Summary of Safety and Effectiveness Data

I. GENERAL INFORMATION

Device Generic Name:	Endovascular Graft
Device Trade name:	Relay® Thoracic Stent-Graft with Plus Delivery System
Device Procode:	MIH
Applicant's Name and Address:	Bolton Medical, Inc., 799 International Parkway, Sunrise, Florida 33325
Premarket Approval Application Number:	P110038
Date of Panel Recommendation:	None
Date of FDA Notice of Approval:	September 21, 2012
Expedited:	Not Applicable

II. INDICATIONS FOR USE

The Relay® Thoracic Stent-Graft with Plus Delivery System is indicated for use in the endovascular repair of fusiform aneurysms and saccular aneurysms/penetrating atherosclerotic ulcers in the descending thoracic aorta in patients having appropriate anatomy, including

- Iliac or femoral access vessel morphology that is compatible with vascular access techniques, devices and/or accessories
- Non-aneurysmal aortic neck diameter in the range of 19 – 42 mm
- Non-aneurysmal proximal aortic neck lengths between 15 and 25 mm and distal aortic neck lengths between 25 and 30 mm, depending on the diameter stent-graft required

III. CONTRAINDICATIONS

The Relay® Thoracic Stent-Graft with Plus Delivery System is contraindicated in the following clinical scenarios:

- Patients who have a condition that threatens to infect the graft

- Patients who are sensitive to, or have known allergies to, the device materials

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Instructions for Use for the Relay® Thoracic Stent-Graft with Plus Delivery System.

V. DEVICE DESCRIPTION

A. Relay® Thoracic Stent-Graft with Plus Delivery System

The Relay® Thoracic Stent-Graft with Plus Delivery System is comprised of two components:

- Relay® Thoracic Stent-Graft
- Plus Delivery System

The Relay® Thoracic Stent-Graft is intended to be delivered endoluminally via access through the femoral or iliac artery to the site of the lesion using the Plus Delivery System. The stent-graft is constrained within the secondary sheath (2nd stage), which was further constrained within the primary sheath (1st stage) until deployed at the intended site of treatment. The pre-loaded system is advanced to the diseased location over a guidewire. Upon deployment, the stent graft self-expands due to the superelastic properties of the nitinol stent. Following expansion of the device within the aorta, the proximal and distal ends of the stent-graft are intended to conform to the shape and size of the proximal and distal seal zones of the targeted lesion due to the radial force of the stents.

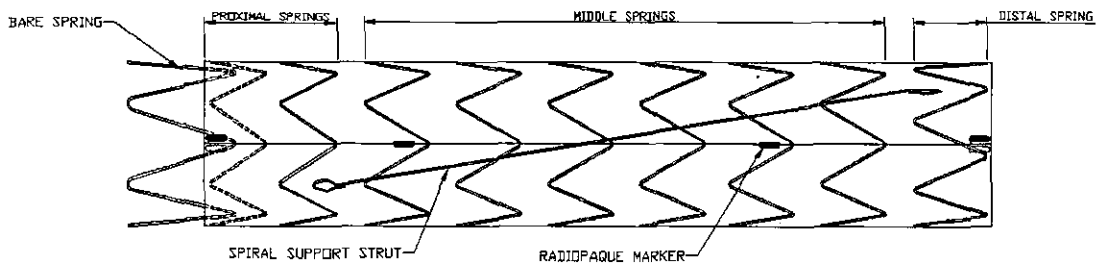
B. Relay® Thoracic Stent-Graft

Relay® Thoracic Stent-Grafts are composed of self-expanding nitinol stents sutured to polyester graft fabric. The skeleton of these devices is a series of sinusoidal nitinol stents sewn along the length of the graft fabric with surgical suture. The Relay® Thoracic Stent-Graft features a bare proximal terminating stent and a covered distal terminating stent. Relay® stent-grafts are constructed with four different types of stents, each having a specific function at their location. ***Figure 5-1*** *shows the Relay® graft with associated* stent types. In addition, there is nitinol spiral support strut for longitudinal support. Platinum-iridium, radiopaque, dumb-bell shaped markers are strategically placed on the graft to facilitate radiographic visualization of the graft material edge.

Relay® Thoracic Stent-Grafts are offered with diameters ranging from 22 mm to 46 mm and covered lengths ranging from approximately 90 mm to 250 mm. Additionally, Relay® Thoracic Stent-Grafts are available in straight configurations, where the diameter is uniform over the length of the stent-graft, or tapered configurations where the diameter decreases over the length of the implant.

During manufacturing, the Relay® Thoracic Stent-Grafts are preloaded into a delivery system.

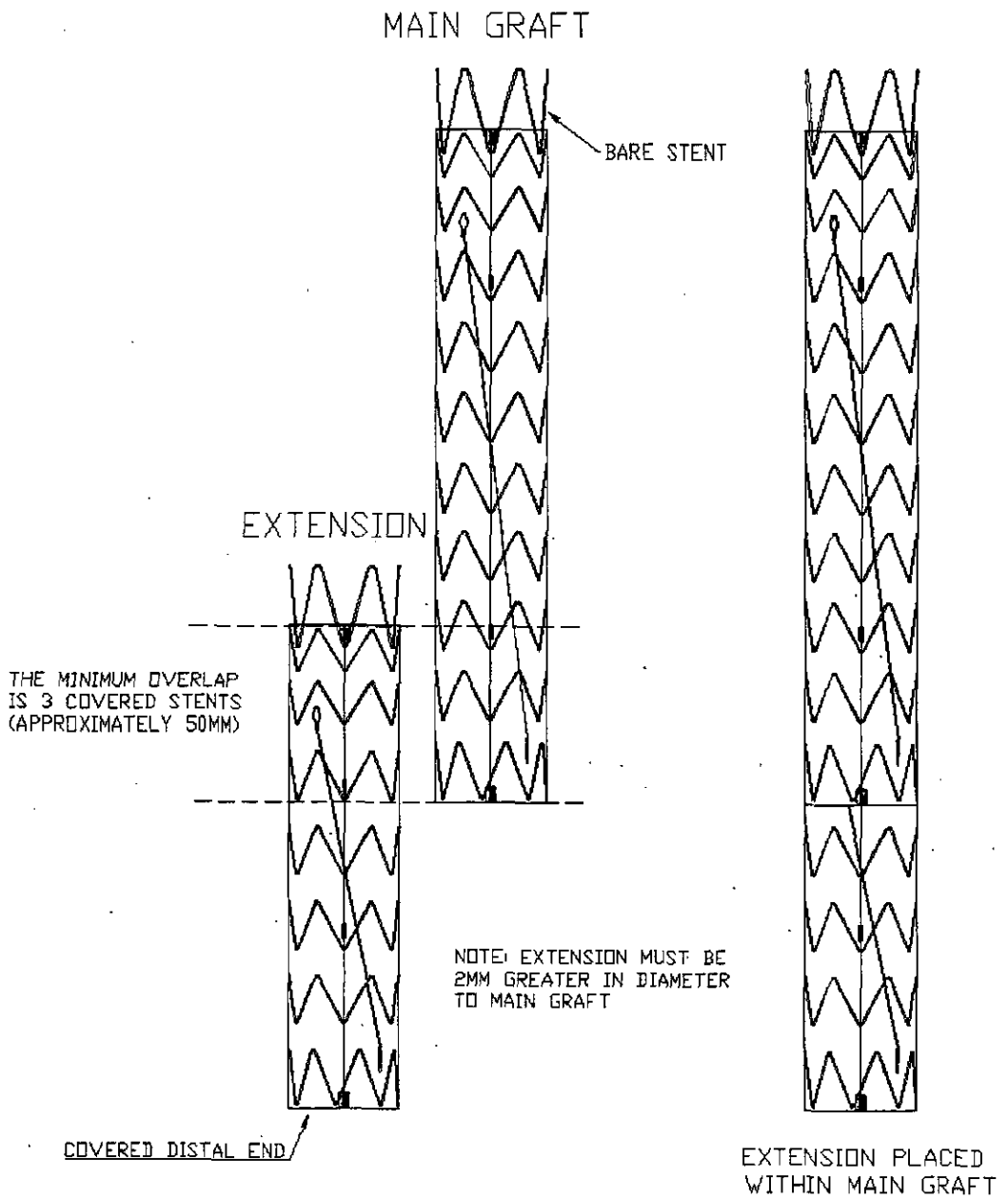
Figure 5-1: Relay® Stent-Graft Configuration with Types of Stents



C. Relay® Thoracic Stent-Graft Configuration and Placement

The Relay® Thoracic Stent-Graft is a modular device that accommodates the use of additional stent-graft sections depending on the configuration of the anatomy where single or multiple components may be required to achieve sufficient coverage of the diseased aorta. If the vessel diameter and condition require variable proximal and distal diameter devices, the smallest diameter stent-graft should be placed first, either at the proximal or distal end of the lesion, as appropriate. . The additional section is to be deployed within the primary piece following the oversizing requirements as detailed in the Instructions for Use (IFU) manual. If the vessel diameter and condition require the same proximal and distal diameter devices, the primary section should be placed first at the proximal end of the lesion. To achieve the same final diameter with the proximal and distal sections, a tapered configuration is required for the distal section. The flare of the tapered graft permits the oversizing requirements between components.

Figure 5-2: Combining Relay® Stent-Grafts



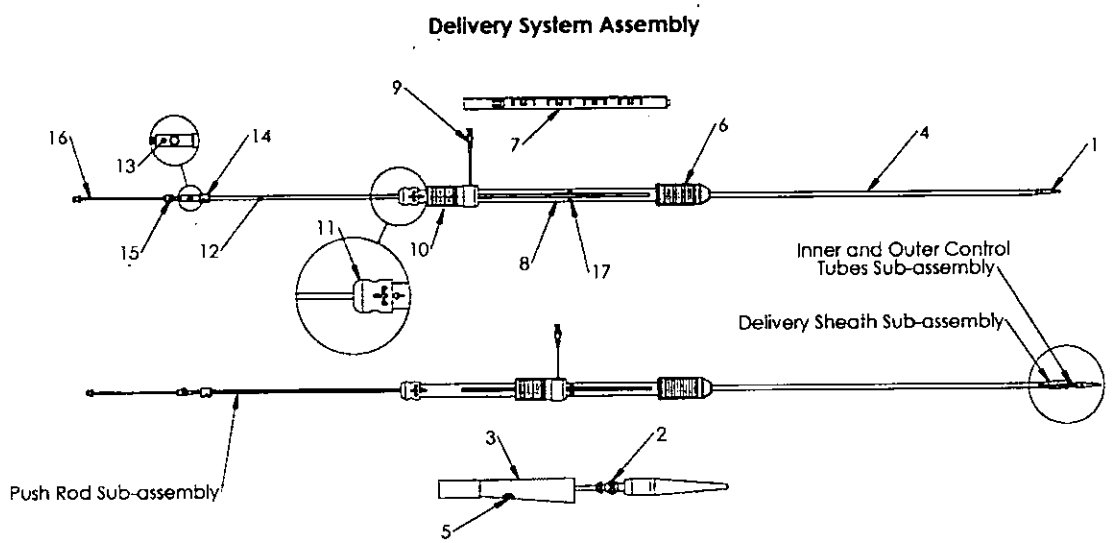
D. Plus Delivery System

The Plus delivery system is a single-use, disposable, two-stage delivery device consisting of sheaths and catheters (primary introduction sheath, secondary delivery sheath, through lumen), as well as a handle and apex release mechanism. It is available in outer diameters ranging from 22 to 26 Fr depending on stent-graft size, and has a working length of 90 cm. The distal end of the system features a pre-formed curve, intended to

facilitate alignment of the stent-graft upon deployment. The stent-graft is constrained within the secondary sheath (2nd stage), which was further constrained within the primary sheath (1st stage). The delivery system is designed to be tracked over a 0.035" guide wire to facilitate introduction of the device through the femoral and iliac arteries. Once the system reaches the placement location, the proximal handle of the delivery system is advanced to exit the secondary sheath from the primary sheath in preparation for deployment. The secondary sheath, composed of thin wall, flexible polyester, enables the thoracic stent-graft to be more easily advanced and deployed in curved and tortuous portions of the anatomy than a polymeric sheath would allow. The secondary sheath, which was connected to the delivery catheter and the delivery handle (deployment grip), is retractable to deploy the constrained stent-graft in a controlled fashion.

The system features an apex release mechanism which constrains the bare stent. This mechanism is controlled by sliding the outer control tube over the guide wire lumen after the deployment from the secondary sheath. This feature provides the ability to reposition the device in a partially deployed state. In addition, this feature provides a controlled apposition of the bare stent to the vessel wall. **Figure 5-3** shows the complete delivery system.

Figure 5-3: Delivery System Schematic



Legend			
1. Delivery System Tip	5. Radiopaque Marker	9. Flush Port / Stopcock	13. Apex Release Retainer
2. Apex Holder	6. Stationary Grip	10. Deployment Grip	14. Apex Release Grip
3. Inner Secondary Sheath	7. Shipping Retainer	11. Controller	15. Guidewire Luer
4. Outer Primary Sheath	8. Main Body	12. Stainless Steel Rod	16. Flushport
			17. Handle Body Mark

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of thoracic aortic aneurysms (TAA) including endovascular repair using another endovascular grafting system, surgical implantation of a synthetic graft within the aneurysmal vessel, and medical management. Each alternative has its own advantages and disadvantages. The physician should fully discuss these alternatives with his/her patient to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Relay® Thoracic Stent-Graft has been commercially available for distribution in Europe since April 2005. Approval of the Plus Delivery System was granted in March 2009. The Relay® Thoracic Stent-Graft with Plus Delivery System is currently sold in several other nations including Australia, Argentina, Brazil, and Mexico.

The Relay® Thoracic Stent-Graft has not been withdrawn from the market for any reason related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events or complications associated with the use of the Relay® Thoracic Stent-Graft with Plus Delivery System that may occur and that may require intervention include, but are not limited to, those listed in **Table 8-1**.

Table 8-1: Potential Adverse Effects

Access Failure	Dysphagia	Reaction to Anesthesia
Adynamic Ileus	Edema (e.g., leg, foot)	Reaction / Pain at Catheter Insertion Site
Allergic Reaction (to contrast, antiplatelet therapy, stent-graft materials)	Embolism (with transient or permanent ischemia or infarction)	Renal Complications (failure, insufficiency)
Amputation	Endoleak	Reoperation
Anaphylaxis	Excessive / Inappropriate Radiation Exposure	Seizure
Anesthetic Complications	Extrusion / Erosion	Seroma
Aneurysm Expansion	Fever / Localized Inflammation	Shock
Aneurysm / Lesion Rupture	Fistulas (aorto-bronchial, aorto-enteric, aorto-esophageal, arteriovenous, lymph)	Stent-Graft Dilatation / Rupture
Angina	Gastrointestinal Complications (bleeding, diarrhea, nausea, vomiting)	Stent-Graft Failure
Bleeding Complications (hemorrhage, hematoma, coagulopathy, procedural bleeding, post-procedural bleeding)	Genitourinary Complications (urinary incontinence, hematuria)	Stent-Graft Infection
Blindness	Hepatic Failure	Stent-Graft Migration
Bowel Ischemia	Impotence	Stent-Graft Misplacement
Bowel Necrosis	Incision Site Complications	Stent-Graft Tearing/Wear
Bowel Obstruction	Infection/Sepsis (including wound infection)	Stent-Graft Twisting/Kinking
Cardiac events (arrhythmia, tachyarrhythmia, cardiac tamponade, myocardial infarction, congestive heart failure, hypertension, hypotension, tachycardia, bradycardia)	Intramural Hematoma	Suture Fracture
Catheter Breakage	Ischemia (spinal cord, perfusion pathways, peripheral, limb, vascular)	Tissue Necrosis
Cerebral Vascular Accident – CVA (stroke)	Lymphocele	Transient Ischemic Attack
Change In Mental Status	Neuropathy (e.g., femoral)	Vascular Access Complications
Claudication (buttock, lower limb)	Pain (e.g., intercostals pain, general pain, etc.)	Vascular Spasm/Trauma
Compartment Syndrome	Paralysis/Paraplegia/ Paresthesia/Paraparesis/Spinal Neurological Deficit	Vessel Damage /Trauma/Rupture
Contrast Toxicity	Perforation (vessel / device)	Vessel Dissection
Conversion To Open Repair	Peripheral Nerve Injury	Vessel (arterial or venous) or Device (Stent-Graft) Occlusion/Thrombosis
Death	Post Implantation Syndrome	Vessel or Stent-Graft Stenosis
Deployment Difficulties/Failures	Pseudoaneurysm	Wire Form Fractures
Device Dehiscence	Pulmonary Complications (atelectasis respiratory failure, respiratory depression, pneumonia, pulmonary edema, pulmonary embolism)	Wound Dehiscence
Device Insertion Or Removal Difficulty	Radiation Overexposure or Reaction	Wound Healing Complications

For adverse events that occurred during the clinical studies, please see Section X, below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Biocompatibility

Biocompatibility testing was conducted on the materials that comprise the Relay® Thoracic Stent-Graft with Plus Delivery System in accordance with ISO 10993-1 and Good Laboratory Practices (21 CFR Part 58). Biocompatibility studies for the Relay® Thoracic Stent Graft were conducted based on the principles of an implant device that is in permanent contact with blood (>30 days), whereas the studies for the Plus Delivery System were based on the principles of an externally-communicating device with limited contact with circulating blood (<24 hr). Bolton Medical utilizes two separate suppliers for the graft fabric (Supplier 1 and Supplier 2). Since the materials from the two suppliers has been confirmed to be equivalent, this testing supports both suppliers.

Table 9-1 and **Table 9-2** provide a summary of the biocompatibility test results for the Relay® Thoracic Stent-Graft and the Plus Delivery System, respectively.

Table 9-1: Stent-Graft Tests

Test	Purpose	Acceptance Criteria	Results
Cytotoxicity ISO Elution Method	To evaluate if the device has the potential to induce cytotoxic effects	Test article must not show evidence of toxicity induction	Pass. No evidence of cell lysis or toxicity induction; test article graded less than 2 (mild reactivity)
Hemocompatibility			

Table 9-1: Stent-Graft Tests

• *In vitro* Hemolysis study	To assess if the device could cause red blood cell hemolysis	Test article must be non-hemolytic.	Pass. Hemolytic index for the test article in direct contact with blood was 1.1%. Hemolytic index for test article extract was 0.1%. As a result the test article was considered non-hemolytic
• C3a Complement Activation Study	To assess if the device activates the complement system	Test article must not exhibit significant activation of the complement system	Pass. C3a concentration for the test article was not higher than for the activated NHS control or the negative control. As such the test article was not considered an activator of the complement system

Table 9-1: Stent-Graft Tests

• SC5b-9 Complement Activation Study	To assess if the device activates the complement system	Test article must not exhibit significant activation of the complement system	Pass. The concentration of SC5b-9 in the test article was statistically higher than both the activated NHS and negative controls and was 17.1% of the positive reference control. However, the SC5b-9 result was within the historical range of the activated NHS and negative controls. As such, the test article was considered to be a low potential activator of the complement system
• Partial Thromboplastin Time	To determine the potential of the test article to cause an effect on the coagulation cascade via the intrinsic coagulation pathway	Test article must not exhibit significant effects on the coagulation pathway	Pass. Plasma exposed to the test article had an average clotting time of 300 seconds and was 100% of the negative control. As such, the test article was considered a non-activator.

Table 9-1: Stent-Graft Tests

• *In vivo* Thromboresistance	To evaluate the potential of the device to resist thrombus formation when placed in the vasculature	Test article should demonstrate thrombus resistance	Pass. No significant thrombus detected on the stent-graft at 1 and 2 weeks. Maximum thrombus score ≤ 1. Results suggest the test article is resistant to thrombus formation
ISO Acute Systemic Toxicity	To evaluate the potential for the device to elicit acute systemic toxic events	Test article must not induce mortality or show evidence of systemic toxicity	Pass. No mortality or evidence of systemic toxicity
Pyrogenicity (USP Materials Mediated Pyrogen Test)	To evaluate if the device has the ability to induce a pyrogenic response	Test article must be non-pyrogenic;	Pass. No temperature increase > 0.5°C detected; therefore, non-pyrogenic.
Irritation (ISO Intracutaneous Study)	To evaluate if the device has the potential to induce irritation	Test article extract must not significantly induce irritation.	Pass. The difference between the overall mean erythema/edema scores for both the sodium chloride and sesame oil test article extracts and control scores was 0.0

Table 9-1: Stent-Graft Tests

Sensitization (ISO Guinea Pig Maximization Test)	To evaluate the potential of the device to cause dermal irritation	Test article must not be a dermal sensitizer.	Pass. No evidence of inducing delayed dermal contact sensitization (not considered a sensitizer) for either the sodium chloride or sesame oil test article extracts. All reaction grades were 0.
Subchronic Toxicity (ISO)	To evaluate the potential of the device to cause systemic toxic effects following repeated exposures	Test article must not show evidence of systemic toxicity.	Pass. No evidence of systemic toxicity. Daily clinical observations were within limits and similar between test and controls. No changes in histopathology, hematology, or clinical chemistry.
Implantation			

Table 9-1: Stent-Graft Tests

• ISO Muscle Implantation Test (4 weeks)	To evaluate the potential for the device to elicit irritation or toxic responses after implantation	Test article must not elicit significant irritation or toxic responses after implantation.	Pass. Macroscopic reaction was not significant compared to the negative control. Microscopically, the test article was classified as a slight irritant compared to the control
• ISO Muscle Implantation Test (12 weeks)	To evaluate the potential for the device to elicit irritation or toxic responses after implantation	Test article must not elicit significant irritation or toxic responses after implantation.	Pass. Macroscopic reaction was not significant compared to the negative control. Microscopically, the test article was classified as a moderate irritant compared to the control
Genotoxicity • ISO Reverse Mutation Study	To evaluate if the device could induce mutagenic changes in selected bacterial test strains	Test article must be non-mutagenic	Pass. In no case was there a 2-fold or greater increase in the mean number of revertent tester strains (TA98, TA100, TA1535, TA 1537, and WP2*uvr*A) in the presence of the test article extract. Therefore considered non-mutagenic.

Table 9-1: Stent-Graft Tests

• *In vivo* Mouse Lymphoma Assay	To determine the ability of the device to induce forward mutations	Test article must be non-mutagenic	Pass. Mutant frequencies and cloning efficiencies of the test article preparations were well within the limits defined for a negative control response. Therefore considered non-mutagenic.
• *In vivo* Mouse Micronucleus Assay	To determine the ability of the device to induce *in vivo* clastogenic events or to damage the mitotic spindle	Test article must be non-mutagenic	Pass. No apparent gross manifestations of toxicity or significant erythropoietic disturbances resulting in delayed mutagenesis. Also no increases in mPCE production as compared to controls. Therefore considered non-mutagenic.

Table 9-2: Delivery System Tests

Test	Purpose	Results	Pass/Fail
Cytotoxicity (ISO Elution Method)	To evaluate if the device has the potential to induce cytotoxic effects	Test article must not show evidence of toxicity induction	Pass No evidence of cell lysis or toxicity induction; test article graded less than 2 (mild reactivity).
Hemocompatibility • *In vitro* Hemolysis Study	To assess if the device could cause red blood cell hemolysis	Test article must be non-hemolytic.	Pass. Hemolytic index for test article extract and for test article direct contract was 0%. As such, the test article was considered non-hemolytic
• Partial Thromboplastin Time	To determine the potential of the test article to cause an effect on the coagulation cascade via the intrinsic coagulation pathway	Test article must not exhibit significant effects on the coagulation pathway	Pass. Plasma exposed to the test article had an average clotting time of 303.7 seconds and was 77% of the negative control. As such, the test article was considered a minimal activator.

