Summary of Safety and Effectiveness Data

1.0 General Information

Device Generic Name:

Endovascular graft

Device Trade Name:

Valiant® Thoracic Stent Graft with the Captivia Delivery System

Applicant's Name and Address:

Medtronic Vascular
3576 Unocal Place
Santa Rosa, CA 95403
USA

Premarket Approval Application (PMA) Number:

P100040

Date of Panel Recommendation:

None

Date of Notice of Approval to the Applicant:

April 1, 2011

2.0 Indications for Use

The Valiant® Thoracic Stent Graft with the Captivia Delivery System is intended for the endovascular repair of fusiform aneurysms and saccular aneurysms/penetrating ulcers of the descending thoracic aorta in patients having appropriate anatomy, including:

- iliac/femoral access vessel morphology that is compatible with vascular access techniques, devices, and/or accessories;
- non-aneurysmal aortic diameter in the range of 18–42 mm; and
- non-aneurysmal aortic proximal and distal neck lengths $\geq$ 20 mm.

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3.0 Contraindications

The Valiant Thoracic Stent Graft with the Captivia 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 allergies to, the device materials.

4.0 Warnings and Precautions

The warnings and precautions can be found in the Instructions for Use for the Valiant Thoracic Stent Graft with the Captivia Delivery System.

5.0 Device Description

5.1 Valiant Thoracic Stent Graft with the Captivia Delivery System

The Valiant Thoracic Stent Graft with the Captivia Delivery System is comprised of two components:

- Valiant Thoracic Stent Graft
- Captivia Delivery System

The Valiant 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 Captivia Delivery System. The stent graft is constrained by the delivery system outer sheath (graft cover) until deployed at the intended site of treatment. The pre-loaded stent graft 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.

