control Patients
1	2	7
2	2	6
3	2	4
4	0	2
5	0	1
Unknown*	0	4*
TOTAL	**6**	**24**

* Laminectomy surgeries performed at location other than investigative site; additional information regarding # of levels not available.

Explant retrieval analysis is provided in Amendment 3, Attachment E. All explant analyses include spacer assembly assessment, surface wear analysis, and release torque if applicable. The explant surgical reports did not contain any notations regarding the status of the surrounding tissue or implant appearance. Postoperative pathology was not performed.

Time course of Adverse events

Table 1.2: Adverse Events Summary[1]

Type of Adverse Event/Complication		Surgery/ Discharge		6 Week		6 Months		12 Months		24 Months		Overall # Events		Overall # Patients	
Treatment Group (X = X STOP; C = Control)		**X**	**C**	**X**	**C**	**X**	**C**	**X**	**C**	**X**	**C**	**X**	**C**	**X**	**C**
# of Patients at Each Follow-up Interval		**100**	**91**	**100**	**91**	**99**	**91**	**98**	**89**	**98**	**83**				
ADVERSE EVENTS RELATED TO LSS, SURGERY OR EPIDURAL INJECTION															
Coronary episode, ischemic		1										1	0	1	0
Heart attack					1							0	1	0	1
Epidural injection reaction			1		2						1	0	4	0	4
Epidural injection failed			1									0	1	0	1
Hematoma at surgical site				1								1	0	1	0
Incisional pain				1								1	0	1	0
Pain and progressive neurological deficit					1							0	1	0	1
Pain worsening in low back										1		1	0	1	0
Pain, stenosis			2		3	3	9	1	4	2	8	6	26	6	26
Pulmonary edema				1								1	0	1	0
Respiratory distress		1										1	0	1	0
Wound dehiscence				1								1	0	1	0
Wound swelling		1										1	0	1	0
DEVICE RELATED ADVERSE EVENTS															
Device migration/dislodgement				1								1	0	1	0
Malpositioned implant				1								1	0	1	0
Spinous process fracture								1				1	0	1	0
SYSTEMIC EVENTS*															
System	**Code/Event**														
Body as a Whole	Cancer						1	2		2		4	1	4	1
	Death			1		1	1		1	2	2	4	4	4	4
	Injury, Accidental			3		2	2	6	2	3		14	4	11	4
	Weight Gain			1								1	0	1	0
Cardiovascular	CV Disorder							2		2		4	0	4	0
Endocrine	Diabetes							1				1	0	1	0
Gastrointestinal	GI Disorder					2		1		1		4	0	3	0
Genitourinary	Chronic Renal Failure					1						1	0	1	0
	GU Infection			1								1	0	1	0
	Pain, Groin			2								2	0	2	0
Hematological	Anemia					1						1	0	1	0
Hepatobiliary	Gallstones							1				1	0	1	0
Immunological	Allergy	1										1	0	1	0
Musculoskeletal	Back, Unspecified					1		1		1		3	0	3	0
	Hip					4		4	1	5	2	13	3	11	3
	Lower Back			3		5	2	5	3	8	2	21	7	16	7
	Lower Extremity			1	2	6	1	6	2	3		16	5	13	3
	Rib									1		1	0	1	0
	Upper Back					2		1		1		4	0	4	0
	Upper Extremity				1			2		2	1	4	2	4	2
	Unspecified							1				1	0	1	0
	Pain, Groin						1	1	1			1	2	1	2
Neurological	Headache			1								1	0	1	0
	Neurological Disorder						1	1				1	1	1	1
	Neuropathy					2		2				4	0	4	0
	Stroke								1	1		1	1	1	1
Neuropsychological	NP Disorder			1		1			1	3		5	1	5	1
Peripheral Vascular	PV Disorder							1				1	0	1	0
Respiratory	Respiratory Infection			2		1						3	0	3	0
	Respiratory Disorder								1			0	1	0	1
TOTAL # of Events		**4**	**4**	**22**	**10**	**32**	**18**	**40**	**17**	**38**	**16**	**136**	**65**		

* Systemic events are defined as those events unrelated to device or study-related procedures

[1] As reported in the PMA (Vol 1, Tables 49 and 50, pp. 86-87), there were no statistically significant differences between the study groups in any single category of adverse events, with two exceptions: 1) the incidence of lower extremity disorders was significantly higher in the X STOP group (13/100 vs. 3/91; $p = 0.018$) and 2) the incidence of stenosis pain was significantly higher in the control group (26/91 vs. 6/100; $p < 0.001$).