Table 9-2: Delivery System Tests

Test	Purpose	Results	Pass/Fail
• C3a Complement Activation Study	To assess if the device activates the complement system	Test article must not exhibit significant activation of the complement system	Pass. C3a concentration for the test article was not higher than for the activated NHS control or the negative control. As such the test article was not considered an activator of the complement system
• SC5b-9 Complement Activation Study	To assess if the device activates the complement system	Test article must not exhibit significant activation of the complement system	Pass. SC5b-9 concentration for the test article was not higher than for the activated NHS control or the negative control. As such the test article was not considered an activator of the complement system

Table 9-2: Delivery System Tests

Test	Purpose	Results	Pass/Fail
• *In vivo* Thromboresistance	To evaluate the potential of the device to resist thrombus formation when placed in the vasculature	Test article should demonstrate thrombus resistance	Pass. Thrombus was detected only on the flexible inner delivery sheath. This was believed to be due to flow disturbance rather than biomaterial effect. Overall, the device was relatively resistant to thrombus formation
Acute Systemic Toxicity (ISO)	To evaluate the potential for the device to elicit acute systemic toxic events	Test article must not induce mortality or show evidence of systemic toxicity	Pass. No mortality or evidence of systemic toxicity from the test article
Pyrogenicity (USP Pyrogen Test)	To evaluate if the device has the ability to induce a pyrogenic response	Test article must be non-pyrogenic	Pass; no temperature increases > 0.5°C, therefore, non-pyrogenic
Irritation (ISO Intracutaneous Study)	To evaluate if the device has the potential to induce irritation	Test article must not induce significant irritation.	Pass. The difference between test article extracts and control was 1.0 or less.

Table 9-2: Delivery System Tests

Test	Purpose	Results	Pass/Fail
Sensitization (ISO Maximization Test)	To evaluate the potential of the device to cause dermal irritation	Test article must not be a dermal sensitizer.	Pass. No evidence of inducing delayed dermal contact sensitization for either the sodium chloride or sesame oil test article extracts. All reaction grades were 0.

Bench Testing

Bolton Medical conducted comprehensive pre-clinical, bench and analytical testing on the Relay® Thoracic Stent-Graft with Plus Delivery System. The *in vitro* testing was intended to verify that the performance attributes of the Relay® Thoracic Stent-Graft with Plus Delivery System are sufficient to minimize adverse events under anticipated clinical conditions. Testing was conducted in accordance with ISO 25539-1, Cardiovascular implants --- Endovascular devices --- Part 1: Endovascular prostheses. This testing included both the stent-graft and the delivery system. The testing details include results from T=0 (baseline) as well as results using samples accelerated aged to 3 years (T=3). An asterisk (*) indicates testing was performed at both T=0 and T=3. Testing verified that the Relay® Thoracic Stent-Graft with Plus Delivery System met its product performance and design specifications. **Table 9-3** outlines the tests performed.

Results obtained from these *in vitro* studies support the safety and effectiveness of the Relay® Thoracic Stent-Graft with Plus Delivery System.

Table 9-3: Relay® Thoracic Stent-Graft with Plus Delivery System Bench Test Results

Tests	Purpose	Acceptance Criteria	Results
Delivery System Verification Tests			
General Appearance and Physical Checks (*)	To verify that the system appearance characteristics are acceptable to the end-use, and to verify that the components of the system are working properly	The device must not exhibit signs of objectionable discoloration or damage, and all aspects of the system should be in proper working order and in the intended positioning as required by the IFU	All samples met specification
Bond strength (*)	To determine the bond strength of the joints and/or fixed connections of the delivery system	Sub-assemblies tested must meet pre-determined pull forces depending on the bond. Acceptance criteria ranged from 5 lbs to 25 lbs (22.24 N to 111.2N)	All samples met specification

Table 9-3: Relay® Thoracic Stent-Graft with Plus Delivery System Bench Test Results

Tests	Purpose	Acceptance Criteria	Results
Component dimensional compatibility (includes dimensional verification) (*)	To determine the system dimensions for verification to design specification, and to evaluate the dimensional compatibility between the system and its accessory devices listed in the Instructions for Use (IFU)	• System must be compatible with 0.035" guide wire and 0.036" mandrel • Delivery system sheath O.D. must meet pre-determined tolerances. • Useable length must meet predetermined specifications: 600 mm +/- 5 mm (non-deployed); 895 mm min (deployed)	All samples met specification
Simulated Use (includes pushability, trackability and torqueability) (*)	To evaluate the performance of the delivery system using an aortic model that simulates the intended use conditions. This test includes a qualitative assessment of simulated use, flex/kink, pushability, torqueability, and trackability of the thoracic system	Characterization study	Guide wire acceptance, pushability, trackability, torqueability, kink resistance, and flushing of the guide wire lumen were all evaluated and determined to be acceptable.

Table 9-3: Relay® Thoracic Stent-Graft with Plus Delivery System Bench Test Results

Tests	Purpose	Acceptance Criteria	Results
Profile/diameter Test (*)	To determine the system maximum diameter at the loaded stent-graft section (largest profile) in order to evaluate the dimensional component compatibility between the delivery system and the vasculature	The device must pass through a Go Gauge over the loaded section of the device	All dimensions for the test samples met the acceptance criteria.
Torsional Bond Strength	To determine the torque required to cause failure of the bonded joints of the delivery system components	The delivery system sheath introducer must be torqued at 180° without any damage to the sheath bond.	All samples were torqued 180° without any sheath attachment damage.
Tubing tensile strength	To determine the strength of the tubing used in the delivery system.	Introducer Sheath: 7% maximum elongation at 25 lbs (111.2 N)	All test samples were within 7% elongation at 25 lbs.(111.2N)

Table 9-3: Relay® Thoracic Stent-Graft with Plus Delivery System Bench Test Results

Tests	Purpose	Acceptance Criteria	Results
Force to deploy (*)	To determine the force to advance and deploy the stent-graft from the delivery system as well as testing for all relevant characteristics pertaining to deployment (e.g., accuracy, re-seating, system removal, etc.).	– Advancement force: ≤ 25 lbs. (111.2N) – Deployment force: ≤ 25 lbs. (111.2 N)* – Clasp Release ≤ 10lbs (44.5N)	All samples met acceptance criteria.
Flex / Kink	To determine the minimum radius of curvature that the system can accommodate without kinking	The loaded delivery system must permit deployment around the tested radii arches without kinking that would prevent deployment or cause damage to the stent-graft or delivery system	All samples met acceptance criteria.
Assessment of hemostasis (*)[a]	To evaluate the system's ability of any seals or valves to maintain adequate hemostasis	Amount of water obtained through leaking in 1 minute should be ≤ 15 g.	Samples met the acceptance criteria. The maximum amount of water lost was 6.7g
Visibility	To evaluate the ability to visualize the system using the imaging techniques specified in the IFU.	Test units must be visible under fluoroscopy	All samples met acceptance criteria.

Table 9-3: Relay® Thoracic Stent-Graft with Plus Delivery System Bench Test Results

Tests	Purpose	Acceptance Criteria	Results
Lubricity test (*)[b]	To determine the lubricity of the Plus delivery system sheath	Force of the coated sheath must be lower than an non-coated sheath	There was a significant difference between coated and non-coated sheaths/tips.
Manual alignment	To evaluate the ability of the Plus system to manually align while still in the secondary sheath	Characterization study	All samples were able to be manually rotated 360° without difficulty
Tracking through tortuous vessel	To evaluate the ability of the Plus delivery system to tract through extreme tortuous aortas	Characterization study	All samples were evaluated for pushability, tracking, kinking and torqueability.
Vessel Wall Rigidity	To evaluate the ability of the Plus delivery system to track through an extremely tortuous aorta	Characterization study	No excessive force against the vessel wall was noted.
Particulate Test	To determine the amount of particulate matter associated with the hydrophilic coating of the introducer and tip (as compared to original uncoated system)	Characterization Study	No statistically significant difference between the uncoated sheaths and coated sheaths, thus confirming that hydrophilic coating does not create a greater incidence of loose particulates.

Table 9-3: Relay® Thoracic Stent-Graft with Plus Delivery System Bench Test Results

Tests	Purpose	Acceptance Criteria	Results
Stent-Graft Design Verification Tests			
Stent-graft Dimensional verification (*)	To determine the dimensions of the stent-graft in the deployed state for verification to design specifications	Straight Configuration: Length must be within +/- 2 mm of the drawing dimension Tapered Configuration: Inner diameter must be within +/- of drawing dimensions.	All dimensions met the acceptance criteria
Visibility	To evaluate the ability to visualize the system using the imaging techniques specified in the IFU.	Test units must be visible under fluoroscopy	All test units were visible under fluoroscopy
Implant length to diameter relationship	To determine the relationship between implant length and expanded implant diameter	The length of the stent-graft must be within specification (+/- 2 mm of the assembly drawing value) while compressed in the minimum and maximum simulated vessel sized tubes.	All samples met the acceptance criteria.
Strength of stent/attachment to graft bond (*)[c]	To determine the strength of the fixations or bond between the graft material and the stent/attachment	5 lbs (22.2 N) per apex	All samples met the acceptance criteria.

Table 9-3: Relay® Thoracic Stent-Graft with Plus Delivery System Bench Test Results

Tests	Purpose	Acceptance Criteria	Results
	system.		
Recoil (*)	To determine the outer diameter of the stent-graft in the deployed state for verification to design specifications. The purpose of this test was to show that the implant can withstand the strains experienced in radial compression during loading and unloading without any significant change to dimensions or geometry	Stent-graft recoil outer diameter must be within – 0 mm and + 2 mm of the nominal diameter at the proximal and distal ends. (-1 / +2 for Relay® Plus Shelf Life)	All dimensions met the acceptance criteria
Flex/Kink	To determine the minimum radius of curvature that the stent-graft can accommodate without kinking	The stent-graft must bend into various radii arches without kinking, which was defined as 25% or more of the graft lumen not being patent	All samples met specification

Table 9-3: Relay® Thoracic Stent-Graft with Plus Delivery System Bench Test Results

Tests	Purpose	Acceptance Criteria	Results
Flex / Kink -- Apposition Test	To determine if the stent-graft can be deployed in a straight section of the simulated vessel to verify the pre-curve of the nitinol inner control tube does not affect graft apposition	The graft loaded in the delivery system must be deployed with complete apposition.	All stent-grafts had complete apposition up to the first covered stent
Stent-graft Integrity (post-deployment) (*)	To demonstrate that the stent-graft retains its physical integrity after the deployment process	The sample must not exhibit physical damage that will negatively impact the performance of the device. Any observed damage will be analyzed on an individual basis.	There were no negative observations noted.
Crush resistance	To determine the force required to permanently radially deform or fully collapse the stent-graft as measured perpendicular to the longitudinal axis	Observations were documented as pass/fail along with the forces used to crush the stent-graft and the deflection observed. Any deformation to the stent-graft was considered a failure.	All samples were crushed to collapse without damage.
Local compression	To determine the deformation of the stent-graft in response to localized compressive forces, perpendicularly applied to the	Observations were documented as pass/fail along with the forces used to compress the stent-graft and the deflection observed. Any deformation to the stent-graft was	All samples were compressed to collapse without damage.

Table 9-3: Relay® Thoracic Stent-Graft with Plus Delivery System Bench Test Results

Tests	Purpose	Acceptance Criteria	Results
	longitudinal axis of the stent-graft.	considered a failure.	
Migration resistance and sealing	To determine the force required to displace the stent-graft in a mock artery. This test provides an indication of the resistance to migration provided by the fixation mechanisms of the stent-graft. In addition, it determined if the fixation points were against the mock artery completely in order to address sealing characteristics.	Safety coefficient (representing the stability of the device and based on the ratio of ultimate contact shear to actual contact shear) must be > 1	Coefficient for 34mm size = 2.29; coefficient for 46 mm size = 2.00
Radial outward force (hoop strength) (*)[c]	To determine the force exerted by a self-expanding implant as a function of the implant diameter	Characterization study / Positive outward force expected	The Relay® stent-graft demonstrated positive outward radial force. Proximal seal zone radial force ranged from 2.8 N to 3.9 N; distal seal zone ranged from 3.4 N to 5.3 N.

Table 9-3: Relay® Thoracic Stent-Graft with Plus Delivery System Bench Test Results

Tests	Purpose	Acceptance Criteria	Results
Burst/circumferential strength	To determine the pressurized burst strength or circumferential strength of the stent-graft if used with an accessory balloon.	The stent-graft must withstand 1.5 ATM of pressure without damage	All samples withstood the 1.5 ATM without damage
Longitudinal tensile strength	To determine the longitudinal tensile strength of the stent-graft	25 lbs (111.2N)	All samples met the acceptance criteria.
Pull test for modular components	To determine the force required to separate the modular components of a stent-graft in the deployed state.	Characterization study / 4 N minimum	All samples exhibited forces ranging from 6N to 10 N on average. Average separation force was 8.7N
Factory anastomotic strength	To determine the tensile strength of any manufactured anastomosis (in this case, graft seam)	16 lbs (71.2 N) per 2 cm section	Average force was 37.8N.
Porosity/water permeability	To determine the rate of fluid flow through the wall of the stent-graft as virgin material and with sutures	Characterization study	Seamed Relay® material had a higher permeability than the non-seamed material (413 mL/min/cm^2 versus 232 mL/min/cm^2).

Table 9-3: Relay® Thoracic Stent-Graft with Plus Delivery System Bench Test Results

Tests	Purpose	Acceptance Criteria	Results
Integral water permeability	To determine the rate of water leakage through the entire stent-graft, incorporating all modular components and extension devices.	Characterization study	The integral water permeability for the stent-graft was 168 ml / min / cm^2. All of the samples were tested at hypertensive blood pressure (150mmHg) and one was at (140mmHg). The integral water permeability was similar to the non-seamed fabric (205 mL/min/cm^2 vs. 168 mL/min/cm^2)
Corrosion	To evaluate corrosion resistance of the stent-grafts metal components	Characterization study	The test was conducted per ASTM F2129 and evaluated the general resistance to pitting corrosion. Results indicated resistance to localized corrosion. Average breakdown potentials on pre and post fatigued stents were greater than 600 mV vs. SCE

Table 9-3: Relay® Thoracic Stent-Graft with Plus Delivery System Bench Test Results

Tests	Purpose	Acceptance Criteria	Results
MR compatibility Conducted per ASTM F 2052 and ASTM F 2182	To characterize the stent-graft's performance in the magnetic resonance environment	1) The presence of the stent-graft must not pose an additional unacceptable risk to patients when subjected to 1.5T and 3.0T magnetic fields. 2) To characterize image artifact	No observed magnetic field interactions (e.g., translational attraction, migration, or torque) and no MR-related heating at levels to present risk. Image artifact was characterized.
Durability ---Stress/strain analysis (Finite Element Method Analysis)	Finite element method analysis was used to determine the maximum strains in compression when subjected to catheter loading and an *in vivo* pulsatile loading environment.	Characterization study	The worst case stent design was identified. Information was used as a reference in appropriate *in vitro* testing including pulsatile fatigue testing.
---Fatigue (stent apex)	To evaluate the durability of the stents	Test samples must demonstrate a stent fatigue life in excess of 400 million cycles (10 years *in vivo* simulation).	No fractures after 400 million cycles
---Fatigue (fabric seam)	To evaluate the durability of the fabric	Test samples must demonstrate a seam fatigue life in excess of 400 million cycles. (10 years *in vivo* simulation).	No suture breaks, fabric tears, suture hole elongation, or seam separations after 400 million cycles

Table 9-3: Relay® Thoracic Stent-Graft with Plus Delivery System Bench Test Results

Tests	Purpose	Acceptance Criteria	Results
--Fatigue (pulsatile whole device; single section)	To evaluate the durability of the stent-graft in a simulated *in vivo* environment	Devices must demonstrate structural and lumen integrity over 400 million cycles. (10 years *in vivo* simulation).	Devices retained basic structural and lumen integrity
--Fatigue (pulsatile whole device, overlap)	To evaluate the durability of overlapped stent-grafts in a simulated *in vivo* environment	Devices must demonstrate structural and lumen integrity over 400 million cycles. (10 years *in vivo* simulation).	Devices retained basic structural and lumen integrity
--Fatigue (pulsatile, whole device, bending, overlap)	To evaluate the durability of overlapped stent-grafts in a bent configuration in an *in vivo* environment	Devices must demonstrate structural and lumen integrity over 400 million cycles. (10 years *in vivo* simulation).	Devices retained basic structural and lumen integrity

Table 9-3: Relay® Thoracic Stent-Graft with Plus Delivery System Bench Test Results

Tests	Purpose	Acceptance Criteria	Results
--Fatigue (longitudinal / orbital)	To evaluate the durability of the stent-graft in a simulated *in vivo* environment	Devices must demonstrate structural and lumen integrity over 400 million cycles (10 years *in vivo* simulation).	Devices retained basic structural and lumen integrity, no fractures of longitudinal support system detected

(*) indicates testing done at both T = 0 and T = 3.

[a]Shelf-life testing on original Relay® system only since there was no change to the delivery system with regard to the hemostatic control mechanism in the Relay® with Plus Delivery System

[b]Shelf-life testing on the Relay® with Plus Delivery System only since the original system did not have a hydrophilic coating

[c]Shelf-life testing on original Relay® system only since there was no change to the stent-graft with the introduction of the Plus Delivery System

[d]Package integrity testing was conducted as part of the shelf-life studies of the original Relay® system and successfully demonstrated that the package remains integral after 3 years simulated aging. Since the packaging configuration was not changed with the introduction of the Plus delivery system, this test was not repeated

B. Animal Studies

Preclinical, *in vivo* animal testing, using full-scale devices, manufactured under the same conditions as product to be commercialized was conducted for up to 26 weeks (6 months) in 15 ovine test systems to evaluate the delivery/deployment, functionality (e.g., patency, integrity, visibility, etc.), and healing associated with the Relay® Thoracic Stent-Graft when placed in the thoracic aorta of sheep to ensure the effects of implantation on this part of the vascular anatomy were adequately evaluated. This study was conducted in accordance with applicable portions of Good Laboratory Practice Regulations (21 CFR Part 58).

The results demonstrated adequate performance of the Relay® Thoracic Stent-Graft with it original delivery system, Transport® as assessed by adequate access, advancement, deployment, deployment accuracy, visibility and other related features. Although the *in vivo* animal testing was conducted with the prior delivery system (i.e. Transport®), the vast majority of the testing evaluated the stent-graft which remained unchanged. Stent-graft patency, integrity and histopathological responses were acceptable. A summary of the *in vivo* animal testing is provided in **Table 9-4.**

Table 9-4: Summary of Relay® Ovine Implant Study

Study	Number / Type of Animal*	Test Article	Objectives	Success Criteria	Results
Preclinical Evaluation of the Bolton Medical Thoracic Stent Graft in an Ovine Model (UA-04-BOL1) – 4 and 26 weeks	6 sheep – 4 week arm 7 sheep – 26 week (6 month) arm	Relay® Thoracic Stent-Graft	To evaluate the delivery/deployment, functionality (e.g., patency, integrity, visibility, etc.), and healing associated with the Relay® Stent-Graft when placed in the thoracic aorta of sheep	To ensure the effects of implantation on this part of the vascular anatomy are adequately evaluated; including adequate device handling, integrity and healing (histopathological) response	The Relay® device was easily deployed and the implant was well-tolerated by the sheep. The devices remained intact and widely patent without evidence of migration through explant at 4 and 26 weeks. Histological evaluation verified cellular incorporation of all implants. The development of a stable, anti-thrombogenic luminal cellular lining was observed in all grafts by 26 weeks. There was evidence mild-to-moderate inflammatory response but no histological evidence of infection.

*Fifteen (15) sheep entered the study. Two (2) were withdrawn early due to complications. One sheep had abnormal intestinal distention at the time of the procedure, making isolation of the aorta difficult and prolonging procedure time. It was not possible to extubate this animal and it was euthanized. Another sheep suffered post-operative paraplegia, a known complication for this species, which did not resolve. The animal was euthanized.

C. Additional Studies

Packaging, Shelf Life Testing and Sterilization

The Relay® Thoracic Stent-Graft with Plus Delivery System is a single-use device provided sterile to the end user. The Relay® Thoracic Stent-Graft with Plus Delivery System is sterilized by gamma irradiation and is validated to demonstrate a Sterility Assurance Level (SAL) of 10^{-6}.

Packaging performance testing demonstrates that the packaging design for the Relay® Thoracic Stent-Graft with Plus Delivery System is sufficient to adequately protect the device and maintain the integrity of the device package throughout its three-year shelf life claim.

Shelf-life testing results are presented within the *in vitro* bench test results as part of **Table 9-3.** Accelerated shelf-life product testing conducted on the Relay® Thoracic Stent-Graft with Plus Delivery System supports a 3-year shelf-life claim.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The safety and effectiveness data supporting the Relay® Thoracic Stent-Graft with Plus Delivery System included data from a multi-center pivotal study across the United States, a multi-center feasibility study conducted across the United States, data from a Continued Access arm of the pivotal trial, and a post-market European Registry. These sources of data are summarized in **Table 10-1**.

Table 10-1: Summary of Clinical Studies

Study	Study Design	Objective	# Sites	# Enrolled
Relay® Phase II study G040175	Prospective, non-randomized, multi-center with comparison to a combination concurrent/historical control	To evaluate the safety and effectiveness of the Relay® Thoracic Stent-Graft with Plus Delivery System	27	180
Relay® Feasibility study (Phase I)	Prospective, single-arm multi-center	To evaluate the safety and preliminary performance	6	30
Continued Access	Prospective, non-randomized, multi-center	To continue gathering safety and effectiveness data of the device	16 (20 permitted)	12 subjects presented; enrollment ongoing
European registry (RESTORE)	Post-market, multi-center single-arm	Evaluate clinical performance post-market	22	304

Relay® Phase II Study

The applicant performed a clinical study to establish a reasonable assurance of the safety and effectiveness of the Relay® Thoracic Stent-Graft for treating descending thoracic aortic aneurysms (fusiform aneurysm and saccular aneurysms/penetrating ulcers) in the U.S. under IDE number G040175. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The study was an open-label, non-randomized, prospective, multicenter, two-arm clinical study. There was no masking. This study was designed to evaluate the safety and effectiveness of the Relay® Thoracic Stent-Graft in subjects with a diagnosed thoracic aortic aneurysm or penetrating atherosclerotic ulcer compared with subjects who underwent open surgical repair for the same pathologies. The study included 120 subjects treated with the Relay® Thoracic Stent-Graft (Relay® cohort) and 60 surgical control subjects (surgical control cohort). The study included 29 investigational sites, 27 of which enrolled subjects. The surgical control cohort was a combination of prospectively- and retrospectively-treated subjects.

During the course of the study, two changes were implemented. The delivery system was modified from the original system to the Plus Delivery System. At the same time, inclusion criteria of the protocol was modified to permit enrollment of subjects with isolated penetrating ulcers (PAUs). Due to these changes, two subgroup analyses were performed for subjects who were treated with the Relay® Stent-Graft.

1. Clinical Inclusion and Exclusion Criteria

a) Type of Controls

The surgical control group consisted of 60 subjects and was a combination of prospectively-treated (n=7) and retrospectively-treated (n=53) subjects. Prospective subjects were those who underwent open surgical repair after the date of the institutional review board (IRB) approval at the institution in which they were treated. The number of prospective controls was augmented by data from retrospective subjects. The necessary number of retrospective controls to achieve a total of 60 controls were identified by collecting consecutive lists of subjects who had undergone surgical repair within the 10 years prior to IRB approval for the institution in which they were treated and enrolling the 60 most recently treated surgical subjects among all the participating institutions who meet the eligibility criteria and consent to participate.

It was not feasible to randomize subjects to implantation of the Relay® Thoracic Stent-Graft or surgical repair due to physician preferences, subject preferences, and ethical concerns. Subjects were enrolled on a first come/first serve basis; however, a single investigational site was not permitted to enroll more than 30% of the enrollment total. Subjects were enrolled in the Relay® cohort if they met all of the inclusion criteria and none of the exclusion criteria. In order to minimize selection bias, similar inclusion/exclusion criteria applied to both the endovascular and surgical cohorts. Subjects in the surgical control cohort did not have to meet the anatomical criteria required for placement of the Relay® device. In addition, enrollment of surgical subjects at the same sites that were enrolling endovascular subjects was encouraged to minimize differences in subject care between the two groups.