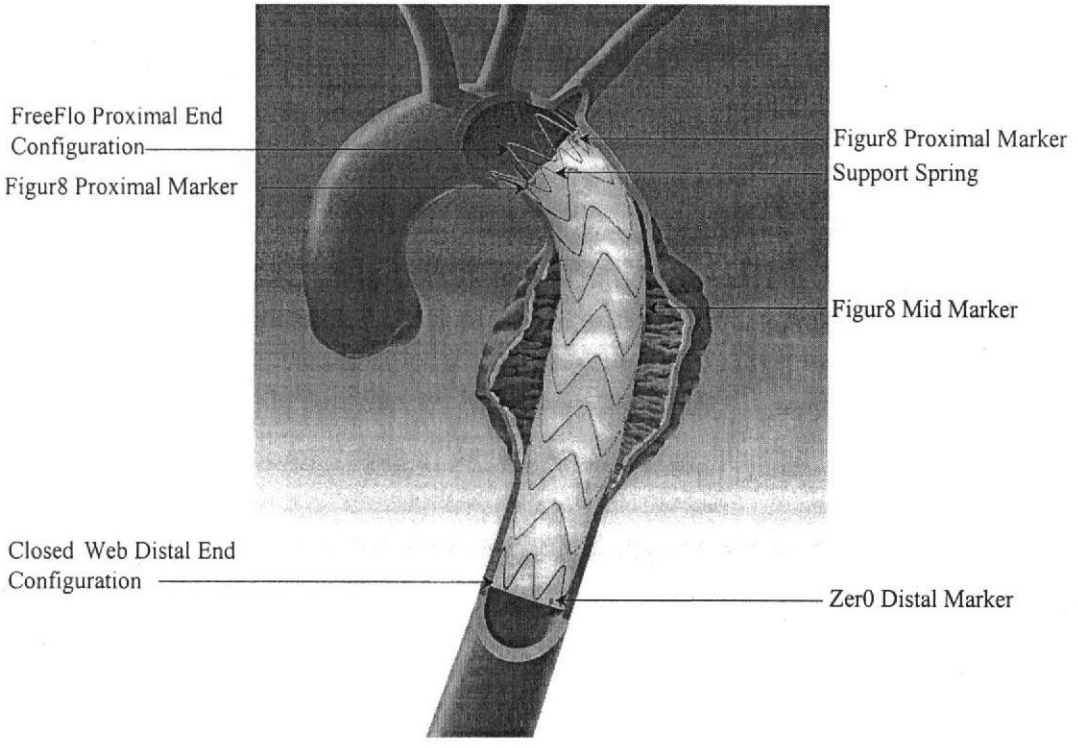
5.1.1 Valiant Thoracic Stent Graft

The Valiant Thoracic Stent Graft is a self-expanding, tubular endoprosthesis composed of a polyester graft fabric and a spring scaffold made from nitinol wire. The metal scaffolding is composed of a series of serpentine springs stacked in a tubular configuration. The springs are sewn onto a polyester fabric with non-absorbable sutures.

Platinum-iridium radiopaque markers are sewn to the fabric to facilitate radiographic visualization of the graft material edge and the minimum overlap required when multiple stent grafts are used. The four proximal **Figur8** markers, (shaped as a figure 8), and the two distal **Zer0** markers, (shaped as a zero), indicate the extremities of the covered stent graft. The single **Figur8** "mid-marker" indicates the minimum amount of overlap required for multiple components.

During manufacturing, the Valiant Thoracic Stent Graft is pre-loaded into a delivery system. See **Figure 5-1** for a drawing of the Valiant Thoracic Stent Graft.

Figure 5-1: The Valiant Thoracic Stent Graft



5.1.1.1 Valiant Thoracic Stent Graft Configuration and Placement

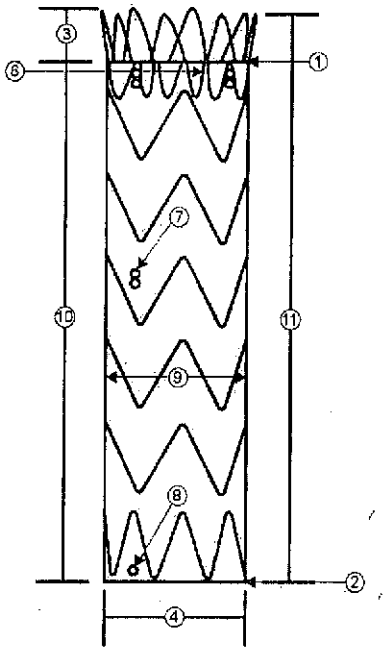
The Valiant Thoracic Stent Graft is a modular device that accommodates the use of additional stent graft sections depending on the configuration of the anatomy where single or multiple components may be required to achieve sufficient coverage of the diseased aorta.

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.

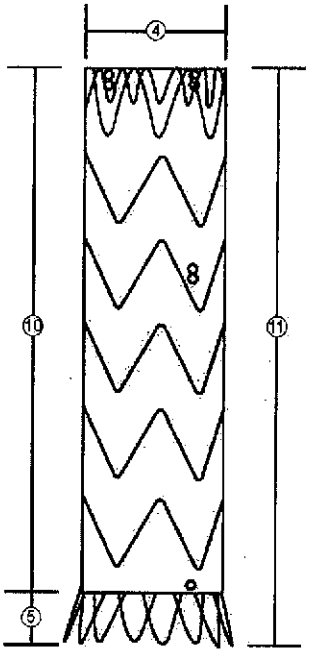
If the vessel diameter and condition require the same proximal and distal diameter devices, the primary section should be placed first at the proximal end of the lesion. To achieve the same final diameter with the proximal and distal sections, a tapered configuration is required for the distal section. The flare of the tapered graft permits the oversizing requirements between components.

Different end configurations are available to further accommodate anatomical dimensions. The proximal end comes in two configurations: FreeFlo or Closed Web (**Figure 5-2**). Devices with a FreeFlo proximal end configuration have a bare spring extending beyond the edge of the fabric at the proximal end of the stent graft and should be implanted in the most proximal position only. The Closed Web proximal end configuration, which has a covered spring at the proximal end of the stent graft, is implanted distally. The distal end configurations of the stent grafts are Closed Web or Bare Spring. The Closed Web distal end configuration has a covered spring at the distal end of the stent graft. The Bare Spring distal end configuration has a bare spring at the distal end of the stent graft that extends beyond the edge of the fabric.