Subgroup analysis

Patients with longer duration of symptoms had greater numbers of adverse events due to systemic and surgical procedure or stenosis, however the results did not reach statistical significance..

A total of 55 adverse events occurred among the subgroup of 43 X STOP patients who had stenosis symptoms for 2 years or less prior to study entry (55/43; 1.3 events per patient). A total of 81 adverse events occurred among the subgroup of 57 X STOP patients who had stenosis symptoms for more than 2 years prior to study entry (81/57; 1.4 events per patient). No statistically significant differences between the two subgroups were observed overall or in any single adverse event category. Similarly, no significant differences were noted between the subgroups of control patients based on symptom duration.

Summary of Adverse Events by Symptom Duration = 2 Years vs. > 2 Years – X STOP Group and Control Groups

Type of Adverse Event/Complication		X STOP					Control				
		= 2Yrs (N = 43)		> 2 Years (N = 57)		p-value	= 2 Yrs (N =36)		> 2 Years (N =55)		p-value
(N = # of pts with reported event; n = total # of reported events)		n	N	n	N		n	N	n	N	
ADVERSE EVENTS RELATED TO SURGERY, TREATMENT OR LSS											
Coronary episode, ischemic		1	1	0	0	0.430	0	0	0	0	-
Heart attack		0	0	0	0	-	0	0	1	1	1.000
Epidural injection reaction		0	0	0	0	-	2	2	2	2	0.647
Epidural injection failed		0	0	0	0	-	0	0	1	1	1.000
Hematoma at surgical site		0	0	1	1	1.000	0	0	0	0	-
Incisional pain		0	0	1	1	1.000	0	0	0	0	-
Pain and progressive neurological deficit		0	0	0	0	-	1	1	0	0	0.396
Pain worsening in low back		1	1	0	0	0.430	0	0	0	0	-
Pain, stenosis		3	3	3	3	1.000	11	11	15	15	0.814
Pulmonary edema		1	1	0	0	0.430	0	0	0	0	-
Respiratory distress		0	0	1	1	1.000	0	0	0	0	-
Wound dehiscence		0	0	1	1	1.000	0	0	0	0	-
Wound swelling		0	0	1	1	1.000	0	0	0	0	-
DEVICE RELATED ADVERSE EVENTS											
Device migration/dislodgement		1	1	0	0	0.430	0	0	0	0	-
Malpositioned implant		1	1	0	0	0.430	0	0	0	0	-
Spinous process fracture		0	0	1	1	1.000	0	0	0	0	-
SYSTEMIC EVENTS*											
System	**Code/Event**										
Body as a Whole	Cancer	1	1	3	3	0.632	1	1	0	0	0.396
	Death	2	2	2	2	1.000	3	3	1	1	0.297
	Injury, Accidental	7	5	7	6	1.000	2	2	2	2	0.647
	Weight Gain	0	0	1	1	1.000	0	0	0	0	-
Cardiovascular	CV Disorder	1	1	3	3	0.632	0	0	0	0	-
Endocrine	Diabetes	1	1	0	0	0.430	0	0	0	0	-
Gastrointestinal	GI Disorder	2	1	2	2	1.000	0	0	0	0	-
Genitourinary	Chronic Renal Failure	1	1	0	0	0.430	0	0	0	0	-
	GU Infection	0	0	1	1	1.000	0	0	0	0	-
	Pain, Groin	1	1	1	1	1.000	0	0	0	0	-
Hematological	Anemia	1	1	0	0	0.430	0	0	0	0	-
Hepatobiliary	Gallstones	0	0	1	1	1.000	0	0	0	0	-
Immunological	Allergy	0	0	1	1	1.000	0	0	0	0	-
Musculoskeletal	Back, Unspecified	0	0	3	3	0.257	0	0	0	0	-
	Hip	3	3	10	8	0.343	1	1	2	2	1.000
	Lower Back	8	5	13	11	1.000	2	2	5	5	0.699
	Lower Extremity	7	5	9	8	0.773	5	3	0	0	0.059
	Rib	0	0	1	1	1.000	0	0	0	0	-
	Upper Back	2	2	2	2	1.000	0	0	0	0	-
	Upper Extremity	3	3	1	1	0.312	1	1	1	1	1.000
	Unspecified	0	0	1	1	1.000	0	0	0	0	-
	Pain, Groin	1	1	0	0	0.430	1	1	1	1	1.000
Neurological	Headache	0	0	1	1	1.000	0	0	0	0	-
	Neurologic Disorder	0	0	1	1	1.000	0	0	1	1	1.000
	Neuropathy	2	2	2	2	1.000	0	0	0	0	-
	Stroke	0	0	1	1	1.000	0	0	1	1	1.000
Neuropsychological	NP Disorder	4	4	1	1	0.162	1	1	0	0	0.396
Peripheral Vascular	PV Disorder	0	0	1	1	1.000	0	0	0	0	-
Respiratory	Respiratory Infection	0	0	3	3	0.257	0	0	0	0	-
	Respiratory Disorder	0	0	0	0	-	0	0	1	1	1.000
	TOTAL	**55**		**81**			**31**		**34**		