The surgical control group consisted of both prospectively-treated and retrospectively-treated subjects. Surgical subjects were considered prospective subjects if they

underwent surgical repair after the date of IRB approval at the institution. Subjects were considered retrospective subjects if they already had surgical repair prior to the date of IRB approval. The retrospective portion of the cohort was assembled based on medical record review. Subjects were selected for screening from a master list of all patients who underwent open surgical repair in the 10 years prior to IRB approval across all participating hospitals. The most recently treated were screened first.

b) Treatment Arms

Subject meeting eligibility criteria for the Relay® Stent-Graft were enrolled into the Relay® cohort. Subjects who did not meet the criteria for the Relay® cohort and who underwent surgical repair were enrolled into the surgical control cohort. Similarly, surgically-treated subjects retrospectively identified were enrolled into the surgical control cohort.

c) Clinical Inclusion/Exclusion

Enrollment in the Relay® cohort was limited to patients who met the following selection criteria as shown in **Table 10-2.**

Table 10-2: Inclusion and Exclusion Criteria for Relay® Cohort

Inclusion Criteria	Exclusion Criteria
a.) Subject was ≥18 years of age.	a) Subject had any of the following conditions in his/her descending thoracic aorta: 1. dissections – acute or chronic, in ascending or descending aorta 2. intramural hematoma (current or previous) 3. acute transection or acute traumatic injury 4. pseudoaneurysm (false aneurysm) 5. symptomatic aneurysm, including ruptured lesions.
b.) Subject must have met at least one of the following: 1. descending thoracic fusiform aneurysm, 5 cm in diameter or greater 2. descending thoracic aneurysm that was 4 cm or more in diameter that had increased in size by 0.5 cm in last 6 months 3. descending thoracic aneurysm with a maximum diameter that exceeded 2 times the diameter of the	b) Subject's proximal neck diameter, measured outer-wall to outer-wall on a sectional image or multiplanar reconstruction CT was <18 or >42 mm.

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Table 10-2: Inclusion and Exclusion Criteria for Relay® Cohort

Inclusion Criteria	Exclusion Criteria
nonaneurysmal, adjacent aorta 4. saccular aneurysm in the descending thoracic aorta or PAU.	
c.) Subject had proximal and distal aortic neck suitable for stent-graft placement, with diameter ranging between 18 mm and 42 mm.	c) Subject's distal neck diameter, measured outer-wall to outer-wall on a sectional image or multiplanar reconstruction CT was <18 or >42 mm.
d.) Subject had a proximal attachment zone distal to the left common carotid and a distal attachment zone proximal to the origin of the celiac artery. The length of the attachment zones depended on the intended stent-graft diameter. The proximal attachment zone was 15 mm for 22 to 28 mm grafts, 20 mm for 30 to 38 mm grafts, and 25 mm for 40 to 46 mm grafts. The distal attachment zone was 25 mm for 22 to 38 mm grafts and 30 mm for 40 to 46 mm grafts. Note that coverage of the left subclavian artery was permitted. Additionally, coverage of the celiac artery was permitted but only if this artery was already occluded at the time of the procedure.	d) Subject had prohibitive calcification, occlusive disease, or tortuosity of intended fixation sites.
e.) Subject's vascular dimensions (e.g., aortic diameters, length from left subclavian to celiac artery) were in the range that could safely be treated with the Relay® Delivery System.	e) Subject had circumferential thrombus in region of intended fixation sites.
f.) Subject had adequate vascular access (e.g., patent iliac or femoral arteries) for introduction of the delivery system (26 Fr maximum outer diameter [8.7 mm]). Alternatively, subject may have had femoral or iliac arteries that were extended via an access conduit.	f) Subject had an increasing tapered proximal neck with ≥3 mm increase in diameter from proximal fixation site to the aneurysm.
g.) Subject agreed to comply with 1-month, 6-month, and 1-year follow-ups, in addition to, an annual visit out to 5 years.	g) Subject had a decreasing tapered distal neck with ≥3 mm increase in diameter from distal fixation site to the aneurysm.
h.) Subject (or legally authorized representative) agreed to sign an ICF prior to treatment.	h) Subject's aneurysm or distal thoracic aortic neck angle precluded advancement of the introduction system.

Table 10-2: Inclusion and Exclusion Criteria for Relay® Cohort

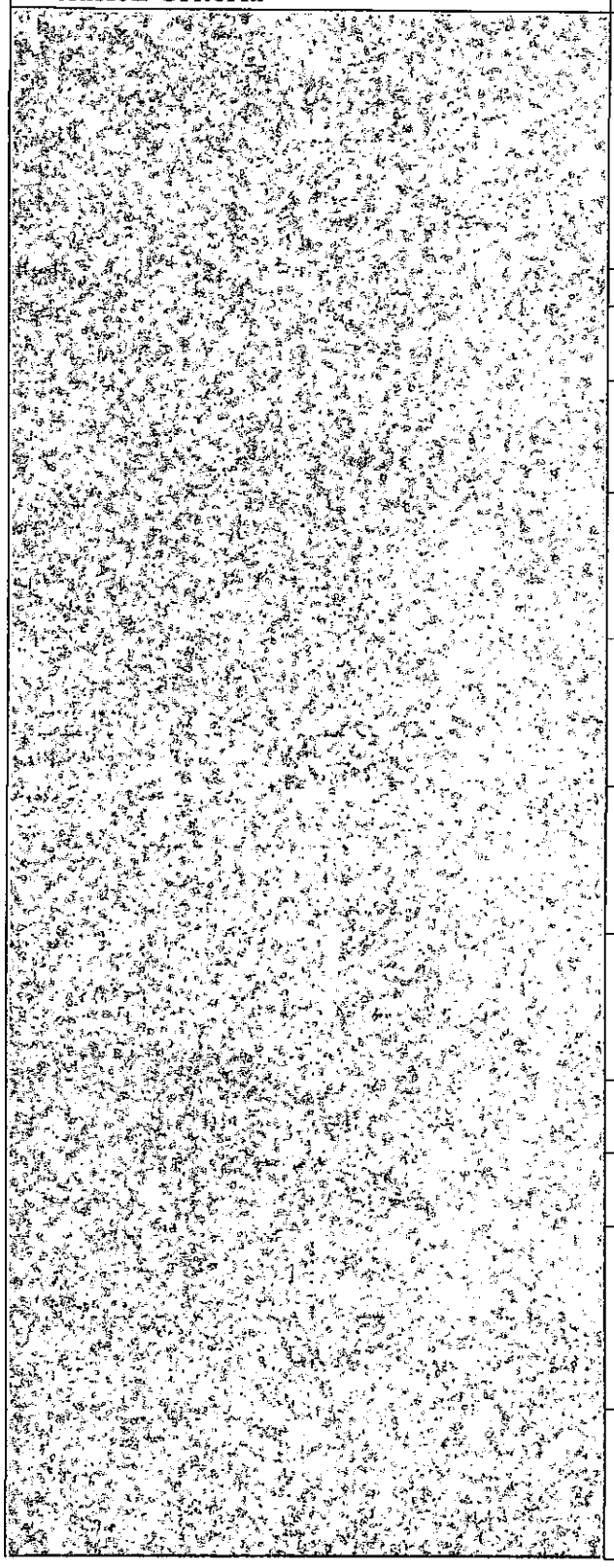
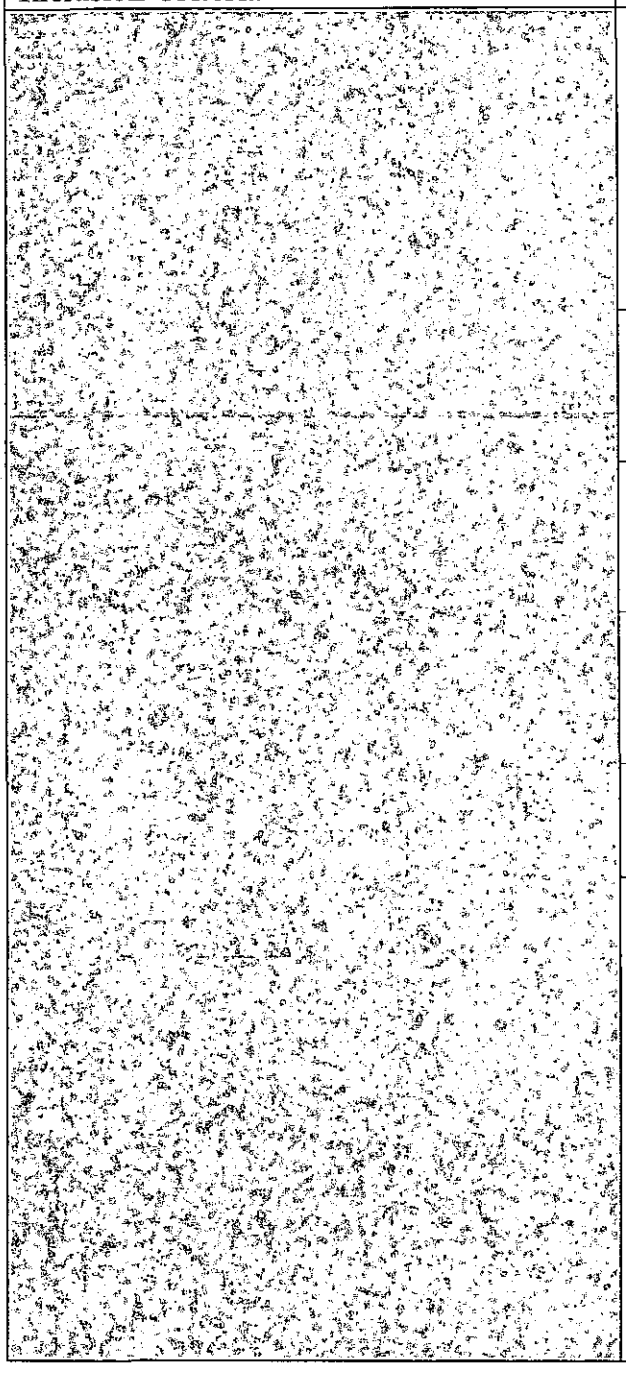
Inclusion Criteria	Exclusion Criteria
	i) Subject had an anatomical variance that would compromise circulation to the carotid, vertebral, or innominate arteries after device placement that was not amenable to subclavian revascularization. This did not apply to subjects with occluded celiac arteries.
	j) Subject was pregnant.
	k) Subject was morbidly obese preventing adequate x-ray visualization of the aorta.
	l) Subject had known or suspected connective tissue disorder (e.g., Marfan's syndrome, Ehlers-Danlos syndrome).
	m) Subject had a blood coagulation disorder or bleeding diathesis for which treatment could not be suspended for 1 week pre and post repair.
	n) Subject had coronary artery disease (CAD) with unstable angina and had not received coronary revascularization within the last 3 months.
	o) Subject had chronic obstructive pulmonary disease (COPD) requiring the routine need for oxygen therapy outside the hospital setting (e.g., daily or nightly home use).
	p) Subject had acute renal failure or renal insufficiency with a creatinine value ≥2.5 mg/dL and was not on renal replacement therapy or dialysis.
	q) Subject had active systemic infection and/or mycotic aneurysms.
	r) Subject had a stroke within 3 months of the treatment date.
	s) Subject had less than 1-year life expectancy as evidenced by factors prohibiting major medical intervention (e.g., presence of malignant tumor, advanced age).
	t) Subject was participating in another research study or had received an investigational research study drug or device within 30 days of screening.

Table 10-2: Inclusion and Exclusion Criteria for Relay® Cohort

Inclusion Criteria	Exclusion Criteria
	u) Subject was confronted with other medical, social, or psychological issues that the investigator believed might have interfered with treatment and/or follow-up. These reasons were documented. For example, adherence to a theological or personal doctrine with aversion or opposition to blood transfusion, etc.
	v) Subject had a coexisting abdominal aortic aneurysm (AAA), which the investigator believed required concomitant treatment within 45 days.
	w)Subject had a prior AAA repair (endovascular or surgical) that was performed less than 6 months prior to treatment.
	x) Subject had a prior endovascular repair (e.g., stent, stent-graft) in the descending thoracic aorta. Device could not have been placed within any prior surgical graft.
	y) Subject had an untreatable allergy or sensitivity to contrast media or device components.
	z) Subject had been admitted to the hospital for a major surgical or medical procedure within 45 days of the planned procedure or was planning to undergo other major surgical or medical procedure within 45 days post implantation (e.g., coronary artery bypass graft, organ transplantation). This excluded any planned procedures for the prospective stent-graft placement (e.g., common carotid to left subclavian transposition/bypass, left carotid to axillary bypass, were acceptable. Carotid to carotid bypasses were not permitted).

A comparison of the inclusion and exclusion criteria for the Relay® cohort and the surgical control cohort is described in **Table 10-3**. Differences in inclusion and exclusion criteria were intended to accomplish the following:

- reflect that the surgical cohort did not need to meet specific anatomical requirements necessary for implantation of the Relay® device;

- accommodate the different clinical follow-up practices for subjects undergoing surgical repair; and
- address the variances in clinical procedures typical for endovascular versus surgical operations.

Table 10-3: Comparison of Clinical Inclusion and Exclusion Criteria – Relay® and Surgical Control Cohorts

Relay®		Surgical Control
Inclusion Criteria		
	Criteria c – h	Not required for the surgical cohort since the anatomic requirements for proper implantation of the device are not essential
	Subject agreed to comply with 1-month, 6-month, and 1-year follow-ups, in addition to, an annual visit out to 5 years.	Prospective Subjects Only: Subject (or legally authorized representative) agreed to provide data from 1-month, 6-month, and 1-year follow-up visits and was encouraged to return annually out to 5 years. Retrospective Subjects Only: Subject (or legally authorized representative) agreed to provide/release all available data surrounding subject's surgical repair and/or use of historical data as permitted by institutional policies.
	Subject (or legally authorized representative) agreed to sign an ICF prior to treatment	Institutional requirements regarding informed consent of retrospective subjects were observed
Exclusion criteria		
	Criteria b – i	Not required for the surgical cohort since the anatomic constraint for successful implantation of the device are not essential
	Subject was morbidly obese preventing adequate x-ray visualization of the aorta.	Not required for surgical subjects since x-ray visualization is not required.
	Subject had an untreatable allergy or sensitivity to contrast media or device components	Surgical subjects will not receive the Relay® device; therefore allergy to these components did not need to be assessed.
	Not applicable for endovascular procedures	Subject required hypothermic arrest, great vessel revascularization, or visceral debranching.

2. Follow-up Schedule

The first Relay® subject was enrolled in the study on January 23, 2007 (treatment date for first subject) and the last Relay® subject was enrolled on May 5, 2010. The 1-year visit for the last subject enrolled was on 25 April 2011. The prospective controls were enrolled between May 2007 and July 2009. Retrospective controls were treated between October 1998 and April 2007 and enrolled on the basis of chart review.

The study follow-up schedule for the Relay® cohort included clinical assessments at hospital discharge, 1, 6, and 12 months post-procedure and annual visits thereafter. The protocol-required imaging was provided to the core laboratory for assessment. For prospective surgical subjects, study assessments were similar. Data collected included baseline and demographic information, procedural information, and follow-up data at 1 month, 6 months, and 1-year. Annual follow-up visits (including a spiral CT scan at the 1-year follow-up visit) out to 5 years were strongly encouraged but not required. Follow-up data (e.g., 1-month, 6-month, and 1-year and annual data) for retrospective subjects was derived via medical chart review, using the hospital visits closest in time to date of the protocol prescribed follow-up regimen. Where possible, the imaging used to determine subject eligibility as well as a 1-year spiral CT scan was collected.

3. Clinical Endpoints

The analysis included clinically-relevant endpoints for patients with thoracic aortic pathologies. The endpoints used by Bolton Medical to demonstrate the safety of the device were adequate to describe the adverse events resulting from using the Relay® Thoracic Stent-Graft with Plus Delivery System. Similarly, the endpoints used by Bolton Medical to demonstrate the effectiveness of the device were adequate to demonstrate the treatment effect.

a) Safety

The primary safety analysis compared the distribution of Relay® and surgical control subjects experiencing major adverse events (MAEs) within 1 year post-procedure. MAEs included aneurysm-related mortality, stroke, paralysis / paraplegia, myocardial infarction, procedural bleeding, respiratory failure, renal failure, and wound healing complications. The distribution of subjects experiencing at least 1 event in 1 year was compared for each group using the Kaplan-Meier method. The Kaplan Meier method estimates the probability of experiencing events over time. Since the probability of not having an event plus the probability of experiencing 1 or more events will sum to 1, then the probability of experiencing at least 1 event is calculated as 1 minus the probability of surviving (not having an event) within 1 year. The null hypothesis was that the probability of patients experiencing at least 1 major adverse event within 1 year is equivalent between both treatments using a two-sided alpha level of 0.05. Rejection of the null hypothesis would provide evidence that the probability of experiencing at least 1 major adverse event is not the same between the two treatments. The 1-year time-to-event distribution was compared between the Relay® and surgical control groups using the log-rank test.

Several sensitivity analyses were conducted for the primary safety endpoint. An unadjusted Cox proportional hazards model was used to calculate the hazard ratio, its 95% confidence interval, and the p-value for treatment effect. A hazard ratio (Relay:Surgical) < 1 and an associated p-value < 0.05 were intended to provide evidence of superiority of the Relay treatment.

Additionally, adjustment for potentially confounding variables was based on the propensity score. This is a method of adjusting a comparative analysis for the biases caused by non-random treatment assignments, using logistic regression to assign a score to each individual based on the probability of being classified as part of the Relay group. The propensity score model included the following important covariates, which are known to affect patient outcome: age, gender, smoking status, maximum lesion diameter, coronary artery disease, renal function, chronic obstructive pulmonary disease, diabetes and history of stroke. In addition, any other baseline variables that were significantly different ($p < 0.10$) between the groups were considered as possible covariates in a stepwise selection, forcing the variables above into the model. If more than 10% of the values are missing for any covariate, they were excluded from the model. In order to include all subjects in the analysis, missing values of any covariate in the final model were replaced by the treatment-group mean for that covariate. A Cox proportional hazards model adjusting for quintiles of the propensity score was used to calculate the hazard ratio, its 95% confidence interval, and the p-value for treatment effect.

b) Effectiveness

The primary effectiveness endpoint was freedom from major device-related adverse events: endoleak (Types I, III and IV), stent migration (> 10mm as compared to the 1 month visit), lumen occlusion, aneurysm rupture, and deployment failure/conversion to surgical repair occurring through 1-year post-procedure. The proportion of subjects in the Effectiveness sample who were free from major device-related AEs at 1-year post-procedure was compared against a performance goal of 0.80 using a 1-sided z-test (normal approximation to the binomial) at an alpha level of 0.025. Rejection of the null hypothesis would provide evidence that this performance goal (proportion-free greater than 0.80) was met.

c) Secondary Endpoints

The secondary effectiveness analyses for major device-related AEs [endoleak (excluding Type II), stent migration (migration $\geq$ 10 mm as compared to the 1-month visit), lumen occlusion, aneurysm rupture, conversion to surgery] at the 1-month and 6-month follow-up visits were analyzed. The individual components of the primary endpoint are presented descriptively as event rates. Other secondary effectiveness endpoints included lesion measurement changes from the 1-month visit as compared with the 6-month and 1-year visits, device integrity failures, and vascular access complications.

The secondary safety analyses for the composite endpoint of MAEs (stroke, paraplegia, myocardial infarction, respiratory failure, renal failure, and aneurysm related mortality) at time points other than the 1-year follow-up (i.e., at the 1-month and 6-month follow-up

visits), as well as individual components of the composite endpoint, were compared between Relay® and surgical cohorts using Cox models. All-cause mortality was also analyzed.

In addition, clinical utility parameters (duration of procedure, transfusions required, length of hospital stay, time in the ICU) were compared between Relay® implantation and surgical procedures using *t* tests for continuous data and chi-square tests for binary (yes/no) or categorical data.

d) Success / Failure Criteria

The Relay® Thoracic Stent-Graft clinical study was considered successful if the null hypotheses for primary effectiveness and the primary safety endpoints (as described in sections X.A.3.a. and X.A.3.b.) were rejected.

e) Pre-Specified Statistical Analysis Plan

(1) Study Hypothesis

Analysis of the Relay® clinical trial results included hypothesis testing of both safety and effectiveness endpoints. Secondary effectiveness endpoints were presented as descriptive statistics. Secondary safety endpoints were also presented descriptively, and in addition, these data were subjected to a Cox proportional hazards analysis (as described in sections X.A.3.a and X.A.3.e.(7)) to evaluate differences in treatment effects. The Relay® Thoracic Stent-Graft clinical study would be considered a success if the null hypotheses of both the primary effectiveness and the primary safety endpoints (as described in sections X.A.3.a. and X.A.3.b.) were rejected.

(2) Comparator

Safety data for the Relay® cohort was compared to a cohort of surgical control subjects treated at trial institutions within the past 10 years of site initiation. The surgical control cohort was a combination of prospectively- (n=7) and retrospectively-treated (n=53) subjects. In addition to covariate analysis, propensity score analysis was used to assess comparability of the groups. The control group was analyzed to justify the use of both retrospectively- and prospectively-enrolled patients.

(3) Methodology

This study was designed as a non-adaptive frequentist trial. The sample size was fixed by design and not adapted as a function of preliminary results.

(4) Sample Size Justification

The sample size for the Relay® cohort was driven by the primary effectiveness analysis. Assuming that the proportion of subjects remaining free from major

device-related adverse events is 0.90, 108 endovascular subjects (with one year follow-up) was intended to provide 80% power for a one-sided z-test (normal approximation to the binomial) at an alpha level of 0.025 against an alternative of 0.80. Accounting for an expected 10% loss to follow-up, 120 subjects yield 80% power.

The sample size for the surgical control group was based on the primary safety analysis. A log-rank test was proposed to compare the one-year time-to-event distributions of the Relay® and surgical control groups. A total of 108 subjects in the Relay® (endovascular) arm and 50 surgical subjects (both with one year follow-up) was intended to provide 90% power at a two-sided alpha level of 0.05 to detect a difference in the distribution of subjects experiencing major adverse events if the one-year event probabilities are 0.25 in the Relay® cohort and 0.50 in the surgical control cohort. Assuming withdrawal and loss to follow-up of 20%, approximately 60 subjects were required for the surgical control cohort.

(5) Statistical Test

Hypothesis testing and other statistical testing was conducted as described in sections X.A.3.e.

(6) Method for Accommodating Missing Data

In general, missing data were not imputed and analyses were based on available data. However, missing or incomplete adverse event start dates were imputed based on a predefined algorithm. Sensitivity analyses were conducted as part of the primary safety and effectiveness analyses.

In addition, tipping point analyses were conducted on the two primary endpoints to account for the impact of non-evaluable subjects. The start of the 1-year visit window (337 days) was used as the cutoff point for converting censored subjects to subjects with events. The lower bound of the 97.5% confidence interval (CI) for freedom from event was displayed using the following methods:

- Greenwood's variance, loglog transformation
- Peto (Lao, 1995)

The CIs for event probabilities were calculated as 1-"lower bound" found for the event-free, which employs the failure variance as the survival variance. For Greenwood's 97.5% one-sided lower bound, the lower bound of the two-sided 95% CI was used. For Peto, the za is the ath quantile of the standard normal cumulative distribution function (a=0.975).

The tipping point analysis of the primary effectiveness endpoint was performed utilizing the one-sided z-test and point estimates and the lower limit of the one-sided 97.5% CI. Primary effectiveness was based on all 120 subjects in the Relay® treatment. The tipping point analysis kept the denominator at 120 subjects. Starting with the 4 subjects identified who actually experienced a major

device-related adverse event (AE), subjects who did not have 1 year follow-up (21 subjects) were added one by one as having experienced an event at each increment. There were 21 stages provided that converted each of the 21 subjects without 1 year follow-up.

The inclusion of 12 additional subjects with a major device-related AE still provided a proportion free estimate of 0.867 and lower bound of the one-sided 97.5% CI of 0.806, meaning a total of 16 subjects out of the 120 subjects could have experienced a device-related AE before seeing failing results.