Figure 5-2: Valiant Thoracic Stent Graft End Configurations

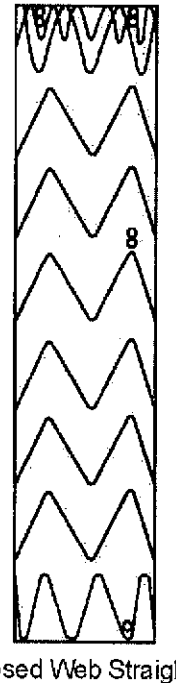


FreeFlo Straight
(Proximal Component)

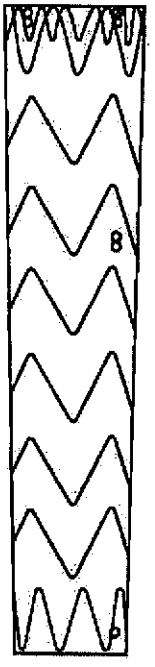


Distal Bare Spring
Straight (Distal Component)

1. Proximal End
2. Distal End
3. FreeFlo
4. Closed Web
5. Bare Spring
6. Mini Support Spring
7. Figure8 Marker
8. Zer0 Marker
9. Diameter
10. Covered Length
11. Total Length



Closed Web Straight
(Distal Component)



Closed Web Taper
(Distal Component)

NOTE: This and all other product graphics appearing in this summary are not drawn to scale, are for graphical representation only, and may appear differently under fluoroscopy.

5.1.2 Captivia Delivery System

The Captivia Delivery System is available in an outer diameter of 22, 24 and 25 French and consists of a single use, disposable catheter with an integrated handle to provide the user with controlled deployment. The working length of the Captivia Delivery System is 83 cm +/- 2 cm. The Captivia Delivery System (**Figure 5-3**) is the generic name for the following two delivery system configurations:

- The FreeFlo Stent Graft Delivery System (Tip Capture)
- The Closed Web Stent Graft Delivery System (non-Tip Capture)

5.1.2.1 The FreeFlo Stent Graft Delivery System

The FreeFlo Stent Graft Delivery System is used with the FreeFlo Straight configuration, the stent graft configuration that is implanted in the most proximal position. The delivery system features a tip capture mechanism from which the proximal stent graft is deployed in two stages:

(1) Deployment of the stent graft with the apices of the bare stent of the FreeFlo configuration still constrained by the tip capture mechanism; and