?? "Systemic events" are defined as those events that were determined to be unrelated to device or study-related procedures

Safety Conclusions

The safety of the profile of the device is not remarkable. Device related events are minor and few in number. However, the incidence of what the sponsor calls "systemic" events particularly the musculoskeletal and accidental events which are much higher in those patients receiving the X-Stop implant. It is not clear if these events are related to prior

co-morbid conditions, lumbar stenosis symptoms unrecognized preoperatively, or progressive symptoms as a result of implantation and/or biomechanical changes due to a change in the function of the spine and adjacent segments to the level of the implant.

Other Cohorts

As of May 2004, 17 patients have been enrolled into the continued access program(CAP), 10 patients have enrolled in the crossover program (COS) and 2 patients have been implanted under compassionate use. Patients in the COS and CAP have been followed to 6 months with some improvement. Two level implantation outcome success was greater than one level. Compassionate use patients had not reached the 6 week follow up yet. Two adverse events UTI and spinal fracture were reported in the CAP patients at 6 weeks. A vasomotor incident and malpositioned implant was noted in the COS cohort at 6 weeks. There is one protocol deviation based on inclusion symptoms.

Conclusions

This minimally invasive surgically implanted device has shown to be statistically superior to continued conservative care in patients greater than 50 years old, with greater than 6 months duration in symptoms associated with a diagnosis of lumbar spinal stenosis, who have mild to moderate symptoms including claudication, who have failed epidural injections, and who have comorbidities associated with their health status. Although the device can be inserted with a minimally invasive operative technique as an outpatient procedure with generally a local anesthetic a decision as to the safety and effectiveness of this device is based solely on 24 month data because information on the patient outcomes after 24 months is not available. This information becomes important when looking at pain relief and return to function. Even though the goal of the study was accomplished showing a significant, statistical difference between the investigational and control groups, more patients report improvement at 12 months than at 24 months.

Contrary to what has been observed in spinal fusion studies, in this study, a percentage of patients whose symptoms improved at 6 and 12 months show a trend of regression of pain and function symptoms toward baseline levels.. There appears to be a trend with early pain relief but the data suggests that in about 15% of patients initially successfully treated by the X-stop had only temporary relief.

The sponsor continued to collect effectiveness results on patients after they had failed treatment and had progressed to laminectomy. Then provided a comparison of the outcomes of the treated laminectomy patients, and patients undergoing laminectomy in a literature article review to the outcomes of the successful X-stop group.

Overall the success of patients was less than 50% in the X-stop group and less than 5% in the control group which is much lower than that predicted in the pre-study stage based on the historical literature. With such a low effectiveness result, the panel will be asked to comment on the indications for the device and what population might benefit from this device.

Labeling

In the draft instructions for use, (Volume 2, Tab VIIIa., page 1/6,) the section entitled "Mechanism of Action" describes the "biomechanical effects on the implanted and adjacent levels," and provides values describing the kinematics, spinal canal and foraminal dimensions, intervertebral disc pressures, restoration of disc height, sagittal balance and facet loads. This reference is found in Amendment 3, Attachment J. The sponsor has not made a link between the findings of the cadaveric study and the clinical study with respect to the biomechanical effects of the device. Data collected in the cadaveric study were different than that collected in the clinical trial. Axial MRI images were obtained from cadaver specimens, allowing for measurements of the area of the spinal canal, while plain film radiographs were used in the Pivotal Trial, from which this measurement cannot be made. Measurements made from radiographs show no significant differences between the X STOP and the control group in measurements of the L1-L5 coronal curve or the L1-L5 angulation at 24 month follow-up. These data are included in Table 52 (Vol 1, p 91) of the PMA

Enclosure: The Zurich Claudication Questionnaire is attached.