Tipping point analyses of the effectiveness endpoint via the Kaplan-Meier analyses were also performed, through repeatedly treating all censored subjects as having experienced a device-related event at the time of their leaving the study for any reason. Two approaches were taken – one with the tipping point analysis starting with the earliest (smallest) censored time and the other with the tipping point using the latest (largest) censored time. In each approach, subjects were added into the tipping point analysis based on their censored time and were converted from event-free to experiencing a major device-related AE. Subjects were imputed based on the days since procedure (censored time) and if more than one subject had the same day, the subject entered based on subject number.

The original Kaplan-Meier analysis conducted per the study protocol data showed the probability of remaining event-free through 1-year post-procedure as 0.96 with the two-sided 97.5% CI (Greenwood's, loglog) of (0.89, 0.99). The analysis was repeated with the lower bound of the one-sided 97.5% CI using the two techniques described above. All results on these lower bounds are above 0.80 (Greenwood=0.902, Peto=0.925). Starting with the earliest (smallest) censored time yielded all CI's to be in agreement and to be above 0.80 until a total of 14 subjects (the original 4 who actually experienced an event, plus 10 additional subjects) were considered to have experienced a major device-related AE (Greenwood=0.809, Peto=0.821). In contrast, starting with the latest censored time all CI's were in agreement until a total of 13 subjects experienced a major device-related AE. At this stage, days since procedure ranged from 166 to 333 days and the CI's were Greenwood=0.802 and Peto=0.819.

Tipping-point analyses of the primary safety endpoint were performed. These Kaplan-Meier analyses were repeated by progressively converting censored subjects' times to first major adverse event times. As with the effectiveness analysis, the analyses were done starting with the earliest (smallest) censored time and also starting with the latest (largest) censored time. In addition, since the safety analysis considered the control group as well, an analyses was done with the Relay® treatment starting at the earliest (smallest) censored time and Surgical treatment starting at the latest (largest) time as well as with the tipping point starting at latest (largest) censored time within the Relay® treatment and earliest (smallest) censored time for Surgical treatment.

In each approach, subjects were added into the tipping point analysis based on their censored time and were converted from event-free to experiencing a major adverse event. Subjects were imputed based on the days since procedure (censored time) and if more than one subject had the same day, the subject entered based on subject number.

The original Kaplan-Meier analysis of the study data showed the probability of experiencing at least 1 major adverse event through 1-year post-procedure with the two-sided 97.5% CI (Greenwood's, loglog) for Relay® treatment as 0.27 (0.19, 0.38) and for Surgical treatment as 0.51 (0.38, 0.67). The p-value for the log rank test was <0.001, showing the distribution of Relay® subjects experiencing at least 1 major adverse event within 1 year post-procedure was significantly lower than the distribution of surgical control subjects. The analysis was repeated with the upper bound of the one-sided 97.5% CI using the two techniques described above. The upper bounds for Relay® treatment were Greenwood=0.361 and Peto=0.354. The upper bounds for Surgical treatment were Greenwood=0.650 and Peto=0.691. Again, the log rank statistic showed a significant difference between the two treatments.

Considering all approaches, there were only 15 additional subjects to be converted in the Surgical group, and 9 within the Relay® group. Showing within the first 9 stages is where both treatments converted subjects to event status. After the 9th stage, the Surgical values are carried forward. All comparisons to the two treatments at each stage, still showed a p-value of the log rank test <0.001 with the Relay® treatment having lower event probabilities.

Overall, the various revised estimates of variance based on the observed analyses provide results similar to one another. Also, the tipping point analyses show that the analyses planned in the protocol are robust to assumptions about missing data. The primary effectiveness tipping point analysis showed that the original primary analysis planned in the study protocol was fairly robust, as over half of the 21 censored subjects are converted to having events before the lower bound of the CI falls below 0.800. The primary safety tipping point analyses showed that the original effectiveness analyses planned in the protocol for the time to major device-related AE were very robust with respect to assumptions about censored observations. The Relay® treatment had significantly fewer events at each stage, regardless of the combination of the order of censoring used.

(7) Assumptions

Based on the use of the same inclusion / exclusion criteria, it was assumed that the Relay® and surgical cohorts were comparable and that the distribution of patients experiencing at least 1 major adverse event within 1 year (i.e., the primary safety endpoint) was equivalent in both treatment groups. Several sensitivity analyses were conducted for the primary safety endpoint. An unadjusted Cox proportional hazards model was used to calculate the hazard ratio, its 95% CI, and the p-value for treatment effect. A hazard ratio (Relay®:surgical) of <1 and p<0.05 would

provide evidence of superiority of the Relay® treatment.

f) External Evaluation Groups

(1) Core Laboratory

An independent Core Laboratory (Cleveland Clinic Peripheral Vascular Core Laboratory) reviewed computed tomography (CT) scans and thoracic x-rays to assess aneurysm changes, device position and integrity, and the absence or presence of endoleaks. The Core Laboratory determined the major device-related adverse events (AEs) of endoleak, stent migration, and stent fracture which were included in the primary effectiveness endpoint.

(2) Clinical Events Committee

The Clinical Events Committee (CEC) reviewed AEs to categorize the type of event, seriousness, and relationship to the device and procedure. In particular, the CEC determined major device-related AEs relating to lumen occlusion and conversion to surgical repair which were included in the primary effectiveness endpoint as well as serious AEs (SAEs) which were included in the primary safety endpoint. All CEC reviews were blinded to subject- and site-identifying information.

(3) Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) was responsible for assuring the study was conducted safely and ethically. The DSMB membership included 2 key medical disciplines involved with endovascular repair, a vascular surgeon and an interventional radiologist, in addition to a statistician. All of the members possessed endovascular experience. None of the members were involved with the clinical study or had financial interests in Bolton Medical. The DSMB reviewed safety data on a regular basis (generally twice per year).

(4) Imaging Review

Imaging for each potential trial subject was submitted for an anatomical eligibility evaluation. The review was conducted by a cadre of experienced trial investigators. Reviewers evaluated CT imaging and documented vessel measurements. To ensure no conflict of interest, investigators could not review subjects submitted from their institutions.

g) Prospectively-Defined Subgroup Evaluations

Potential differences based on lesion type were tested through a subgroup analysis of the primary safety endpoint (distribution of experiencing 1 or more major adverse event) and primary effectiveness endpoint (freedom from major device related adverse events) and selected secondary endpoints, in which fusiform aneurysms and saccular aneurysms/penetrating aortic ulcers were examined separately. Potential differences

based on delivery system design were also tested through subgroup analysis based on comparisons of treatment assessments, requirements for additional treatments, and final procedure results between subjects treated with the original and modified delivery systems. Finally, potential gender-based differences in treatment outcomes were also explored on a *post hoc* basis for both the primary safety and primary effectiveness endpoints.

B. Accountability of PMA Cohort

Twenty-seven (27) sites enrolled 120 Relay® subjects and 60 (7 prospective, 53 retrospective) surgical controls. Of the 120 Relay® subjects, 95 were treated with the original Relay® delivery system, while 25 were treated with the Plus delivery system. Thirteen (13) institutions enrolled both treatment and control subjects. Twelve (12) institutions enrolled only endovascular subjects, and two (2) institutions enrolled only surgical subjects. Finally, two (2) sites enrolled no subjects. Subject compliance is presented in **Table 10-4**.

At the time of database lock, data from the 120 Relay® subjects were used to complete the primary safety analysis. In the surgical control group, data from 60 subjects were included in the evaluation of the primary safety endpoint. The primary effectiveness analysis was conducted considering all 120 Relay® subjects as well as the 99 who had some 1-year follow-up information. Although, as noted in **Table 10-4**, only 97 subjects were eligible for a 1-year visit, 99 subjects were evaluated as part of the primary effectiveness endpoint since two subjects who experienced major device-related adverse events died prior to 1-year and were included in the total analyzed.

Although **Table 10-4** indicates that only 89 patients had data for the 1-year visit reported by the core lab, additional 1-year data were obtained to allow for the inclusion of 99 patients in the primary effectiveness analysis. These data consisted of a combination of site-reported data and imaging data obtained after the 1-year interval. Use of the later imaging provided a conservative estimate of the device effectiveness, as any events identified at a later follow-up time were considered to have been present at 1 year and because it is unlikely that an event would have been present at 1 year with spontaneous resolution before the later follow-up. In addition, alternate effectiveness analyses considering only those subjects with interpretable CTs at 1 year showed that study endpoints were still met. The number of data points evaluable for each endpoint is reported in the results sections.

Table 10-4 **Compliance Imaging and Follow-up (Core Lab Reported)**

Visit Interval[a]	Eligible for Follow-Up[b]	Subjects with[c] n (%)			Adequate Imaging to Assess Parameter n (%)				Events Occurring Before Next Interval[c] n (%)					
		Data for Visit	CT Scan	X-Ray	Size↑[d]	Endo-leak[d]	Mi-gration[d]	Fracture[e]	Death	Tech-nical Failure[f]	Con-version	Lost to Follow-Up	With-drawn Early	Not Due for Next Visit[g]
Operative (Day 0 – 15)	120	120 (100)	NA	NA	NA	NA	NA	NA						
Events between operative and 1 month visit									3 (2.5)	3 (2.5)	0	3 (2.5)	0	0
1 Month (Day 16 – 151)	114	108 (94.7)	107 (93.9)	100 (87.7)	NA	97 (85.1)	NA	97 (85.1)						
Events between 1 month and 6 month visit									7 (6.1)	0	1 (0.9)	0	0	0
6 Month (Day 152 – 336)	106	97 (91.5)	94 (88.7)	90 (84.9)	92 (86.8)	85 (80.2)	89 (84.0)	89 (84.0)						
Events between 6 month and 1 year visit									7 (6.6)	0	0	0	2 (1.9)	0
1 Year (Day 337 – 673)	97	89 (91.8)	89 (91.8)	86 (88.7)	86 (88.7)	81 (84)	87 (89.7)	83 (85.6)						
Totals									17	3	1	3	2	
Deaths after conversion									0					
Total Deaths									17					

NA= Not Applicable.

[a] Visit intervals took into account the follow-up visit windows. The visit windows were ±2 weeks for 30 days, ±4 weeks for 6 months and 1 year, and ±8 weeks for 2 to 5 years. 1 year visit window is 337 - 393

[b] Eligible for follow-up if subject reached the start of the visit window and was not a technical failure, was not lost to follow-up, did not die, did not withdraw early, or did not convert to open repair. Eligible for follow-up included any subject who reached the start of the visit window, but who had not reached the end of the visit window.

[c] Percentages are calculated based on the number of subjects eligible for follow-up. Data for visit information is site-reported. CT scan and x-ray reflect images received for evaluation by the core laboratory.

[d] Size increase, endoleak, and migration were assessed by CT Scan (core lab-reported data).

[e] Fracture was assessed by x-ray (core lab-reported data).

[f] Subjects for whom the procedure was attempted but aborted and who did not receive a Relay® Stent-Graft at a later additional procedure.

[g] Not due for next visit if subject had not reached the start of the visit window. Subjects who died, had a technical failure, converted to open repair, were lost to follow-up, withdrew early, or were not due for a previous visit are not counted.

[h] Considers imaging re-examined during application review.

C. Study Population Demographics and Baseline Parameters

Table 10-5 through Table **10-6** provide the demographic and baseline medical history of the Relay® cohort and surgical control cohort. Table **10-7** through **Table 10-9** provide baseline aneurysm and anatomical characteristics Relay® cohort and surgical control cohort. **Tables 10-10** and **10-11** present the types and distribution of Relay® Thoracic Stent Grafts implanted at the initial procedure.

As shown in **Table 10-5**, the mean age for the Relay® subjects was 72.8 years (range: 28 to 91 years); 101 subjects (84.2%) were greater than or equal to 65 years of age. The surgical control cohort was similar with a mean age of 70.0 years (range: 35 to 84 years); 48 subjects (80.0%) were greater than 65 years of age. Overall, the age stratification as presented in **Table 10-5** was similar between the 2 treatment groups. The number of males and females in the Relay® cohort was evenly split (51.7% male, 48.3% female) while there were twice as many males as females in the surgical control cohort (66.7% male, 33.3% female). Overall, demographics and baseline characteristics were similar between the treatment groups, for age, gender, race, medical history, weight, and height.

Table 10-5 Demographics: Age, Gender, and Race – Relay® and Surgical

	Relay® Thoracic Stent-Graft Repair	Surgical Repair	p-value[a]
Age (years)[b]			0.093
n	120	60	
Mean (SD)	72.8 (11.02)	70.0 (9.17)	
Median	74.0	71.0	
Min, Max	28, 91	35, 84	
Age categories (years)			0.648
18 to 64	19/120 (15.8%)	12/60 (20.0%)	
65 to 74	45/120 (37.5%)	24/60 (40.0%)	
≥75	56/120 (46.7%)	24/60 (40.0%)	
Gender			0.056
Male	62/120 (51.7%)	40/60 (66.7%)	
Female	58/120 (48.3%)	20/60 (33.3%)	
Race			0.165
White	106/120 (88.3%)	50/60 (83.3%)	
Black	6/120 (5.0%)	6/60 (10.0%)	
Asian	0/120	2/60 (3.3%)	
Hispanic	5/120 (4.2%)	1/60 (1.7%)	
Other	3/120 (2.5%)	1/60 (1.7%)	

Notes: Percentages and summary statistics are based on the number of subjects in each treatment group with data available.

[a] Comparison using a 2-sample *t* test for continuous data or a chi-square test for categorical data.

[b] Age = (date of procedure minus date of birth plus 1)/365.25.

Table 10-6 Demographics: Baseline Medical History/Risk Factors - Relay® and Surgical

	Relay® Thoracic Stent-Graft Repair	Surgical Repair	p-value[a]
Medical history/Risk factors			
– History of peripheral vascular disease	30/120 (25.0%)	15/60 (25.0%)	>0.999
– Documented coronary artery disease	57/120 (47.5%)	31/60 (51.7%)	0.598
– Documented chronic obstructive pulmonary disease	40/120 (33.3%)	20/60 (33.3%)	>0.999
– History of neurologic disease	30/120 (25.0%)	8/60 (13.3%)	0.071
– History of diabetes mellitus	24/120 (20.0%)	13/60 (21.7%)	0.794
– Hypertension and/or treatment for hypertension	106/120 (88.3%)	54/60 (90.0%)	0.737
– Hypercholesterolemia	90/120 (75.0%)	37/60 (61.7%)	0.064
– History of smoking	94/120 (78.3%)	47/58 (81.0%)	0.677
– History of impaired renal function	27/120 (22.5%)	9/60 (15.0%)	0.236
– Subject currently taking any antiplatelet or anticoagulant medications	73/120 (60.8%)	29/57 (50.9%)	0.210
– History of limb ischemia	8/120 (6.7%)	7/59 (11.9%)	0.238
– History of gastrointestinal complications	60/120 (50.0%)	27/60 (45.0%)	0.527
– History of other relevant medical history and/or clinical status	103/120 (85.8%)	49/60 (81.7%)	0.467
– History of vascular/endovascular intervention	54/120 (45.0%)	22/60 (36.7%)	0.286
Weight (lbs)			0.169
n	120	52	
Mean (SD)	167.75 (41.457)	176.72 (33.050)	
Median	166.30	179.00	
Min, Max	65.6, 289.0	105.8, 244.6	
Height (in)			0.326
n	120	48	
Mean (SD)	65.80 (4.310)	66.51 (3.930)	
Median	65.00	66.00	
Min, Max	56.0, 76.0	58.0, 74.0	

Notes: Percentages and summary statistics are based on the number of subjects in each treatment group with data available.

[a] Comparison using a 2-sample *t* test for continuous data or a chi-square test for categorical data.

Table 10-7 shows the types of lesions treated in each study cohort. A greater percentage of subjects in the surgical group (Relay®, 71.6%; surgical, 86.7%) had a descending thoracic fusiform aneurysms, while fewer surgical subjects had a saccular aneurysm in the descending thoracic aorta or PAU (Relay®, 28.3%; surgical, 10.0%).

Table 10-7 Demographics: Lesion Type - Relay® and Surgical

Lesion type	Relay® Thoracic Stent-Graft Repair	Surgical Repair	p-value[a]
Fusiform Aneurysms	86/120 (71.7%)	54/60 (28.3%)	0.011
– Descending thoracic fusiform aneurysm, 5 cm in diameter or greater	83/120 (69.2%)	50/60 (83.3%)	
– Descending thoracic aneurysm is 4 cm or more in diameter that has increased in size by 0.5 cm in the last 6 months	3/120 (2.5%)	2/60 (3.3%)	
– Descending thoracic aneurysm with a maximum diameter of aneurysm exceeds 2 times the diameter of the non-aneurysmal, adjacent aorta	0/120	2/60 (3.3%)	
Saccular Aneurysm or Penetrating Atherosclerotic Ulcers (PAU)	34/120 (28.3%)	6/60 (10.0%)	
Fusiform Aneurysm Average Maximum Diameter	6.22 cm	5.72 cm	
Saccular Aneurysm/PAU Average Maximum Diameter	4.84 cm	5.91 cm	

Notes: Percentages and summary statistics are based on the number of subjects in each treatment group with data available.

[a] Comparison using a 2-sample *t* test for continuous data or a chi-square test for categorical data.

Tables 10-8 and **10-9** show the baseline vessel dimensions and lesion diameters for the Relay® and surgical control cohorts. **Table 10-8** shows the results for all subjects in each cohort, regardless of lesion type. **Table 10-9** shows that the overall lesion diameter reported by the sites was similar for the subjects in the 2 treatment groups, with the majority of the subjects having an aneurysm diameter between 50 mm and 70 mm (70.8% Relay®, 68.2% surgical). When isolating Relay® subjects with saccular aneurysms/PAUs, the majority had lesion diameters between 40 mm and 70 mm.

Table 10-8 Demographics: Baseline Vessel Dimensions - Relay® and Surgical

	Relay® Thoracic Stent-Graft Repair	Surgical Repair	p-value[a]
Length of proximal neck (mm)			0.590
n	120	13	
Mean (SD)	53.1 (35.40)	47.5 (35.26)	
Median	42.5	33.0	
Min, Max	15, 185	10, 126	
Length of lesion (mm)			0.034
n	120	15	
Mean (SD)	107.5 (60.84)	143.7 (69.61)	
Median	100.0	130.0	
Min, Max	12, 273	7, 260	
Length of distal neck (mm)			<0.001
n	120	14	
Mean (SD)	57.3 (41.85)	31.1 (20.34)	
Median	40.0	30.0	
Min, Max	20, 208	7, 90	
Length from lesion to celiac (mm)			0.019
n	119	14	
Mean (SD)	97.5 (57.83)	59.4 (48.14)	
Median	86.0	50.5	
Min, Max	20, 263	7, 175	
Total treatment length (mm)			0.177
n	120	14	
Mean (SD)	191.7 (68.78)	217.9 (64.77)	
Median	200.0	211.5	
Min, Max	70, 350	110, 311	
Diameter of proximal neck (mm)			0.214
n	120	20	
Mean (SD)	32.2 (4.70)	34.1 (6.46)	
Median	32.0	34.5	
Min, Max	21, 42	22, 43	
Diameter of lesion (mm)			0.734
n	120	44	
Mean (SD)	58.3 (13.77)	57.4 (16.54)	
Median	60.0	60.5	
Min, Max	5, 98	5, 80	

Table 10-8 Demographics: Baseline Vessel Dimensions - Relay® and Surgical

	Relay® Thoracic Stent-Graft Repair	Surgical Repair	p-value[a]
Diameter of distal neck (mm)			0.033
n	119	22	
Mean (SD)	31.2 (5.25)	36.0 (9.73)	
Median	31.0	34.0	
Min, Max	19, 42	20, 60	
Diameter of access artery (mm)		N/A	N/A
n	118		
Mean (SD)	9.3 (2.43)		
Median	9.0		
Min, Max	5, 26		
Right iliac access site minimum diameter (mm)		N/A	N/A
n	116		
Mean (SD)	9.9 (2.57)		
Median	9.0		
Min, Max	6, 22		
Left iliac access site minimum diameter (mm)		N/A	N/A
n	114		
Mean (SD)	9.5 (2.18)		
Median	9.0		
Min, Max	5, 16		
Right femoral access site minimum diameter (mm)		N/A	N/A
n	115		
Mean (SD)	8.9 (1.87)		
Median	9.0		
Min, Max	5, 14		
Left femoral access site minimum diameter (mm)		N/A	N/A
n	114		
Mean (SD)	8.6 (1.91)		
Median	9.0		
Min, Max	0, 13		
Calcification in access artery		N/A	N/A
None	35/120 (29.2%)		
Mild	57/120 (47.5%)		
Moderate	24/120 (20.0%)		
Severe	4/120 (3.3%)		
Tortuosity of access artery		N/A	N/A
None	16/120 (13.3%)		
Mild	81/120 (67.5%)		
Moderate	19/120 (15.8%)		
Severe	4/120 (3.3%)		

Notes: Percentages and summary statistics are based on the number of subjects in each treatment group with data available.

[a] Comparison using a 2-sample *t* test for continuous data or a chi-square test for categorical data.

Table 10-9 Demographics: Baseline Maximum Lesion Diameters - Relay® and Surgical

Diameter (mm)	Relay® Thoracic Stent-Graft (fusiform TAA) (%)	Relay® Thoracic Stent-Graft (Saccular TAA and PAU) (%)	Relay® Thoracic Stent-Graft (all lesion types) (%)	Surgical Control Group (%)
5 to < 10	0	2/34 (5.9%)	2/120 (1.7%)	3/44 (6.8%)
10 to < 20	0	1/34 (2.9%)	1/120 (0.8%)	0
20 to < 30	0	1/34 (2.9%)	1/120 (0.8%)	0
30 to < 40	0	6/34 (17.6%)	6/120 (5.0%)	1/44 (2.3%)
40 to < 50	1/86 (1.2%)	7/34 (20.6%)	8/120 (6.7%)	1/44 (2.3%)
50 to < 60	33/86 (38.4%)	6/34 (17.6%)	39/120 (32.5%)	14/44 (31.8%)
60 to < 70	38/86 (44.2%)	8/34 (23.5%)	46/120 (38.3%)	16/44 (36.4%)
70 to < 80	10/86 (11.6%)	3/34 (8.8%)	13/120 (10.8%)	7/44 (15.9%)
80 to < 90	2/86 (2.3%)	0	2/120 (1.7%)	2/44 (4.5%)
90 to < 100	2/86 (2.3%)	0	2/120 (1.7%)	0
100 to < 110	0	0	0	0
110 to < 120	0	0	0	0
120 and greater	0	0	0	0
Lesion Diameter < 50 mm	1/86 (1.2%)	17/34 (50%)	18/120 (15%)	5/44 (11.4%)
Lesion Diameter ≥ 50 mm	85/86 (98.8%)	17/34 (50%)	102/120 (85%)	39/44 (88.6%)

Note: Percentages are based on the number of subjects in each treatment group with data available.

One hundred sixteen (116) subjects received the Relay® device during the initial implant procedure. **Table 10-10** shows that the majority of the subjects had 1 (48.3%) or 2 (38.8%) Relay® device(s) implanted during the initial procedure. None of the subjects had more than 4 Relay® device implants during the initial procedure. A total of 192 Relay® devices were implanted during the initial procedures for an average of 1.7 devices per subject. The number of Relay® devices implanted by size is shown in **Table 10-11**.

Table 10-10 Number of Relay® Devices Implanted During the Initial Procedure

Number of Relay® Devices Implanted	Relay® Thoracic Stent-Graft % (m/n)
1	56/116 (48.3%)
2	45/116 (38.8%)
3	13/116 (11.2%)
4	2/116 (1.7%)
5	0/116

Note: The Effectiveness sample include All Enrolled subjects who underwent implantation of the Relay® device. Percentages were based on the number of subjects in the Effectiveness sample who had at least 1 device implanted in the initial procedure. Four (4) subjects did not receive the Relay® device during the initial procedure.

m = number of subjects who received the indicated number of devices; n = total number of devices implanted during the initial procedure.