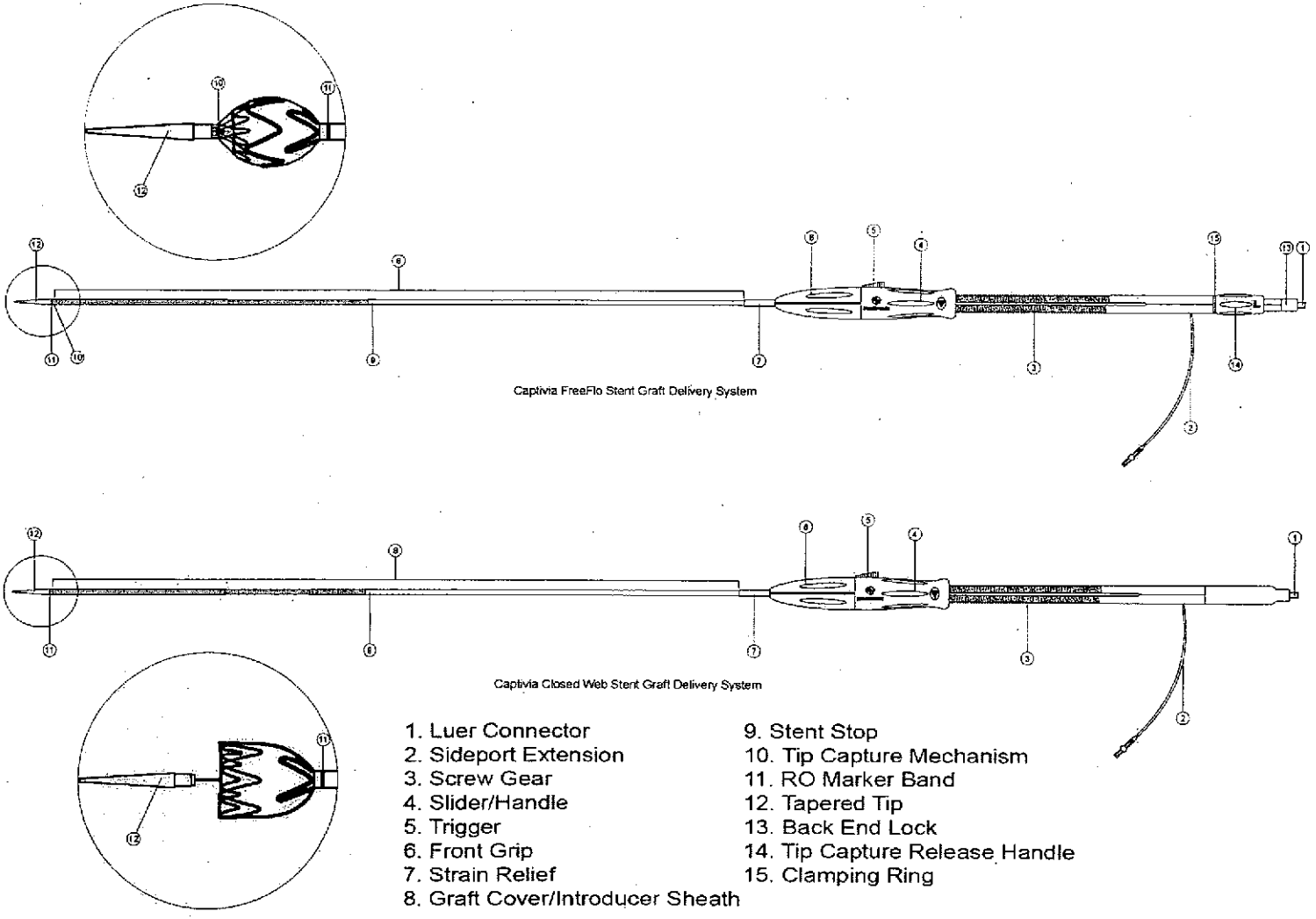
(2) Release of the proximal bare spring portion of the stent graft.

5.1.2.2 Closed Web Stent Graft Delivery System

The Closed Web Stent Graft Delivery System is used with the Closed Web Straight, Distal Bare Spring Straight, and Closed Web Tapered configuration stent grafts. Because these devices do not have a bare spring configuration at the proximal end of the stent graft, the Closed Web Delivery System does not include a tip capture mechanism. As a result, deployment using the Closed Web Delivery System is accomplished in a single step when the outer sheath is removed from the stent graft.

Figure 5-3: Captivia Delivery System

(The FreeFlo Stent Graft Delivery System on Top, Closed Web Stent Graft Delivery System on Bottom)



1. Luer Connector
2. Sideport Extension
3. Screw Gear
4. Slider/Handle
5. Trigger
6. Front Grip
7. Strain Relief
8. Graft Cover/Introducer Sheath
9. Stent Stop
10. Tip Capture Mechanism
11. RO Marker Band
12. Tapered Tip
13. Back End Lock
14. Tip Capture Release Handle
15. Clamping Ring

6.0 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.

7.0 Marketing History

The Valiant Thoracic Stent Graft with the Captivia Delivery System has been commercially available for distribution outside of the United States since September 2009.

The Valiant Thoracic Stent Graft with the Captivia Delivery System has not been withdrawn from the market for any reasons related to safety or effectiveness.