Table 10-11 Diameter of Relay® Devices Implanted During the Initial Procedure

Relay® Stent-Graft Diameter (Proximal/Distal, mm)	Number of Devices % (m/n)
28/24	1/192 (0.5%)
28/28	4/192 (2.1%)
30/26	1/192 (0.5%)
30/30	7/192 (3.6%)
32/28	6/192 (3.1%)
32/32	19/192 (9.9%)
34/30	9/192 (4.7%)
34/34	13/192 (6.8%)
36/32	10/192 (5.2%)
36/36	20/192 (10.4%)
38/34	3/192 (1.6%)
38/38	18/192 (9.4%)
40/36	17/192 (8.8%)
40/40	12/192 (6.3%)
42/38	11/192 (5.7%)
42/42	15/192 (7.8%)
44/40	5/192 (2.6%)
44/44	10/192 (5.2%)
46/42	3/192 (1.6%)
46/46	9/192 (4.7%)

Note: m is the number of devices of the identified size; n is the total number of devices implanted at the initial procedure.

D. Safety and Effectiveness Results

1. Acute Procedural Data

Acute procedural data (Treatment Assessments) are presented in **Table 10-12.** The Relay® Thoracic Stent-Graft was successfully implanted in 116 of 120 subjects (96.7%). For the majority of subjects (70/119, 58.8%) access was achieved via the native right femoral artery. In 20% of the cases, the left subclavian artery was completely covered by the fabric portion of the device, and it was partially covered in 12.2% of cases. Although the Relay® device does not require balloon expansion, balloons were used in 37 cases (37/120, 30.8%). The lesion was excluded in 92.5% of the subjects during the initial implantation. The completion angiogram for 5 subjects (4.2%) demonstrated an endoleak.

Physicians rated the performance of the device during implantation. Of the 116 subjects who were successfully implanted with the Relay® Stent-Graft during the initial

procedure, no fractures or lumen occlusions were detected at the time of implant. There were also no reports of poor deployment accuracy. Kinking and twisting was reported at the time of deployment for 1 subject, although there was no corresponding report of lumen occlusion. Due to difficulties with vessel access and proper device positioning, 4 of the 120 procedures (3.3%) were aborted. Implantation was successfully re-attempted for 1 of these 4 subjects.

Table 10-12 Acute Procedure Detail /Treatment Assessments -- Relay® Cohort

	Relay® Subjects N = 120
Total Relay® implanted (successful delivery/deployment)[a]	116/120 (96.7%)
Final procedure result	
- Excluded lesion	111/120 (92.5%)
- Endoleak: not excluded during the procedure	5/120 (4.2%)
- Conversion from endovascular to open repair	0/120
- Procedure attempted, but aborted	4/120 (3.3%)
Evaluation of Relay® system	
- Stent-graft deployed[b]	116/116 (100%)
- Accurate deployment[b]	116/116 (100%)
- Deployment without stent-graft kinking or twisting[b]	115/116 (99.1%)
- Stent-graft patent[b]	116/116 (100%)
- Stent-graft integral (e.g., no fractures)[b]	116/116 (100%)
Anesthesia[c]	
- Local	4/120 (3.3%)
- Regional / Epidural	20/120 (16.7%)
- General	100/120 (83.3%)
Spinal Protection	74/120 (61.7%)
Vascular access	
- Native right femoral artery	70/119 (58.8%)
- Native left femoral artery	16/119 (13.4%)
- Native right iliac artery	5/119 (4.2%)
- Native left iliac artery	2/119 (1.7%)
- Conduit, left iliac artery	11/119 (9.2%)
- Conduit, right iliac artery	15/119 (12.6%)
Left Subclavian Artery (LSA) Revascularization	
- Transposition	16/120 (13.3%)
- Carotid-LSA Bypass	None reported
Coverage of the Left Subclavian Artery (LSA)[d]	
- Complete	23/115 (20%)
- Partial	14/115 (12.2%)
- None	78/115 (67.8%)

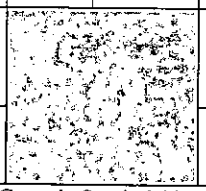
Percentages are based on the number of subjects in each treatment group with data available, unless noted. All treatment assessments are based on the initial procedure.

a One subject received the device during a secondary attempt
b Responses entered only for those cases in which a stent-graft was implanted.
c Multiple types of anesthesia may be used on a single subject
d Based on core laboratory assessment

2. Safety and Effectiveness Results

Table 10-13 presents the key outcomes of the Relay® cohort and the surgical control cohort; detailed analyses may be found in the following sections.

Table 10-13 Summary of Key Outcomes Relay® and Surgical

Interval	Total number of subjects reaching Follow-up		Aneurysm Rupture[a]		Conversion to Surgical Repair		Death		Aneurysm-Related Mortality		Major Adverse Event	
	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control
Intraoperative (Day 0)	120	60	0	0	0	NA	0	0	0	0	14 (11.7%)	18 (30%)
≤ 30 days	120	60	0	0	0	NA	7 (5.8%)	6 (10%)	7 (5.8%)	6 (10%)	26 (21.7%)	29 (48.3%)
≥ 31 – 365 days	110	47	0	0	1 (0.9%)[b]	NA	10 (9.1%)	4 (8.5%)	1 (0.9%)	0	6 (5.5%)	1 (2.1%)
0 – 365 days	120	60	0	0	0	NA	17 (14.2%)	10 (16.7%)	8 (6.7%)	6 (10%)	32 (26.7%)	30 (50%)
Kaplan Meier Summaries			Freedom from Aneurysm Rupture[c]		Freedom from Surgical Conversion		Freedom from All-Cause Death		Freedom from Aneurysm-Related Mortality		Freedom from Major Adverse Events[d]	
1 year Kaplan Meier[e]			100%	100%	99%	NA	85%	81%	93%	89%	73.3%	50%

Test= Relay®; Control= Surgical; NA = Not applicable

[a]Aneurysm-related mortality was defined as defined as death due to a rupture, death prior to 30 days or hospital discharge from primary procedure, or death less than 30 days or prior to hospital discharge for a secondary procedure designed to treat the original aneurysm. Excluded are aneurysms in other anatomic segments other than the segment treated with the Relay® stent-graft.

[b]One surgical conversion occurred during the trial but was ruled by the CEC not to meet the criteria to be included in the primary effectiveness analysis.

[c]Aneurysm rupture analyses were tracked as part of the primary effectiveness endpoint, which applied only to the Relay® cohort. However, since no ruptures were reported for the surgical control cohort, the same KM estimate can be assumed.

[d]The primary safety endpoint was the occurrence of at least one major adverse event, and KMs were calculated accordingly. Freedom from major adverse events was therefore tabulated as 100 – MAE rate per Table 10-14.

[e]KM are based on information through the end of the 1 year visit window which extended to Day 393. None of the identified events occurred between Day 365 and Day 393.

3. Safety Results

a) Primary Safety Objective

The primary safety endpoint was the distribution of subjects experiencing at least 1 of the major adverse events (aneurysm-related mortality, stroke, paralysis/paraplegia, myocardial infarction, procedural bleeding, respiratory failure, renal failure, and wound healing complications) within 1 year post-procedure. These events were considered by definition to be serious in nature.

Of the 120 subjects who were treated with the Relay® device, 32 subjects (26.7%) experienced a major adverse event within 1 year post-procedure compared with 30 (50.0%) of the 60 subjects who underwent surgical repair. Kaplan-Meier analysis, using

both a log rank test (**Table 10-14**) and a normal approximation with variance estimated by Greenwood's formula, indicated that the distribution of major adverse events in the surgical control cohort was greater than in the Relay® device cohort ($p<0.001$ and $p=0.002$, respectively). The time to the first major adverse event is graphically presented in **Figure 10-1**. Sensitivity analyses were performed on the primary safety endpoint using an unadjusted Cox proportional hazards model to calculate the hazard ratio, the 95% CI, and the p-value for treatment effect. The calculated hazard ratio of 0.43 (Relay®:surgical) showed a statistically significant difference between the 2 treatment methods ($p=0.001$) with the results in favor of the Relay® device (hazard ratio <1). Thus, superiority of the Relay® device treatment relative to the surgical arm was shown. The primary safety and sensitivity analyses show the primary safety objective was achieved.

Table 10-14 Kaplan-Meier: First Major Adverse Event Within 1 Year

	Relay® Thoracic Stent-Graft (N = 120)	**Surgical Repair (N = 60)**	**p-value[a]**
Major adverse event[b, c]	32/120 (26.7%)	30/60 (50.0%)	
Censored (subjects without observed events)[b, d]	88/120 (73.3%)	30/60 (50.0%)	
Kaplan-Meier estimated probability of (upper limit of the one-sided 97.5% CI[e]) of major adverse event within 1 year	0.27 (0.361)	0.51 (0.650)	<0.001

Notes: The Safety sample includes All Enrolled subjects who underwent implantation of the Relay® device or surgical repair. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a second procedure, the time to event is based on the initial procedure date if the adverse event occurred before the second procedure date; otherwise, time to event is based on the second procedure date.

[a] p-value from Log Rank test.

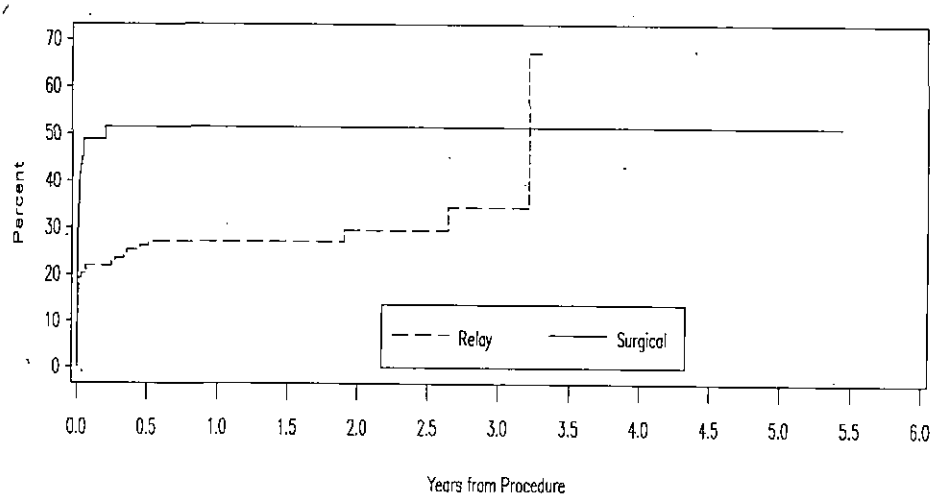
[b] Percentages are based on the *number* of subjects in each treatment group.

[c] Adjudicated by the CEC. In the event that the CEC determines an event could never be adjudicated, it will be assumed that the site investigator's report is accurate and it is used in place of an adjudication.

[d] Subjects without observed events were censored at the last follow-up (up to 1 year).

[e] Using Greenwood. The upper limit of the one-sided 97.5% CI was constructed using Greenwood's variance (loglog transformation). An upper limit of the one-sided 97.5% CI was also constructed using Peto's method (see Section X.A.3.e.(6)) which produced similar results with respect to the primary safety analysis.

Figure 10-1 Time to First Major Adverse Event



Notes: The Safety Sample includes All Enrolled subjects who underwent implantation of the Relay® device or surgical repair. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a secondary procedure, the time to event is based on the initial procedure date if the event occurred before the second procedure date; otherwise, time to event is based on the second procedure date.

b) Aneurysm Related Mortality (ARM) within 1 year

Aneurysm-related mortality was a component of the primary safety endpoint. The protocol definition of aneurysm-related mortality was any death due to a rupture, death prior to 30 days or hospital discharge from primary procedure, or death less than 30 days or prior to hospital discharge for a secondary procedure designed to treat the original aneurysm. Excluded are aneurysms in other anatomic segments other than the segment treated with the Relay® stent-graft. There were 8 deaths considered aneurysm-related in the Relay® cohort, 7 of which occurred within 30 days. The death that occurred beyond 30 days involved a subject who suffered a contained rupture of an untreated aneurysm. Within 30 days of placing a second Relay® device to treat the contained rupture, the subject died. In the surgical control cohort, there were 6 aneurysm-related deaths, all of which occurred within 30 days of the surgical procedure.

Kaplan Meier analysis of freedom from aneurysm-related mortality within 1 year is presented in **Table 10-15**. Freedom from aneurysm-related mortality and time to aneurysm-related mortality are graphically presented in **Figures 10-2 and 10-3**, respectively.

Table 10-15 Kaplan-Meier: Freedom From Aneurysm-Related Mortality Within 1 Year

	Relay® Thoracic Stent-Graft (N = 120)	Surgical Repair (N = 60)
Aneurysm-related mortality[a, b]	8/120 (6.7%)	6/60 (10.0%)
Censored (subjects without observed events)[a, c]	112/120 (93.3%)	54/60 (90.0%)
Kaplan-Meier estimated probability (95% two-sided CI[d]) of freedom from aneurysm-related mortality within 1 year	0.93 (0.87, 0.97)	0.89 (0.78, 0.95)

Notes: The Safety sample includes All Enrolled subjects who underwent implantation of the Relay® device or surgical repair. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a second procedure, the time to event is based on the initial procedure date if the adverse event occurred before the second procedure date; otherwise, time to event is based on the second procedure date.

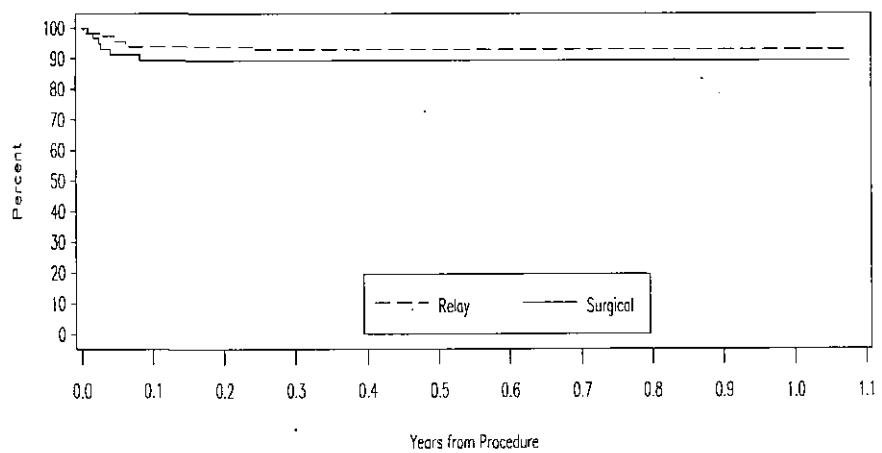
[a] Percentages are based on the number of subjects in each treatment group.

[b] Adjudicated by the CEC. In the event that the CEC determines an event could never be adjudicated, it will be assumed that the site investigator's report is accurate and it is used in place of an adjudication.

[c] Subjects without observed events were censored at the last follow-up (up to 1 year).

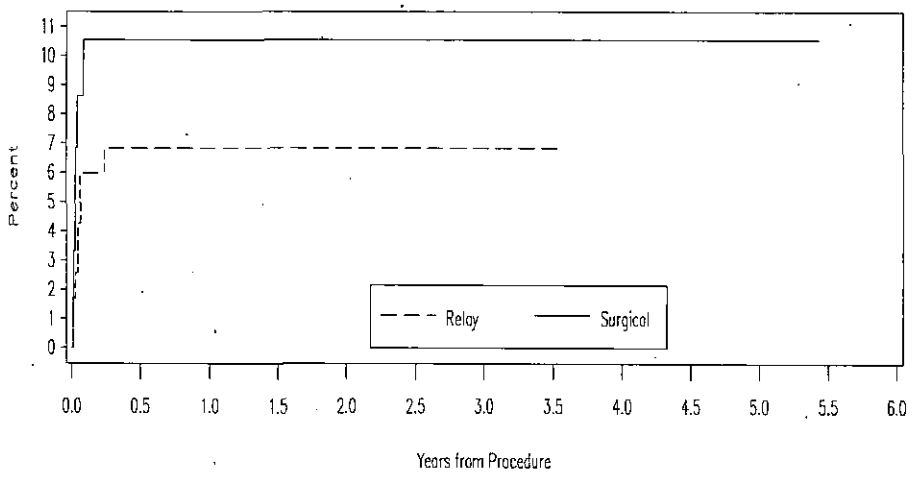
[d] Using Greenwood's variance (loglog transformation). The lower limit of the two-sided 95% CI is equivalent to the lower limit of the one-sided 97.5% CI.

Figure 10-2 Freedom from Aneurysm-Related Mortality



Notes: The Safety Sample includes all enrolled subjects who underwent implantation of the Relay® device or surgical repair. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a secondary procedure, the time to event is based on the initial procedure date if the event occurred before the second procedure date, otherwise time to event is based on the second procedure date.

Figure 10-3 Time to Aneurysm-Related Mortality



Notes: The Safety Sample includes All Enrolled subjects who underwent implantation of the Relay® device or surgical repair. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a secondary procedure, the time to event is based on the initial procedure date if the event occurred before the second procedure date; otherwise, time to event is based on the second procedure date.

Time to event is calculated as 1 minus freedom from event (Kaplan-Meier estimate).

c) Secondary Safety Endpoints

The secondary safety endpoint included evaluation of the major adverse device events at time points other than 1 year. In addition, an evaluation of all-cause mortality was conducted as part of the secondary endpoint. Although not a secondary endpoint per the study protocol, information on serious adverse events and their relationship to the study device and procedure was collected.

Major Adverse Events (including All-Cause Mortality)

Table 10-16 summarizes the number of subjects in the Relay® and surgical control cohorts who experienced major adverse events (MAEs). All data is CEC adjudicated. The percentage of subjects experiencing one or more MAE was higher in the surgical control cohort than in the Relay® cohort (50% vs. 26.7%). The results of an unadjusted Cox proportional hazards analysis of all MAEs post-procedure was conducted. The hazard ratio was 0.49 with a p-value of 0.005.

Stroke (10.8%) accounted for the greatest number of MAEs in the Relay® cohort compared with 6.7% in the surgical cohort.

Based on adjudicated data, fewer aneurysm-related deaths were reported in the Relay® cohort (6.7%) than in the surgical cohort (10.0%). As noted previously, within 30 days of the initial implantation procedure, there were seven deaths in the Relay® cohort. None of these deaths was due to aneurysm rupture. Causes of death included sepsis/bowel perforation, bowel ischemia, respiratory failure, hemorrhagic stroke, pneumonia, cardiopulmonary arrest, and combination respiratory failure/acute renal failure, stroke.

Table 10-17 presents the Kaplan Meier Analysis of Freedom from All-Cause Mortality through the end of the 1-year visit window (Day 393). There were 17 deaths (14.2%) in the Relay® cohort and 10 deaths (16.7%) in the surgical control cohort. Freedom from all-cause mortality and time to all death following implantation through the end of the 1-year visit window are graphically presented in **Figures 10-4 and 10-5**, respectively. An unadjusted Cox proportional hazards analysis of the all-cause mortality was conducted. The hazard ratio was 0.75.

Deaths occurring after the end of the 1-year visit window and before the start of the 2-year follow-up window (Day 674) were also captured. **Table 10-16** presents the full 1-year visit interval which extends from Day 337 to Day 673. In addition, **Table 10-16** presents the cumulative number of deaths from implantation through the end of the 1 year visit interval (Day 673). Cumulatively, there were 23 deaths (19.2%) in the Relay® cohort. Seventeen (17) occurred by Day 393 (1-year visit window) and another 6 occurred between Day 394 and 673. For the surgical control cohort, there were a total of 18 deaths (30%), 10 by Day 393 and another 8 between 394 and Day 673.

Table 10-16 Mortality and Major Adverse Events (MAEs) -- Relay® and Surgical

	Operative ≤15 Days		30-Day Visit 16-151 Days		6-Month Visit 152-336 Days		1-Year Visit 337-673 Days		≤30 Days		Overall (cumulative through 1 year interval)	
	Relay® (N = 120)	Surgical (N = 60)	Relay® (N = 114)	Surgical (N = 51)	Relay® (N = 107)	Surgical (N = 35)	Relay® (N = 97)	Surgical (N = 33)	Relay® (N = 120)	Surgical (N = 60)	Relay® (N = 120)	Surgical (N = 60)
Mortality (all causes)[a]	3 (2.5%)	5 (8.3%)	7 (6.1%)	5 (9.8%)	7 (6.5%)	0	6 (6.2%)	1 (3.0%)	7/ (5.8%)	6 (10.0%)	23 (19.2%)	18 (30.0%)
One or more MAE	24 (20%)	29 (48.3%)	6 (5.3%)	1 (2.0%)	2 (1.9%)	0	0	0	26 (21.7%)	29 (48.3%)	32 (26.7%)	30 (50%)
– Stroke	6 (5.0%)	4 (6.7%)	3 (2.6%)	0	2 (1.9%)	0	0	0	6 (5.0%)	4 (6.7%)	10 (9.2%)[b]	4 (6.7%)
– Paralysis/paraplegia[c]	2 (1.7%)	2 (3.3%)	0	0	1 (0.9%)	0	0	0	2 (1.7%)	2 (3.3%)	3 (2.5%)	2 (3.3%)
– Myocardial infarction	2 (1.7%)	1 (1.7%)	0	0	0	0	0	0	2 (1.7%)	1 (1.7%)	2 (1.7%)	1 (1.7%)
– Procedural bleeding	8 (6.7%)	17 (28.8%)	0	0	0	0	0	0	8 (6.7%)	17 (28.3%)	8 (6.7%)	17 (28.8%)
– Respiratory failure	5 (4.2%)	11 (18.3%)	2 (1.8%)	0	1 (0.9%)	0	0	0	7 (5.8%)	11 (18.3%)	8 (6.7%)	11 (18.3%)
– Renal failure	2 (1.7%)	3 (5.0%)	0	0	1 (0.9%)	0	0	0	2 (1.7%)	3 (5.0%)	3 (2.5%)	3 (5.0%)
– Wound healing complications	6 (5.0%)	3 (5.0%)	1 (0.9%)	5 (9.8%)	1 (0.9%)	0	0	0	7 (5.8%)	4 (6.7%)	8 (6.7%)	7 (11.7%)
– Aneurysm-related mortality[a]	3 (2.5%)	5 (8.3%)	5 (4.4%)	1 (2.0%)	0	0	0	0	7 (5.8%)	6 (10.0%)	8 (6.7%)	6 (10.0%)

Notes: The Safety sample includes All Enrolled subjects who underwent implantation of the Relay® device or surgical repair. Mortality and major adverse events were adjudicated by the CEC. At each level of summarization, a subject is counted once if the subject reported 1 or more events. Percentages are based on the number of subjects in the Safety sample who have sufficient follow-up. A subject has sufficient follow-up if the date of last follow-up minus procedure date is greater than or equal to the start of the time period. Percentages for the overall time period are based on all subjects in the Safety sample. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a second procedure, the time periods are based on the initial procedure date if the adverse event occurred before the second procedure date; otherwise, time periods are based on the second procedure date. In the event that the CEC determines an event can never be adjudicated, it is assumed that the site investigator's report is accurate and it is used in place of adjudication.

[a] While all-cause mortality is presented, the safety endpoint is aneurysm-related mortality.

[b] One subject experienced a stroke in two separate intervals, but is not counted twice in the cumulative interval.

[c] Paraparesis was not one of the events tracked as a major adverse event. Paraparesis was reported in one Relay® subject 2 days post-implant, and it resolved with medication. Paraparesis was also reported in one surgical subject 2 days post-op when the lumbar drain was stopped. This event also resolved.

Table 10-17 Kaplan-Meier: Freedom From All-Cause Mortality Within 1 Year

	Relay® Thoracic Stent-Graft (N = 120)	Surgical Repair (N = 60)
Mortality (All-cause)[a]	17/120 (14.2%)	10/60 (16.7%)
Censored (subjects without observed event)[a, b]	103/120 (85.8%)	50/60 (83.3%)
Kaplan-Meier estimated probability (95% two-sided CI[c]) of freedom from all-cause mortality within 1 year	0.85 (0.78, 0.91)	0.81 (0.67, 0.89)

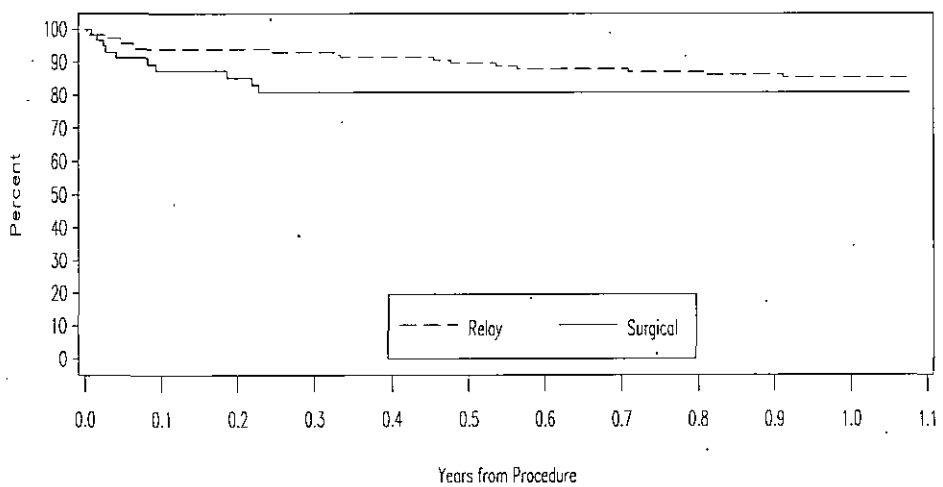
Notes: The Safety sample includes All Enrolled subjects who underwent implantation of the Relay® device or surgical repair. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a second procedure, the time to event is based on the initial procedure date if the adverse event occurred before the second procedure date; otherwise, time to event is based on the second procedure date.

[a] Percentages are based on the number of subjects in each treatment group.

[b] Subjects without observed events were censored at the last follow-up (up to 1 year).

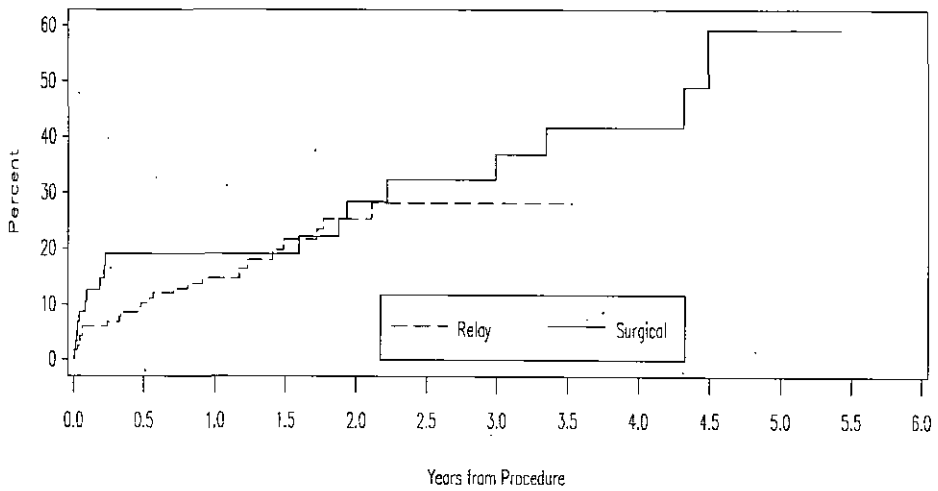
[c] Using Greenwood's variance (loglog transformation). The lower limit of the two-sided 95% CI is equivalent to the lower limit of the one-sided 97.5% CI.

Figure 10-4: Freedom from All-Cause Mortality



Notes: The Safety Sample includes all enrolled subjects who underwent implantation of the Relay® device or surgical repair. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a secondary procedure, the time to event is based on the initial procedure date if the event occurred before the second procedure date, otherwise time to event is based on the second procedure date

Figure 10-5: Time to Mortality (All-Cause)



Notes: The Safety Sample includes all enrolled subjects who underwent implantation of the Relay® device or surgical repair. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a secondary procedure, the time to event is based on the initial procedure date if the event occurred before the second procedure date; otherwise time to event is based on the second procedure date.
Time to event is calculated as 1 minus freedom from event (Kaplan-Meier estimate).

d) Major Adverse Events

Refer to section X.D.3.a and X.D.3.c.

e) Serious Adverse Events

Serious adverse events (SAEs) are those that:

- Are fatal;
- Are life-threatening;
- Result in persistent or significant disability/incapacity;
- Result in permanent impairment of a body function or permanent damage to a body structure;
- Result in hospitalization or require prolonged hospitalization;
- Necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure;

A summary of SAEs reported for all Relay® subjects in the Safety sample is presented in **Table 10-18**. Events are categorized by system/type. SAEs were rated as either unlikely, possibly or definitely related to the device or procedure. The rates specified in the device/procedure-related columns represent those events deemed "definitely" related to the device or procedure. The specific SAEs that were considered device and/or

procedure-related are highlighted separately from the general system category. In the Relay® cohort, 62.5% of subjects experienced one or more SAE.

Table 10-18 Serious Adverse Events – Relay® Cohort through 1 Year Interval[a]

Category	All SAEs	Device-Related SAEs	Procedure-Related SAEs
Bleeding events	12/120 (10.0%)		
• Procedural Bleeding (unplanned transfusion)		1/120 (0.8%)	6/120 (5.0%)
• Post-procedural Bleeding		0	1/120 (0.8%)
• Hematoma		0	4/120 (3.3%)
Cardiac complications	21/120 (17.5%)		
• Myocardial Infarction		0	1/120 (0.8%)
• Hypertension		0	1/120 (0.8%)
• Tachycardia		0	1/120 (0.8%)
Endoleak	4/120 (3.3%)		
Type I Endoleak		1/120 (0.8%)	1/120 (0.8%)
Hematology complications	6/120 (5.0%)		
• Anemia		0	1/120 (0.8%)
• Coagulopathy		0	2/120 (1.7%)
• Decreased Hematocrit		0	1/120 (0.8%)
• Decreased Platelets		0	1/120 (0.8%)
• Increased Creatinine		0	1/120 (0.8%)
• Increased BUN		0	1/120 (0.8%)
Neurological complications	19/120 (15.8%)		
• Stroke		0	3/120 (2.5%)
• Weakness		0	1/120 (0.8%)
• Paraplegia		0	1/120 (0.8%)
Pulmonary complications	20/120 (16.7%)		
• Pleural Effusion		0	3/120 (2.5%)
Renal / genitourinary complications	12/120 (10.0%)		
• Renal Failure		0	1/120 (0.8%)
• Traumatic Foley Insertion		0	1/120 (0.8%)
• Pyelonephritis		0	1/120 (0.8%)
Vascular complications	10/120 (8.3%)		
• Rupture of Untreated TAA		1/120 (0.8%)	0
• Aortic Dissection		1/120 (0.8%)	0
Vascular access complications	4/120 (3.3%)		
• Access Difficulty		1/120 (0.8%)	1/120 (0.8%)
• Iliac Artery Injury		0	3/120 (2.5%)
General	15/120 (12.5%)		
• Volume Overload		0	1/120 (0.8%)
• Sepsis		0	1/120 (0.8%)
• Decreased Nutritional Intake		0	1/120 (0.8%)
Neoplasm	4/120 (3.3%)	0	0
Digestive/ gastrointestinal complications	7/120 (5.8%)	0	0
• Ischemic Bowel		0	1/120 (0.8%)
Dermatology complications	1/120 (0.8%)	0	0
Device malfunction[b]	1/120 (0.8%)	0	0
Trauma	1/120 (0.8%)	0	0
One or more SAE	68/120 (56.7%)		

Notes: The Safety sample includes all enrolled subjects who underwent implantation of the Relay® device or surgical repair. Percentages are based on the number of subjects in the Safety sample. This summary represents all SAEs as recorded on the CRF. In the all SAEs column, a subject is counted once if the subject reported one or more events.

[a] 1 year Interval extends to Day 673
[b] Event was a graft infection deemed by the CEC unlikely related to the device.

4. Effectiveness Results

a) Primary Effectiveness Endpoint

The primary effectiveness endpoint was freedom from major device-related adverse events [endoleak (Types I, III and IV), stent migration (> 10mm as compared to the 1 month visit), lumen occlusion, aneurysm rupture, and deployment failure/conversion to surgical repair] at 1 year post-procedure. The results of this study are summarized in **Table 10-19**. The primary effectiveness analysis was evaluated in three ways. The initial analysis considered the entire cohort of 120 subjects. The second analysis considered 99 subjects who achieved the 1-year visit and/or had some 1-year follow-up information. Specifically, as noted in **Table 10-4**, only 97 subjects were eligible for a 1-year visit, but 99 subjects were evaluated as part of the primary effectiveness endpoint since two subjects who experienced major device-related adverse events died prior to 1-year and were included in the total analyzed. Finally, as noted in **Table 10-4** not all subjects had 1-year imaging evaluated by the core laboratory. Therefore, an alternate analysis considering only those subjects with complete imaging was also conducted.

When the primary effectiveness endpoint is evaluated for the entire cohort of 120 subjects who were implanted with the Relay® stent-graft, 116 (97%) were free of major device-related events out to 1 year. When the primary effectiveness analysis was conducted including only 99 subjects with some follow-up information at 1 year, the freedom from major device-related adverse events at 1 year is 96%. In both analyses (120 subjects and 99 subjects), the lower limit of one-sided 97.5% confidence interval was greater than 0.90. The results of the one-sided z-test rejected the null hypothesis, providing evidence that the performance goal of greater than 0.80 proportion-free of major device-related adverse events within 1 year was met. A Kaplan-Meier analysis resulted in a 96% probability (lower limit of the one-sided 97.5% confidence interval of 0.902) of remaining free from major device-related events at the 1-year follow-up visit (**Table 10-20**). Time to first major device related adverse events is graphically presented in **Figure 10-6**. Tipping point analyses (as described in Section X.A.3.e.(6)) performed to evaluate the impact of non-evaluable subjects demonstrated that the effectiveness analyses conducted were robust.

It should be noted that since only 89 subjects had imaging for the 1-year visit evaluated by the core laboratory, additional 1-year data were obtained to allow for the inclusion of 99 patients in the primary effectiveness analysis. These data consisted of a combination of site-reported data and imaging data obtained after the 1-year interval. Use of the later imaging provided a conservative estimate of the device effectiveness, as any events identified at a later follow-up time were considered to have been present at 1 year and because it is unlikely that an event would have been present at 1 year with spontaneous resolution before the later follow-up. As further support, an alternate effectiveness analysis considering only those subjects with interpretable CTs at 1 year showed that study endpoints were still met. Specifically, the alternative analysis was performed on 70 event-free subjects with 1-year CTs that were interpretable for both endoleak and migration plus 4 subjects with major device-related adverse events. This analysis yielded

a proportion of 0.95 and a lower confidence limit of 0.89. Since the lower limit of the confidence interval was greater than 0.80, the effectiveness endpoint remained satisfied.

Time to first major device related adverse events is graphically presented in **Figure 10-6**.

Table 10-19 Freedom From Major Device-Related Adverse Events at 1 Year

Subjects Free From Major Device-Related Adverse Events at 1 Year Post-Procedure[a]	**Relay® Thoracic Stent-Graft (N = 120)**
Proportion free from event for all subjects who underwent implantation of the Relay® device[b]	116/120 (0.97)
– Lower limit of 97.5% 1-sided confidence interval[c]	0.93
Proportion free from event excluding subjects with less than 1 year of follow-up[d]	95/99 (0.96)
– Lower limit of 97.5% 1-sided confidence interval[c]	0.92

Note: The Effectiveness sample includes All Enrolled subjects who underwent implantation of the Relay® device.

[a] Adjudicated by the CEC and as identified by the Core Laboratory as a major device-related adverse event.

[b] Calculated for subjects in the Effectiveness sample.

[c] Test failed if the lower limit of the 1-sided confidence interval was less than or equal to 0.80.

[d] Excluding subjects in the Effectiveness sample with less than 1 year (minus 1 month to account for the visit window) of follow-up without major device-related adverse event.

Table 10-20 Kaplan-Meier: First Major Device-Related Event Within 1 Year

	Relay® Thoracic Stent-Graft (N=120)
Major device-related adverse event[a, b]	4/120 (3.3%)
Censored (subjects without observed events)[a, c]	116/120 (96.7%)
Kaplan-Meier estimated probability (lower limit of the one-sided 97.5% CI[d]) of free from major device-related adverse event at 1 year	0.96 (0.902)

Notes: The Effectiveness sample includes All Enrolled subjects who underwent implantation of the Relay® device. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a second procedure, the time to event is based on the initial procedure date if the adverse event occurred before the second procedure date; otherwise, time to event is based on the second procedure date.

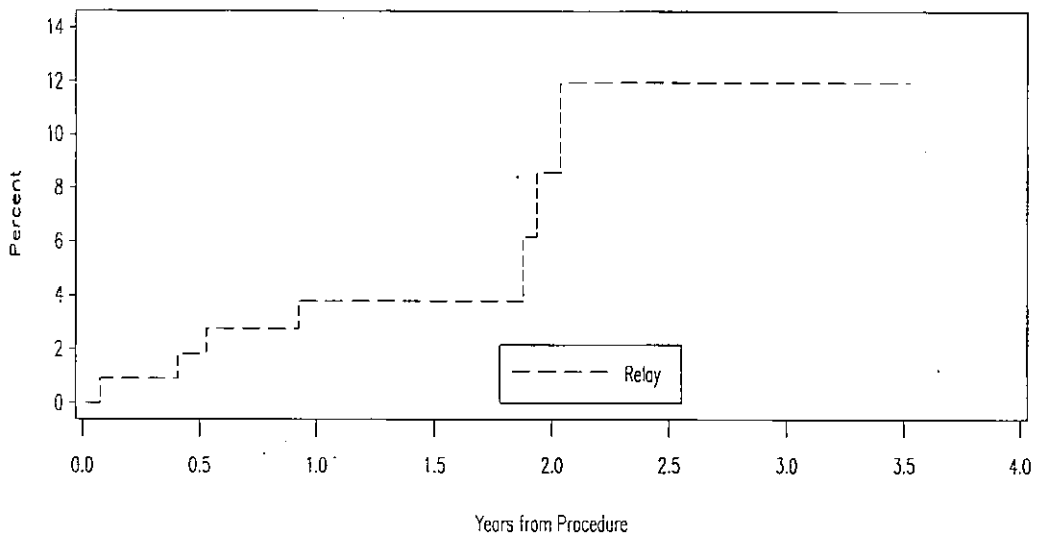
[a] Percentages were based on the number of subjects in the Effectiveness sample.

[b] Adjudicated by the Clinical Events Committee and as identified by the Core Laboratory.

[c] Subjects without observed events were censored at the last follow-up (up to 1 year).

[d] Using Greenwood. The one-sided 97.5% CI was constructed using Greenwood's variance (loglog transformation). A one-sided CI was also constructed using Peto's method (see Section X.A.3.e.(6)) which produced similar results with respect to the primary effectiveness analysis.

Figure 10-6 Time to First Major Device-Related Event



Notes: The Effectiveness sample includes all enrolled subjects who underwent implantation of the Relay® device. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a second procedure, the time to event is based on the initial procedure date if the event occurred before the second procedure date; otherwise, time to event is based on the second procedure date.

b) Secondary Effectiveness Endpoints

The secondary effectiveness analyses included an evaluation of major device-related AEs [endoleak (excluding Type II), stent migration (migration ≥ 10 mm as compared to the 1-month visit), lumen occlusion, aneurysm rupture, conversion to surgery] at times other than 1 year. Other secondary effectiveness endpoints included lesion measurement changes from the 1-month visit as compared with the 6-month and 1-year visits, device integrity failures, and vascular access complications.

Table 10-21 combines the major device-related adverse events as reported by the Core Laboratory with the major device-related adverse events as adjudicated by the CEC. As noted, there have been no treated aneurysm ruptures. One subject has been converted to surgery. The etiology was noted to be due to esophageal erosion into the aorta well below the placement of the Relay® device. On this basis, the CEC concluded that the event was not device-related and should not be considered part of the primary endpoint.

Table 10-21: Major Device-Related Events

	Operative ≤15 Days		30-Day Visit (full window) 16-151 Days		6-Month Visit 152-336 Days		1-Year Visit 337-673 Days		≤ 30 Days		Overall (cumulative through 1 year interval)	
	Core Lab	CEC	Core Lab	CEC	Core Lab	CEC	Core Lab	CEC	Core Lab	CEC	Core Lab	CEC
Any major adverse device-related event	0/107	0/120	2/107 (1.9%)	0/114	2/95 (2.1%)	0/107	2/87 (2.3%)	0/97	1/107 (0.9%)	0/120	6/107 (5.6%)	0/120
Any endoleak	0/103	NA	1/103 (1.0%)	NA	0/90	NA	1/80 (1.3%)	NA	1/103 (1.0%)	NA	2/103 (1.9%)	NA
– Type I	0/103	NA	1/103 (1.0%)	NA	0/90	NA	1/80 (1.3%)	NA	1/103 (1.0%)	NA	2/103 (1.9%)	NA
– Type III	0/103	NA	0/103	NA	0/90	NA	0/80	NA	0/103	NA	0/103	NA
– Type IV	0/103	NA	0/103	NA	0/90	NA	0/80	NA	0/103	NA	0/103	NA
Stent migration	0/107	NA	1/107 (0.9%)	NA	2/95 (2.1%)	NA	2/86 (2.3%)	NA	0/107	NA	3/107 (2.8%)[a]	NA
Lumen occlusion	0/104	0/120	0/104	0/114	0/91	0/107	0/80	0/97	0/104	0/120	0/104	0/120
Treated aneurysm rupture	NA	0/120	NA	0/114	NA	0/107	NA	0/97	NA	0/120	NA	0/120
Conversion to surgery / deployment failure	NA	0/120	NA	0/114	NA	0/107	NA	0/97	NA	0/120	NA	0/120

CEC= Clinical Events Committee; NA= Not Applicable.

Notes: The Effectiveness sample includes All Enrolled subjects who underwent implantation of the Relay® device. Major device-related adverse events were reported by Core Laboratory. Site-reported events were adjudicated by the CEC. At each level of summarization, a subject was counted once if the subject reported 1 or more events. Percentages are based on the number of subjects in the Effectiveness sample who have sufficient follow-up. A subject has sufficient follow-up if the date of last follow-up minus the procedure date is greater than or equal to the start of the time period. Percentages for the Overall time period are based on all subjects in the Effectiveness sample. Sufficient follow-up is calculated separately for site-reported and Core Laboratory data. Sufficient follow-up for Core Laboratory data is based only on follow-up computed tomography (CT) scans or x-ray. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a second procedure, the time periods are based on the initial procedure date if the adverse event occurred before the second procedure date; otherwise, time periods are based on the second procedure date.

[a]In total, 3 subjects experienced migration within the 1 year interval; migration was reported at more than one interval for some subjects.

Lesion Size Changes

A summary of the changes in maximum lesion diameter (≥10 mm) from the 1-month post-procedure visit compared with the lesion length at the 6-months and 1-year visits is presented in **Table 10-22**. Lesion enlargement was detected in a total of 3 study subjects. Enlargement was detected in 1 of these subjects at the 6-month and 1-year visits. The subject's lesion increased a total of 20.8 mm from the time of procedure through the 1-year visit and was associated with both migration and Type I endoleak. Intervention was proposed for this subject, but at the time of datalock, none had been performed. The lesion enlargement detected in the other 2 subjects was not associated with device migration or Type I, III, or IV endoleak.

Table 10-22 Lesion Diameter Changes in Relay® Cohort - Core Laboratory-Reported

6-month visit	
Increase (≥10 mm)	1/92 (1.1%)
Decrease (≥10 mm)	9/92 (9.8%)
No change	82/92 (89.1%)
1-year visit	
Increase (≥10 mm)	3/86 (3.5%)
Decrease (≥10 mm)	20/86 (23.3%)
No change	63/86 (73.3%)

Vascular Access Complications

Vascular access complications were evaluated by the sites and the CEC. Applicable complications included iliac artery injury, femoral artery injury, pseudoaneurysm formation, and access difficulties. The overall incidence of vascular access complications as adjudicated by the CEC was 9.2% (11/120). The majority of these complications were iliac artery injuries (5.8%, 7/120). There were 3 reports of femoral artery injury (2.5%) and 1 incidence of pseudoaneurysm (0.8%, 1/120).

Device Integrity Failures (Wireform Fractures)

Wireform fractures have been detected in two subjects. The fractures were in the longitudinal support system of the graft and in both cases, investigation revealed that the fractures were due to the placement of the device (either completely or partially) along the inferior curvature of the aorta versus the superior curvature as described in the Instructions for Use. Both fractures were detected at the 1-year follow-up interval by the Core Laboratory. Both subjects have been followed regularly as part of the protocol requirements. One of the subjects has achieved the 3-year follow-up with no reports of additional fracture, endoleak, migration, lumen occlusion or other adverse findings. The other subject has achieved the 2-year follow-up visit. The core lab has detected a Type II endoleak, but there is no finding of Type I/III endoleak, migration, or lumen occlusion.

Secondary Interventions

During the course of follow-up, 3 subjects required secondary intervention. Two subjects received additional stent-grafts to treat endoleaks at days 126 and 430 post-procedure respectively. One subject was converted to open surgical repair 91 days post-procedure due to a graft infection secondary to an aorto-esophageal fistula.

Finally, the re-attempted procedure for the subject described previously was documented as a secondary intervention to distinguish it from the initial aborted attempt.

c) Summary of Device-Specific Adverse Events (Site-Reported)

Table 10-23 below summarizes site-reported device-specific events.

Throughout the 1-year interval, Type I endoleak was detected in a total of 7 subjects, and Type III endoleak was detected in 3 subjects. One Type III endoleak and 4 Type I endoleaks were reported within 30 days. All were detected at the time of the procedure. One subject was reported to have a Type I, II, and III endoleak. The Type I and III endoleaks for this subject resolved by the 1-month visit. Of the other 3 subjects with Type I endoleaks detected at implant, 1 resolved by the 1-month visit and the other 2 subjects exited the study before any additional follow-up visits. Three other subjects experienced Type I endoleaks during the 1-year interval. Two of these endoleaks were detected at the 6-month visit and the third was detected at 1 year. Of the 2 detected at the 6-month visit, 1 had resolved by the 1-year visit. None of these 3 subjects were noted to have lesion enlargement or migration, although 2 subjects received additional stent-grafts to treat these endoleaks. Through the 1-year follow-up, 2 other subjects experienced Type III endoleaks. One of these was detected at Day 36, but resolved by the 6-month follow-up, while the other was detected at the 6-month visit and persisted through the 1-year visit.

Four subjects were noted to have lesion enlargement throughout the 1-year interval. Lesion enlargement was noted for two subjects at the 6-month visit. Measurements at the 1-year visit for one of these subjects showed no increase in comparison to the 1-month measurement. Measurements taken at the 1-year visits revealed increases for 3 subjects, including 1 subject which exhibited enlargement at the 6-month visit. None of the subjects had concomitant migration or with Type I, III, or IV endoleak.

Table 10-23: Device-Specific Adverse Events—Site-Reported[A]

Event	≤ 30 days	Overall (cumulative through full 1 year interval, Day 0 - 673)
Endoleak		
• Type I	4/120 (3.3%)	7/120 (5.8%)
• Type II	2/107 (1.9%)	13/107 (12.1%)
• Type III	1/120 (0.8%)	3/120 (2.5%)
• Type IV	0/120 (0%)	0/120 (0%)
• Unknown	1/107 (0.9%)	2/107 (1.9%)
Aneurysm Enlargement (increase of > 10 mm as compared with 1 month measurement)	Not applicable	4/87 (4.6%)
Loss of Patency (Lumen Occlusion)	0/120 (0%)	0/120 (0%)
Migration >10 mm as compared with 1 month images	Not applicable	0
Wireform Fracture[B]	0/120 (0%)	1/120 (0.8%)
Aneurysm Rupture	0/120 (0%)	0/120 (0%)

[A]All data except Type II / unknown type endoleaks and aneurysm enlargement were analyzed as part of primary and secondary effectiveness analyses. As these were tabulated separately, denominators are different.

[B]Two fractures have been detected by the core lab. Only 1 has been detected at the site level.

5. Subgroup Analyses

a) By Delivery System Design

A comparison of the delivery and deployment in procedures involving the Plus delivery system versus those involving the original delivery system was conducted. The subgroup analysis included summaries of the number of subjects who completed and discontinued the study by delivery system used. Demographics, baseline medical history, aneurysm diameter, and clinical utilities were also summarized. Comparisons of treatment assessments, requirements for additional treatments, and final procedure results were made using the chi-square test for categorical data for subjects treated with the original delivery system and the Plus delivery system.

Subjects treated with the original Relay® delivery system and subjects treated with the Plus delivery system were compared (chi-square test) to demonstrate that the following do not differ based on the delivery system used, thus allowing the subjects to be pooled for the evaluation of the primary effectiveness endpoint:

- evaluation of the delivery system
- overall rate of vascular access complications (≤30 days)

- rate of access failures
- rate of deployment system difficulties

Twenty-five (25) of the 120 subjects in the study received treatment with the Plus system. The subjects in the 2 subgroups were similar in age, gender, and race. The subjects in both delivery system subgroups responded similarly during the implantation process. Comparison of the 2 treatment systems using the chi-square test did not show any statistically significant differences between the subjects treated with the 2 delivery systems with respect to major device-related adverse events. The 2 delivery system subgroups were similar in clinical utility measures except for the number of subjects requiring transfusions (Relay® 9.6%; Relay® Plus 4.0%), estimated blood loss (Relay® 248.8 cc; Relay® Plus 152.8 cc), and procedures performed during implant (Relay® had 11 procedures and Relay® Plus had none). The differences may be due to the small number of subjects treated with the Relay® Plus system at the time the data were generated.

Overall, the comparison of the subjects treated with the original Relay® delivery system and the subjects treated with the Plus delivery system showed that the 2 subgroups were similar and that it was appropriate to pool the results for the evaluation of effectiveness and safety.

b) Test Group by Lesion Type

A subgroup analysis compared Relay® subjects based on lesion type, grouping saccular aneurysms with penetrating ulcers and comparing them to the subjects with fusiform thoracic aneurysms. As described for the delivery system subgroup analysis, demographics and baseline medical information were summarized. Additionally, CT scan and x-ray data were summarized as reported by both the sites and the Core Laboratory.

Primary and secondary effectiveness endpoints were compared including freedom from major device-related adverse events (AEs) at 1-year post-procedure (chi-square test); major device-related AEs as reported by the sites, as reported by the Core Laboratory, and as adjudicated by the CEC (chi-square test); time to first major device-related AE (log rank test); and individual components of major device-related AEs (chi-square test). Changes in maximum lesion diameter from 1-month post-procedure were also summarized for the lesion type subgroups. Additionally, the primary and selected secondary safety endpoints were compared. A Kaplan-Meier analysis of time to first major adverse event (MAE) within 1-year post procedure is presented as well as summaries of mortality and the components of MAEs. Fisher's exact test was utilized in place of chi-square test where appropriate.

Subjects with saccular aneurysms in the descending thoracic aorta were grouped with the subjects with penetrating atherosclerotic ulcers (PAU group) and compared to those with fusiform aneurysms (non-PAU group). Of the 120 Relay® subjects enrolled in the study, 34 were categorized as PAU and 86 were non-PAU. A greater number of subjects in the PAU group were in the 18 to 64 year-old category (non-PAU, 8.1%; PAU, 35.3%) with

fewer subjects in the ≥75 year-old category (non-PAU, 52.3%; PAU, 32.4%). The mean total treatment length of the vessel was greater in the non-PAU subjects than in the PAU subjects (non-PAU, 218.7 mm; PAU, 123.5 mm) as was the length of the lesion (non-PAU, 129.0 mm; PAU, 53.0 mm). The length from the lesion to the celiac artery was greater in the PAU subjects than in the non-PAU subjects (non-PAU, 87.0 mm; PAU, 125.1 mm). A greater number of subjects in the PAU group had aneurysm diameters less than 50 mm.

Overall, the comparison of the subjects with PAU and non-PAU lesions showed that the 2 groups were similar and that it was appropriate to pool the results for the evaluation of effectiveness and safety.

c) By Gender

The Relay® cohort accrued a total of 58 (48.3%) female and 62 (51.7%) male subjects. The prevalence of fusiform TAA was 72.4% (42/58) in the female population, 71% (44/62) in males, and 71.7% (86/120) in both groups combined. The prevalence of saccular TAA/penetrating ulcer was 27.6% (16/58) in the female population, 29% (18/62) in males, and 28.3% (34/120) in both groups combined. These data indicate that the distribution of fusiform TAA and saccular TAA/penetrating ulcers were comparable between the male and female subjects.

The primary safety endpoint was the distribution of Relay® and surgical control subjects experiencing at least 1 major adverse event (aneurysm-related mortality, stroke, paralysis/paraplegia, myocardial infarction, procedural bleeding, respiratory failure, renal failure, and wound healing complications) within 1 year post-procedure. The primary effectiveness endpoint was freedom from major device-related adverse events [endoleak (Types I, III and IV), stent migration (> 10mm as compared to the 1 month visit), lumen occlusion, aneurysm rupture, and deployment failure/conversion to surgical repair] at 1 year post-procedure. Fifty-eight (58) female and 62 male subjects were evaluable for the primary safety and effectiveness endpoints.

The occurrence of major adverse events was 25.9% among the female subjects and 27.4% among the male subjects. **Table 10-24** shows the Analysis of Major Adverse Event by Gender. Both the Kaplan Meier estimated probably of major adverse event and Kaplan Meier estimated probability of freedom from major adverse events are presented. Probabilities are similar for both males and females indicating, similar safety outcomes for both genders. Freedom from major adverse events is graphically presented in **Figure 10-7**.

Table 10-24 Kaplan-Meier: Analysis of Major Adverse Events Within 1 Year by Gender

	Females (N = 58)	Males (N = 62)
Major Adverse Event [a,b]	15/58 (25.9%)	17/62 (27.4%)
Censored (subjects without observed events)[b,c]	43/58 (74.1%)	45/62 (72.6%)
Kaplan-Meier estimated probability (95% two-sided CI) of major adverse event within 1 year	0.26 (0.40, 0.17)	0.27 (0.40, 0.18)
Kaplan-Meier estimated probability (95% two-sided CI) of freedom from major adverse event within 1 year	0.74 (0.60, 0.83)	0.73 (0.60, 0.82)

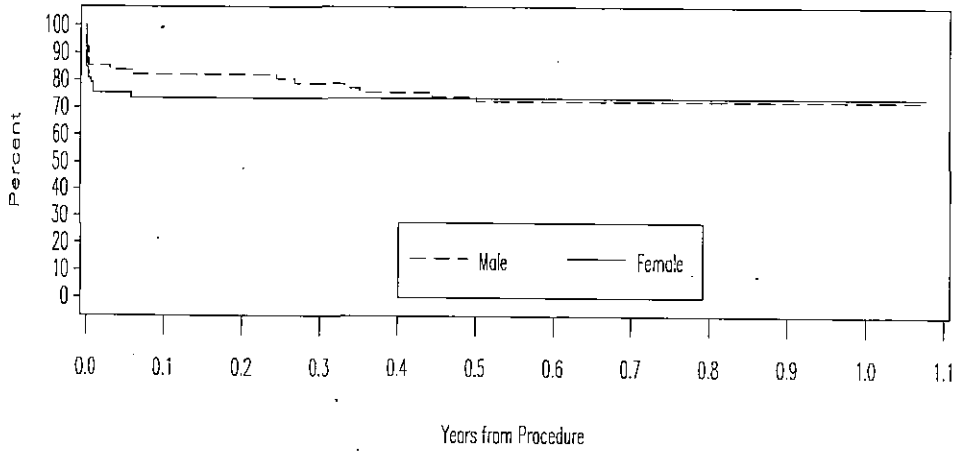
Notes: The Safety sample includes All Enrolled subjects who underwent implantation of the Relay® device or surgical repair. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a second procedure, the time to event is based on the initial procedure date if the adverse event occurred before the second procedure date; otherwise, time to event is based on the second procedure date.

[a] Percentages are based on the number of subjects in each treatment group.

[b] Adjudicated by the CEC. In the event that the CEC determines an event could never be adjudicated, it will be assumed that the site investigator's report is accurate and it is used in place of an adjudication.

[c] Subjects without observed events were censored at the last follow-up (up to 1 year).

Figure 10-7 Freedom from Major Adverse Events within 1 Year by Gender



Of the 120 subjects who underwent implantation of the Relay® Stent-Graft, 56 females (97%) and 60 males (97%) were free of device-related events through the 1-year follow-up visit. When the subjects with less than 1-year follow-up were excluded from the analysis, 96% of both female and male subjects were free of device-related events at the 1-year follow-up visit. These findings indicate similar effectiveness outcomes for males and females. **Table 10-25** and **Figure 10-8** show the Freedom from Major Device-Related Events by Gender.

Table 10-25 Kaplan-Meier: Freedom from Major Device-Related Event Within 1 Year by Gender

	Females (N = 58)	Males (N = 62)
Subjects free from major device-related adverse events at 1 year post-procedure[a]		
Proportion free from event[b]	56/58 (0.97)	60/62 (0.97)
Lower limit of 97.5% one-sided CI[c]	0.92	0.92
Proportion free from event[d]	46/48 (0.96)	49/51 (0.96)
Lower limit of 97.5% one-sided CI[c]	0.90	0.91

Notes: The Effectiveness sample includes All Enrolled subjects who underwent implantation of the Relay® device.

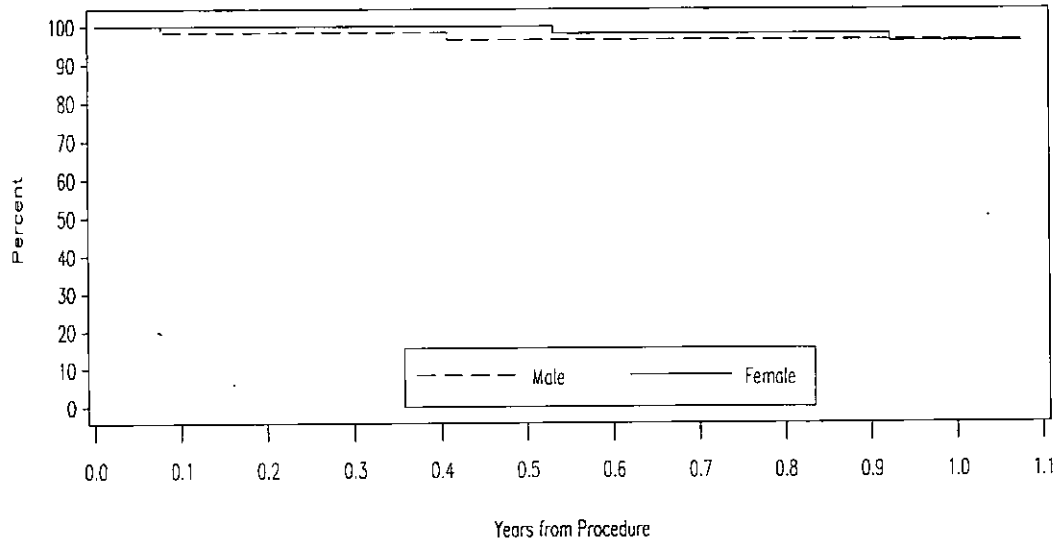
a Adjudicated by the Clinical Events Committee (CEC) and as identified by the Core Laboratory as a major device-related adverse event.

b Calculated for subjects in the Effectiveness sample.

c Test fails if the lower limit of the one-sided confidence interval is less than or equal to 0.80

d Excluding subjects in the Effectiveness sample with less than one year (minus one month to account for the visit window) of follow-up without major device-related adverse event.

Figure 10-8 Freedom from Major Device-Related Adverse Events by Gender



Female and male subjects had similar mortality rates (12.1% and 16.1%, respectively). A Kaplan-Meier analysis of all-cause mortality is presented in **Table 10-26** and **Figure 10-9**.

Table 10-26 Kaplan-Meier: Freedom From All-Cause Mortality Within 1 Year by Gender

	Females (N = 58)	**Males (N = 62)**
Mortality (All-cause)[a]	7/58 (12.1%)	10/62 (16.1%)
Censored (subjects without observed event)[a,b]	51/58 (87.9%)	52/62 (83.9%)
Kaplan-Meier estimated probability (95% two-sided CI) of freedom from mortality (all-cause) at 1 year	0.87 (0.75, 0.94)	0.84 (0.72, 0.91)

Notes: The Safety sample includes All Enrolled subjects who underwent implantation of the Relay® device or surgical repair. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a second procedure, the time to event is based on the initial procedure date if the adverse event occurred before the second procedure date; otherwise, time to event is based on the second procedure date.

[a] Percentages are based on the number of subjects in each treatment group.

[b] Subjects without observed events were censored at the last follow-up (up to 1 year).

Figure 10-9 Freedom from All-Cause Mortality by Gender

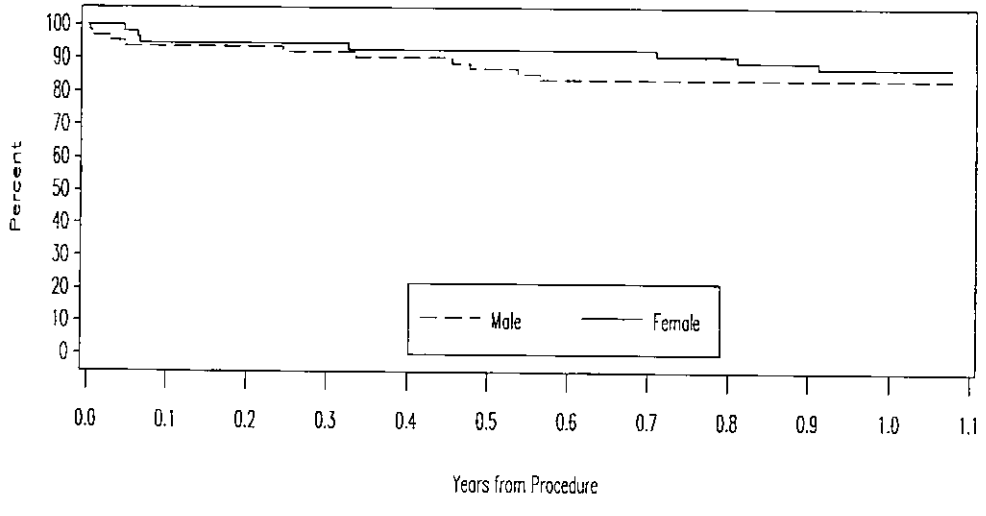


Table 10-27 presents individual rates of safety and effectiveness endpoints as well as other measures by gender. Events within 1 year represent the cumulative number of events between Day 0 and Day 393 (the end of the 1-year visit window).

Table 10-27: Endpoints Within 30 Days and 1 Year[a] by Gender

Safety				
	≤30 Days		**Within 1 year**	
	Females	**Males**	**Females**	**Males**
Primary Safety: Occurrence of one or more major adverse event within 1 year			25.9% (15/58)	27.4% (17/62)
Secondary Endpoints				
Mortality (all causes)	5.2% (3/58)	6.5% (4/62)	12.1% (7/58)	16.1% (10/62)
Major Adverse Events (one or more MAE)	25.9% (15/58)	9.7% (11/62)	25.9% (15/58)	27.4% (17/62)
– Stroke	6.9% (4/58)	3.2% (2/62)	6.9% (4/58)[b]	9.7% (6/62)
– Paralysis/paraplegia	1.7% (1/58)	1.6% (1/62)	1.7% (1/58)	3.2% (2/62)
– Myocardial infarction	0% (0/58)	3.2% (2/62)	0% (0/58)	3.2% (2/62)
– Procedural bleeding	8.6% (5/58)	4.8% (3/62)	8.6% (5/58)	5.2% (3/62)
– Respiratory failure	6.9% (4/58)	4.8% (3/62)	6.9% (4/58)	6.5% (4/62)
– Renal failure	3.4% (2/58)	0% (0/62)	3.4% (2/58)	1.6% (1/62)
– Wound healing complications	8.6% (5/58)	3.2% (2/62)	8.6% (5/58)	5.2% (3/62)
– Aneurysm-related mortality	5.2% (3/58)	6.5% (4/62)	5.2% (3/58)	8.1% (5/62)
Effectiveness				
	≤ 30 Days		**Within 1 year**	
	Females	**Males**	**Females**	**Males**
Primary Effectiveness: Freedom from major device-related adverse events within 1 year			97% (56/58)	97% (60/62)
Secondary Endpoints and other Measures				
Successful delivery and deployment at initial procedure	93.1% (54/58)[c]	100% (62/62)		
Patent graft at initial implant	100% (54/54)[d]	100% (62/62)		
Any major adverse device-related event	0% (0/58)	1.6% (1/62)	3.4% (2/58)	3.2% (2/62)
Any endoleak	0% (0/58)	1.6% (1/62)	1.7% (1/58)	1.6% (1/62)
– Type I	0% (0/58)	1.6% (1/62)	1.7% (1/58)	1.6% (1/62)
– Type III	0% (0/58)	0% (0/62)	0% (0/58)	0% (0/62)
– Type IV	0% (0/58)	0% (0/62)	0% (0/58)	0% (0/62)
Stent migration	0% (0/58)	0% (0/62)	3.4% (2/58)	1.6% (1/62)
Lumen occlusion / Loss of patency	0% (0/58)	0% (0/62)	0% (0/58)	0% (0/62)
Treated aneurysm rupture	0% (0/58)	0% (0/62)	0% (0/58)	0% (0/62)
Conversion to surgery / deployment failure[e]	0% (0/58)	0% (0/62)	0% (0/58)	0% (0/62)
Secondary endovascular procedures due to endoleak after discharge	0% (0/58)	0% (0/62)		
Secondary endovascular procedures due to endoleak after 30 days			1.7% (1/58)	0% (0/62)[f]

[a] Within 1 year includes events from Day 0 through Day 393 (end of the 1 year visit window)
[b] One female experienced two strokes within one year but is only counted once in the total rate.
[c] Four aborted cases at initial implant; one successfully implanted during second attempt
[d] Includes only those subjects who received the graft during the initial attempt
[e] One subject was converted to open repair 91 days post-procedure due to a graft infection secondary to an aorto-esophageal fistula. The etiology was noted to be due to esophageal erosion into the aorta well below the placement of the Relay® device. On this basis, the CEC concluded that the event was not device-related and should not be considered part of the primary endpoint
[f] One male subject underwent secondary intervention for endoleak but not until 430 days post-implant.

A set of *post hoc* analyses were conducted to assess the similarity by gender within the Relay® treatment for the primary safety endpoint, primary effectiveness endpoint, and all-cause mortality. The results suggest that the overall results of this study can be generalized to both genders.

- The primary safety analysis (Kaplan-Meier) was conducted for each gender (**Table 10-24**). The direct comparison (using the log-rank test) between the Kaplan-Meier results for each gender are similar. The result is further supported by the direct comparison (using a Chi-square test) of the observed gender-based point estimates.

- The primary effectiveness endpoint analysis was conducted for each gender (**Table 10-25**). The direct comparison (using a Fisher's Exact test) between the gender-based point estimates showed similarity between genders. Comparable results were also seen when excluding subjects without events and follow-up less than 1 year (sensitivity to the effectiveness endpoint).

- The direct comparison (using a Chi-square test) between gender-based point estimates for freedom from all-cause mortality within 1 year post-procedure showed similarity between genders (**Table 10-26**) .

In summary, women were reasonably represented in the Relay® study. The analyses showed that there may be some differences in the expected event rates for women as compared to men (higher major adverse event rate within 30 days), but the overall incidence of major adverse events within one year was comparable between males and females as was the incidence of typical endovascular events.

6. Clinical Utility Measures

A summary of the clinical utility measures from the time of the treatment procedure through hospital discharge for all enrolled subjects based on the initial procedure is presented in **Table 10-28**. Duration of the procedure, transfusion data, estimated blood loss, and length of ICU and hospital stay were summarized for subjects in both treatment groups. Additionally, for the Relay® subjects, the anesthesia type, contrast injection type, fluoroscopy data, anticoagulant and antiplatelet treatment usage, blood pressure medication usage, cerebral spinal fluid drainage, and procedures prior to and during implant were also summarized.

The Relay® subjects had a shorter average procedure time, required transfusions less often, experienced a lower volume of blood loss, and had shorter post-procedure ICU and hospital stays.

Table 10-28 Summary of Clinical Utility Measures

Clinical Utility Measures		Relay® Thoracic Stent-Graft Repair (N = 120)	Surgical Repair N = 60
Duration of procedure time (hours)	n	119	56
	Mean (SD)	2.39 (1.235)	4.59 (2.275)
	Median	1.98	3.92
	Min, Max	0.1, 6.2	1.4, 14.1
Estimated volume of blood loss (cc)	n	118	30
	Mean (SD)	228.5 (394.47)	2025.0 (1982.26)
	Median	150.0	1300.0
	Min, Max	0, 4000	0, 7000
Transfusion required[a]	Yes	10/119 (8.4%)	50/59 (84.7%)
	No	109/119 (91.6%)	9/59 (15.3%)
Time in intensive care unit (hours)	n	114	42
	Mean (SD)	58.221 (52.2587)	190.777 (190.0883)
	Median	46.660	123.375
	Min, Max	0.00, 256.70	24.00, 745.25
Duration of hospital stay (days)	n	114	56
	Mean (SD)	5.47 (4.206)	13.24 (9.626)
	Median	5.00	9.15
	Min, Max	1.0, 30.0	3.0, 45.0

Notes: Percentages and summary statistics are based on the number of subjects in each treatment group with data available. Clinical utilities are based on initial procedure.

[a] A subject counted as 'Yes' if she/he was given any blood product. Blood products included packed red blood cells, fresh frozen plasma, platelets, and other products. A subject may have been given more than 1 type of blood product.

XI. SUMMARY OF SUPPLEMENTARY CLINICAL INFORMATION

Several other sources of data served to support the safety and effectiveness of the Relay® Thoracic Stent-Graft. These sources of data include longer-term data from the pivotal Relay® Phase II trial, the Relay® Phase I feasibility trial, the ongoing continued access study, and RESTORE, a post-market European registry study.

A. Long-Term Results of Pivotal Relay® Study

The Phase II pivotal study protocol required that subjects in the Relay® cohort be followed through five years. Data will be collected for any subjects remaining in the study up to 5 years. Patient compliance and follow-up from the beginning of the study through 3 years is provided in **Table 10-29**. Of the subjects who reached the beginning

of the 2- and 3-year follow-up intervals, approximately half had returned by the time the analysis was prepared. **Tables 10-30** and **10-31** present major adverse events and major device-related events for subjects at 2 and 3 years post-implant. The only major adverse event reported has been stroke. Major device-related events have been reported in a limited number of subjects. These data continue to support the 1-year conclusions of safety and effectiveness.

Table 10-29 Relay® Phase II Compliance Imaging and Follow-up Through 3 years (Core Lab Reported)

Visit Interval[a]	Eligible for Follow-Up[b]	Subjects with[c] n (%)			Adequate Imaging to Assess Parameter n (%)				Events Occurring Before Next Interval[c] n (%)					
		Data for Visit	CT Scan	X-Ray	Size↑[d]	Endo-leak[d]	Mi-gration[d]	Fracture[e]	Death	Tech-nical Failure[f]	Con-version	Lost to Follow-Up	With-drawn Early	Not Due for Next Visit[g]
Operative (Day 0 – 15)	120	120 (100)	NA	NA	NA	NA	NA	NA						
Events between operative and 1 month visit									3 (2.5)	3 (2.5)	0	3 (2.5)	0	0
1 Month (Day 16 – 151)	114	108 (94.7)	107 (93.9)	100 (87.7)	NA	97 (85.1)	NA	97 (85.1)						
Events between 1 month and 6 month visit									7 (6.1)	0	1 (0.9)	0	0	0
6 Month (Day 152 – 336)	106	97 (91.5)	94 (88.7)	90 (84.9)	92 (86.8)	85 (80.2)	89 (84.0)	89 (84.0)						
Events between 6 month and 1 year visit									7 (6.6)	0	0	0	2 (1.9)	0
1 Year (Day 337 – 673)	97	89 (91.8)	89 (91.8)	86 (88.7)	86 (88.7)	81 (84)[h]	87 (89.7)	83 (85.6)						
Events between 1 year and 2 year visit									6 (6.2)	0	0	0	1 (1.0)	31 (32.0)
2 year (Day 674 to Day 1038)	62[h]	34 (57.6)	33 (55.9)	33 (55.9)	32 (54.2)	33 (53%)[h]	36 (58%)[h]	33 (55.9)						
Events between 2 year and 3 year visit									1 (1.7)	0	0	1 (1.7)	3 (5.1)	24 (40.7)
3 year (Day 1039 to Day 1403)	30	12 (40.0)	11 (36.7)	11 (36.7)	10 (33.3)	10 (33.3)	10 (33.3)	11 (36.7)						
								Totals	24	3	1	4	6	
								Deaths after conversion	0					
								Total Deaths	24					

NA= Not Applicable.

[a] Visit intervals took into account the follow-up visit windows. The visit windows were ±2 weeks for 30 days, ±4 weeks for 6 months and 1 year, and ±8 weeks for 2 to 5 years. 1 year visit window is 337 - 393

[b] Eligible for follow-up if subject reached the start of the visit window and was not a technical failure, was not lost to follow-up, did not die, did not withdraw early, or did not convert to open repair. Eligible for follow-up included any subject who reached the start of the visit window, but who had not reached the end of the visit window.

[c] Percentages are calculated based on the number of subjects eligible for follow-up. Data for visit information is site-reported. CT scan and x-ray reflect images received for evaluation by the core laboratory.

[d] Size increase, endoleak, and migration were assessed by CT Scan (core lab-reported data).

[e] Fracture was assessed by x-ray (core lab-reported data).

[f] Subjects for whom the procedure was attempted but aborted and who did not receive a Relay® Stent-Graft at a later additional procedure.

[g] Not due for next visit if subject had not reached the start of the visit window. Subjects who died, had a technical failure, converted to open repair, were lost to follow-up, withdrew early, or were not due for a previous visit are not counted.

[h] Considers information examined as part of application review.

Table 10-30: Major Adverse Events Beyond 1 Year – CEC-Adjudicated

Event	2-year (Day 674-1038)	3-year (Day 1039 – 1403)
Mortality (all causes)	1/40 (2.5%)	0/15
One or more MAE	2/40 (5.0%)	1/15 (6.7%)
– Stroke	2/40 (5.0%)	1/15 (6.7%)
– Paralysis/paraplegia	0/40	0/15
– Myocardial infarction	0/40	0/15
– Procedural bleeding	0/40	0/15
– Respiratory failure	0/40	0/15
– Renal failure	0/40	0/15
– Wound healing complications	0/40	0/15
– Aneurysm-related mortality	0/40	0/15

NA = Not applicable

Notes: The Safety sample includes All Enrolled subjects who underwent implantation of the Relay® device or surgical repair. Mortality and major adverse events were adjudicated by the CEC. At each level of summarization, a subject is counted once if the subject reported 1 or more events. Percentages are based on the number of subjects in the Safety sample who have sufficient follow-up. A subject has sufficient follow-up if the date of last follow-up minus procedure date is greater than or equal to the start of the time period. Percentages for the overall time period are based on all subjects in the Safety sample. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a second procedure, the time periods are based on the initial procedure date if the adverse event occurred before the second procedure date; otherwise, time periods are based on the second procedure date. In the event that the CEC determines an event can never be adjudicated, it is assumed that the site investigator's report is accurate and it is used in place of adjudication.

Table 10-31: Major Device-Related Events Beyond 1 Year – Core Lab and Site-Reported

Event	2-Year Visit		3-Year Visit	
	Core Lab-Reported	Site-Reported	Core Lab-Reported	Site-Reported
Any endoleak	1/32 (3.1%)	0/40	1/10 (10.0%)	0/15
– Type I	0/32	0/40	1/10 (10.0%)	0/15
– Type III	1/32 (3.1%)	0/40	0/10	0/15
– Type IV	0/32	0/40	0/10	0/15
Stent migration	2/33 (6.1%)	0/40	1/10 (10.0%)	0/15
Lumen Occlusion	0/32	0/40	0/10	
Aneurysm Rupture	NA	0/40	NA	0/15
Deployment Failure/Conversion to Surgery	NA	0/40	NA	0/15
Lesion Size Increase	1/32 (3.1%)	2/32 (6.3%)	1/10 (10%)	1/12 (8.3%)
Fracture	1/33 (3.0%)	0/40	1/11 (9.1%)	0/15

NA = Not applicable

Notes: The Effectiveness sample includes All Enrolled subjects who underwent implantation of the Relay® device. Major device-related adverse events were reported by Core Laboratory. Site-reported events were adjudicated by the CEC. At each level of summarization, a subject was counted once if the subject reported 1 or more events. Percentages are based on the number of subjects in the Effectiveness sample who have sufficient follow-up. A subject has sufficient follow-up if the date of last follow-up minus the procedure date is greater than or equal to the start of the time period. Percentages for the Overall time period are based on all subjects in the Effectiveness sample. Sufficient follow-up is calculated separately for site-reported and Core Laboratory data. Sufficient follow-up for Core Laboratory data is based only on follow-up computed tomography (CT) scans or x-ray. If the initial procedure resulted in an implant failure of the Relay® Stent-Graft and a Relay® Stent-Graft was implanted during a second procedure, the time periods are based on the initial procedure date if the adverse event occurred before the second procedure date; otherwise, time periods are based on the second procedure date.

B. Relay® Phase I Feasibility

Bolton Medical, Inc. conducted a 30-subject Relay® Phase I study using the Relay® stent-graft. The goal of the Phase I study was to evaluate the safety and preliminary performance of the Relay® Thoracic Stent-Graft in subjects with thoracic aortic pathologies.

1. Subject Population and Subject Accountability

The inclusion / exclusion criteria in the Relay® Phase I study protocol required subjects to have diagnosed thoracic aortic aneurysm (TAA) or penetrating atherosclerotic ulcer. Eligible subjects had to be 18 years of age or older. Additionally, subjects had to be considered intermediate risk for traditional thoracic aortic surgery. The Phase I study started in 2005. The population was 60% male (18/30) with an average age of 72.6 years.

At 1 year post-implant, data on 24 subjects were available, and there were 6 subjects who achieved 5-year follow-up. Imaging was submitted to the core laboratory for review and archiving, but only site-reported data was required for analysis. **Table 10-32** presents the imaging and follow-up compliance as determined by the core laboratory.

Table 10-32: Relay® Phase I Imaging and Follow-up Compliance (Core Laboratory-reported)

		# (%)			Adequate imaging to assess the parameter # (%)[A]				Events occurring before next interval # (%)			
Visit	Eligible for follow-up	Subjects with data for that visit	CT	X-ray	Size Increase	Endoleak	Migration	Fracture	Death	Con-version	LTF/wit hdrawal	Not due for next visit
Operative	30	30 (100%)	NA	NA	NA	NA	NA	NA				
Events between operative and 1 month visit									2 (6.7%)	0	0	0
30 day	28	28 (100%)	18 (64.3%)	14 (50%)	NA	18 (64.3%)	18 (64.3%)	14 (50%)				
Events between 1-month and 6- month visit									0	0	2 (7.1%)	0
6 month	26	26 (100%)	9 (34.6%)	17 (42.3%)	6 (23.1%)	8 (30.7%)	6 (23.1%)	10 (38.4%)				
Events between 6-month and 1-year visit									0	0	1 (3.8%)	0
1 year	25	24 (88.9%)	15 (60%)	13 (52%)	10 (40%)	14 (56%)	10 (40%)	11 (44%)				
Events between 1-year and 2-year visit									3 (12%)	0	4 (16%)	0
2 years	18	16 (88.9%)	14 (77.8%)	12 (66.7%)	11 (61.1%)	13 (72.2%)	12 (66.7%)	11 (61.1%)				
Events between 2-year and 3-year visit									2 (11.1%)	1 (5.6%)	3 (16.7%)	0
3 Years	12	12 (92.3%)	9 (75%)	8 (66.7%)	8 (66.7%)	8 (66.7%)	8 (66.7%)	8 (66.7%)				
Events between 3-year and 4-year visit									1 (8.3%)	0	4 (3.3%)	0
4 years	7	6 (85.7%)	6 (85.7%)	6 (85.7%)	6 (85.7%)	6 (85.7%)	6 (85.7%)	6 (85.7%)				
Events between 4-year and 5-year visit									0	0	0	1 (14.2%)
5 years	6	6 (100%)	5 (83.3%)	5 (83.3%)	5 (83.3%)	5 (83.3%)	5 (83.3%)	5 (83.3%)				
								Totals	8	1	14	

2. Safety Evaluation

Safety was assessed by measurement of mortality and major morbidity. Major morbidity included the the events listed in **Table 10-33**, rated as serious by the physician.

Table 10-33: Relay® Phase I Mortality and Major Morbidity

	≤ 30 days Post-procedure (N = 30)	> 30 days post-procedure (N = 28)	Overall (N = 30)
Mortality	2 (6.7%)	6 (20.0%)	8 (27.0%)
Any Major Morbidity:	5 (16.7%)	1 (3.6%)	6 (20%)
Cardiac Complications	2 (6.7%)		2 (6.7%)
Congestive Heart Failure	1 (3.3%)	0	1 (3.3%)
Myocardial Infarction	1 (3.3%)		1 (3.3%)
Atrial Fibrillation	1 (3.3%)		1 (3.3%)
Pulmonary	2 (6.7%)		2 (6.7%)
Pneumonia	1 (3.3%)	0	1 (3.3%)
Respiratory Failure	1 (3.3%)		1 (3.3%)
Renal Failure	1 (3.3%)	0	1 (3.3%)
Neurological Complications	1 (3.3%)		1 (3.3%)
Paraplegia	1 (3.3%)	0	1 (3.3%)
Stroke (CVA)	1 (3.3%)		1 (3.3%)
Post-Procedure Bleeding	2 (6.7%)	0	2 (6.7%)
Procedural Bleeding	2 (6.7%)		2 (6.7%)
Other Serious Complications	2 (6.7%)	0	2 (6.7%)
Coagulopathy	1 (3.3%)		1 (3.3%)
Iliac Artery Injury	1 (3.3%)		1 (3.3%)
Conversion to Surgical Repair	0	1 (3.6%)	1 (3.3%)
Lesion Rupture	0	0	0

3. Performance Evaluation

Performance of the device was evaluated on the basis of the following:

a) Delivery/Deployment: Vessel access was achieved and the physician was able to insert the delivery catheter and deliver it to the treatment site and deploy the device.

b) Stent-Graft Migration: Longitudinal movement of all or part of the stent-graft greater than 10mm relative to its placement as measured by imaging studies at the 1-month follow-up versus the 6-month and 12-month follow-ups.

c) Stent-Graft Patency: The measure of blood flow through the vessel treated and the stent-graft.

d) Stent-Graft Integrity: The assessment of stent-graft fractures, kinking, or twisting.

e) Endoleak: Persistence of flow outside the lumen of the stent-graft but within the native aorta or adjacent vascular segment being treated by the stent-graft.

f) Lesion Size Changes: The change in the diameter (10mm change) of the lesion relative to the measurement at 1 month versus 6-months and 12-months follow-up visit measurements.

The Relay® device was successfully delivered in all 30 subjects. Table 10-34 shows the summary of the major device-related adverse events reported for this cohort through 5 years follow-up.

Table 10-34 Relay® Phase I Major Device-Related Events at 1 Year through 5 Years

Event	1-Month Visit		6-Month Visit		1-Year Visit		2-Year Visit		3-Year Visit		4-Year Visit		5-Year Visit	
	Core Lab	Site	Core Lab	Site	Core Lab	Site	Core Lab	Site	Core Lab	Site	Core Lab	Site	Core Lab	Site
Any endoleak	0/18	1/28 (3.6%)	1/8 (12.5%)	1/26 (3.8%)	0/14	1/24 (4.2%)	3/13 (23.1%)	1/18 (5.6%)	0/8	0/12	0/6	0/6	0/5	0/6
– Type I	0/18	1/28 (3.6%)	1/8 (12.5%)	1/26 (3.8%)	0/14	1/24 (4.2%)	3/13 (23.1%)	1/18 (5.6%)	0/8	0/12	0/6	0/6	0/5	0/6
– Type III	0/18	0/28	0/8	0/26	0/14	0/24	0/13	0/18	0/8	0/12	0/6	0/6	0/5	0/6
– Type IV	0/18	0/28	0/8	0/26	0/14	0/24	0/13	0/18	0/8	0/12	0/6	0/6	0/5	0/6
Stent migration	NA	NA	0/6	0/26	1/10 (10%)	0/24	3/12 (25%)	1/18 (5.6%)	1/8 (12.5%)	0/12	1/6 (16.7%)	0/6	1/5 (20%)	0/6
Lesion Size Increase*	NA	NA	1/6 (16.7%)	0/26	0/10	1/24 (4.2%)	1/11 (9.1%)	2/18 (11.1%)	0/8	0/12	0/6	0/6	0/5	0/6
Fracture	0/14	0/28	0/10	0/26	0/10	0/24	0/11	0/18	0/8	0/12	0/6	0/6	0/5	0/6
Lumen Occlusion	0/18	0/28	0/9	0/26	0/14	0/24	0/14	0/18	0/8	0/12	0/6	0/6	0/5	0/6
Aneurysm Rupture	NA	0/28	NA	0/26	NA	0/24	NA	0/18	NA	0/12	NA	0/6	NA	0/6
Deployment Failure / Conversion to Surgery	NA	0/28	NA	0/26	NA	0/24	NA	1/18 (5.6%)	NA	0/12	NA	0/6	NA	0/6

*Lesion size increases are typically determined using the 1 Month imaging as baseline. If 1 month imaging was not provided or not interpretable by the core laboratory, the earliest available and interpretable imaging was used as baseline.

NA = Not applicable

C. Continued Access Study

Bolton Medical initiated a continued access arm to the Relay® study in order to gain additional information on the device as premarket approval was being secured. Enrollment in this study started once all 120 endovascular subjects of the Relay® Phase II study had been enrolled.

1. Subject Population and Subject Accountability

The same study protocol used for Relay® Phase II was used for continued access. Therefore, inclusion and exclusion criteria are identical. Additionally, the same device design used in Relay® Phase II was used in continued access.

Table 10-36 includes the follow-up and imaging compliance for the continued access subjects.

2. Study Follow-up Data

Table 10-35 below summarizes the results collected at the site-level as well as from the core laboratory for the 12 subjects for which data have been collected.

Table 10-35: Relay® Continued Access Study Summary of Results

	1-month Visit		6-month Visit		1-Year Visit	
	Core Lab-Reported	Site-Reported	Core Lab-Reported	Site-Reported	Core Lab-Reported	Site-Reported
Device-related endoleak	0/11	0/11	0/6	0/6	0/2	0/2
– Type I	0/11	0/11	0/6	0/6	0/2	0/2
– Type III	0/11	0/11	0/6	0/6	0/2	0/2
– Type IV	0/11	0/11	0/6	0/6	0/2	0/2
Stent migration	NA	NA	0/7	0/8	0/3	0/3
Lesion Size Increase	NA	NA	0/8	0/8	0/3	1/3
Fracture	0/11	0/12	0/8	0/8	0/3	0/3
Lumen Occlusion	0/11	0/11	0/6	0/8	0/2	0/3
Aneurysm Rupture	NA	0/12	NA	0/8	NA	0/3
Deployment Failure/Conversion to Surgery	NA	0/12	NA	0/8	NA	0/3

NA= Not Applicable (1 month imaging is typically used as baseline); NR= Not Reviewed; NI= Not Interpretable

Table 10-36 Compliance Imaging and Follow-up for Continued Access Study (Core Laboratory-Reported)

Visit Interval[a]	Eligible for Follow-Up[b]	Subjects with n (%)[C]			Adequate Imaging to Assess Parameter (Core Lab)[c] n (%)				Events Occurring Before Next Interval[c] n (%)					
		Data for Visit (Site)	CT Scan (Core Lab)	X-Ray (Core Lab)	Size[d]	Endoleak[d]	Migration[d]	Fracture[e]	Death	Technical Failure[f]	Con-version	Lost to Follow-Up	Withdrawn Early	Not Due for Next Visit[g]
Operative	12	12 (100%)	NA	NA	NA	NA	NA	NA						
Events between operative and 1 month visit									0	0	0	0	0	0
30 Day	12	12 (100%)	11 (91.7%)	11 (91.7%)	NA	11 (91.7%)	NA	11 (91.7%)						
Events between 1-month and 6-month visit									2 (16.7%)	0	0	0	0	2 (16.7%)
6 Month	8	8 (100%)	8 (100%)	8 (100%)	8 (100%)	6 (75%)	7 (87.5%)	8 (100%)						
Events between 6-month and 1-year visit									0	0	0	0	0	5 (62.5%)
1 Year	3	3 (100%)	3 (100%)	3 (100%)	3 (100%)	2 (66.7%)	3 (100%)	3 (100%)						
								Totals	2	0	0	0	0	

NA= Not Applicable.

a Visit Interval: Operative = Date of Procedure to Day 15, 30 Day = Day 16 to Day 151, 6 Month = Day 152 to Day 336, 1 Year = Day 337 to Day 673, 2 Year = Day 674 to Day 1038, 3 Year = Day 1039 to Day 1403, 4 Year = Day 1404 to Day 1768, 5 Year = Day 1769 to Day 1881. The intervals took into account the follow-up visit windows. The visit windows were ±2 weeks for 30 days, ±4 weeks for 6 months and 1 year, and ±8 weeks for 2 to 5 years.

b Eligible for follow-up if subject reached the start of the visit window and was not lost to follow-up, was not a technical failure, did not withdraw, did not die, or did not convert to open repair. Eligible for follow-up included any subject who reached the start of the visit window, but who had not reached the end of the visit window.

c Percentages are calculated based on the number of subjects eligible for follow-up. Data for visit information is site-reported. CT scan and x-ray reflect images received for evaluation by the core laboratory.

d Size increase, endoleak, and migration were assessed by CT Scan (core laboratory-reported data).

e Fracture was assessed by x-ray (core lab-reported data).

f Subjects for whom the procedure was attempted but aborted and who did not receive a Relay® Stent-Graft at a later additional procedure.

g Not due for next visit if subject had not reached the start of the visit window. Subjects who died, were technical failures, converted to open repair, were lost to follow-up, withdrawn early, or were not due for a previous visit are not counted.

D. OUS Registry (RESTORE)

Bolton Medical supported a multi-center registry study in Europe, RESTORE. The registry enrolled 304 subjects between April 2005 and January 2009, overlapping the course of the Phase II study. The Relay® Thoracic Stent-Graft with original Transport Delivery System was used in this registry. The RESTORE registry included mostly subjects with thoracic aneurysms (52.9%), but subjects with other conditions were also permitted. Nonsurgical candidates were considered eligible for the RESTORE Registry. The subjects in the RESTORE registry were mostly male and were younger on average than those in the Relay Phase II (64.3 years vs. 72.8 years). The information provided regarding this registry did not contradict the results presented for the U.S. studies.

XII. PANEL MEETING RECOMMENDATIONS AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. OVERALL CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness data from the Relay® Phase II study showed that the lower limit of the 1-sided 97.5% confidence interval was greater than 0.90, thus meeting the performance goal of greater than 0.80 and providing evidence of the effectiveness of the Relay® Thoracic Stent-Graft.

B. Safety Conclusions

The primary safety data from the Relay® Phase II study showed that the distribution of subjects experiencing at least 1 major adverse event within 1 year post-procedure was statistically significantly greater in the surgical repair cohort than in the Relay® Stent-Graft cohort, thus providing evidence of the superiority of the Relay® treatment.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in a pivotal clinical study conducted to support PMA approval along with supplementary data, as described above. The probable benefit of the Relay® Thoracic Stent-Graft with the Plus Delivery System is improving outcomes in patients with thoracic aortic aneurysms or penetrating atherosclerotic ulcers, as compared to open surgical repair.

The pivotal study that provided the primary clinical safety and effectiveness evidence was a multi-center, controlled study conducted in the United States. Important clinical outcomes, such as aneurysm-related mortality, aneurysm rupture, and endoleaks, occurred at a low frequency. While complete effectiveness follow-up data were not

available for many subjects, additional statistical analyses and supportive clinical information were used to determine that the one-year effectiveness of the device was satisfactory. There are no reasons to expect that the results of the study will differ from "real world" performance.

Alternative treatments, including the use of other endovascular grafts, open surgical repair, and medical management, were carefully considered. Endovascular repair is often highly valued by patients because it is less invasive than open surgical repair. The results of the pivotal study indicate that the study subject outcomes compare favorably to surgical outcomes. In addition, the risks and benefits of the Relay® Thoracic Stent-Graft with the Plus Delivery System were found to be similar to the risks and benefits of other approved endovascular grafts. Patient risk is minimized by limiting use of the device in patients suitable for endovascular repair and to operators who have the necessary training to use the device safely and effectively.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks when the Relay® Thoracic Stent-Graft with the Plus Delivery System is used to treat fusiform and saccular aneurysms and penetrating atherosclerotic ulcers of the thoracic aorta, and the device provides an additional treatment option for these patients.

D. Overall Conclusions

The data presented constitute valid scientific evidence and provide a reasonable assurance of safety and effectiveness for the Relay® Thoracic Stent-Graft with the Plus Delivery System in the treatment of subjects with fusiform aneurysms and saccular aneurysms/penetrating ulcers of the descending thoracic aorta who are candidates for endovascular repair.

XIV. CDRH DECISION

CDRH issued an approval order on September 21, 2012. The final conditions of approval cited in the approval order are described below.

The sponsor has agreed to provide a clinical update to physician users at least annually as part of the Annual Report to their PMA application. At a minimum, this update will include, for the post-approval study cohort, a summary of the number of patients for whom data are available, with the rates of aneurysm rupture, secondary endovascular procedures, conversion to surgical repair, aneurysm-related mortality, major adverse events, endoleak, aneurysm enlargement, prosthesis migration, and patency. Reports of losses of device integrity, reasons for conversion and causes of aneurysm-related death and rupture are to be described. A summary of any explant analysis findings are to be included. Additional relevant information from commercial experience within and outside of the US is also to be included.

In addition to this Annual Report requirement, the sponsor has agreed to conduct a post-approval study (PAS) to evaluate safety and effectiveness of the Relay® Thoracic Stent-

Graft with Plus Delivery System for the treatment of descending thoracic aortic aneurysms and penetrating aortic ulcers through five years of implantation.

The PAS study will include the 120 Relay Phase II subjects; 13 Relay Continued Access Subjects; and 100 subjects treated post-approval at new centers. Patients are to be followed at 1 month, 12 months and annually thereafter out to 5 years. At each annual visit, a CT scan with and without contrast, and a physical examination have been or will be conducted. All data will be entered into a database, analyzed, and submitted in post-approval reports to the FDA, and a final report will be submitted after completion of the follow-up and analysis. This follow-up plan will allow an evaluation of aneurysm-related mortality, major adverse events, migration, patency, endoleaks, device integrity, aneurysm enlargement, aneurysm rupture, secondary endovascular procedures and conversion to open surgical repair over time.

The primary endpoint for the PAS is freedom from aneurysm-related mortality at *5* years. Aneurysm-related mortality is defined as:

> Death from rupture of the descending thoracic aortic aneurysm (DTAA) or penetrating aortic ulcer (PAU), or from any procedure intended to treat the DTAA or PAU. If a death occurred within 30 days of any procedure intended to treat the DTAA or PAU, or within the hospital stay if the patient was not discharged within 30 days, then it is presumed to be aneurysm-related.

The results from this study will be included in the labeling upon completion of the PAS. The updated labeling will be submitted to FDA in the form of a PMA Supplement.

The sponsor is required to submit PAS Progress Reports every six months during the first two years of the study and annually thereafter.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.