8.0 Potential Adverse Effects of the Device on Health

Adverse events or complications associated with the use of the Valiant Thoracic Stent Graft with the Captivia 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	• Endoleaks	• Procedural bleeding
• Adynamic Ileus	• Excessive or inappropriate radiation exposure	• Prosthesis dilatation
• Allergic reaction (to contrast, anti-platelet therapy, stent graft material)	• Extrusion/erosion	• Prosthesis infection
• Amputation	• Failure to deliver the stent graft	• Prosthesis rupture
• Anesthetic complications	• Femoral neuropathy	• Prosthesis thrombosis
• Aneurysm expansion	• Fistula (including aortoenteric, arteriovenous, and lymph)	• Pseudoaneurysm
• Aneurysm rupture	• Gastrointestinal bleeding/complications	• Pulmonary edema
• Angina	• Genitourinary complications	• Pulmonary embolism
• Arrhythmia	• Hematoma	• Reaction to anaesthesia
• Arterial stenosis	• Hemorrhage/bleeding	• Renal failure
• Atelectasis	• Hypotension/hypertension	• Renal insufficiency
• Blindness	• Infection or fever	• Reoperation
• Bowel ischemia	• Insertion or removal difficulty	• Respiratory depression or failure
• Bowel necrosis	• Intercostal pain	• Sepsis
• Bowel obstruction	• Intramural hematoma	• Seroma
• Branch vessel occlusion	• Leg edema/foot edema	• Shock
• Breakage of the metal portion of the device	• Lymphocele	• Spinal neurological deficit
• Buttock claudication	• Myocardial infarction	• Stent graft migration
• Cardiac tamponade	• Neuropathy	• Stent graft misplacement
• Catheter breakage	• Occlusion – Venous or Arterial	• Stent graft occlusion
• Cerebrovascular accident (CVA)/Stroke	• Pain/Reaction at catheter insertion site	• Stent graft twisting or kinking
• Change in mental status	• Paralysis	• Transient ischemic attack (TIA)
• Coagulopathy	• Paraparesis	• Thrombosis
• Congestive heart failure	• Paraplegia	• Tissue necrosis
• Contrast toxicity	• Paresthesia	
• Conversion to surgical repair	• Peripheral ischemia	• Vascular ischemia
• Death	• Peripheral nerve injury	• Vascular trauma
• Deployment difficulties/ failures	• Pneumonia	• Wound dehiscence
• Dissection, perforation, or rupture of the aortic vessel & surrounding vasculature	• Post-implant syndrome	• Wound healing complications
• Embolism	• Post-procedural bleeding	• Wound infection

9.0 Summary of Preclinical Studies

9.1 Biocompatibility

Biocompatibility testing was conducted on materials that comprise the Valiant Thoracic Stent Graft and Captivia Delivery System in accordance with Good Laboratory Practices (21 CFR § 58), and in accordance with ISO 10993-1, and Jimurenraku No. 36 (Japan-specific biocompatibility tests as specified by Japan's Ministry of Health, Labour, and Welfare (MHLW)).

Biocompatibility studies for the Valiant 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 Captivia Delivery System were based on the principles of an externally communicating device with limited contact with circulating blood (<24 hr). Medtronic utilizes two separate suppliers (Supplier 1 and Supplier 2) for the Valiant Thoracic Stent Graft, both of which met the requirements as specified within the applicable standard.

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

Table 9-1: Summary of Biocompatibility Testing of Valiant Thoracic Stent Graft

Test Description	Purpose	Results* (Medtronic Supplier 1)	Results* (Medtronic Supplier 2)	Results Acceptable (Y/N)
Cytotoxicity, Colony Assay - MHLW	To evaluate the toxicity of the test article when exposed to Chinese Hamster Lung (V79) cells by determining the potential of the test article to inhibit colony formation in V79 cells.	The test article was not cytotoxic. There was no IC_{50} value for the test extract since toxicity was not observed.	The test article was not cytotoxic. There was no IC_{50} value for the test extract since toxicity was not observed.	Y
Material Mediated Pyrogen Study - USP	To evaluate the test article for the potential of inducing a pyrogenic response in rabbits.	All animals <0.5°C increase	All animals <0.5°C increase	Y
Bacterial Reverse Mutation - ISO	To evaluate whether the test article extract would cause mutagenic changes in the average number of revertants for Salmonella typhimurium tester strains TA98, TA100, TA1535, and TA1537, and Escherichia coli tester strain WP2uvrA in the presence and absence of S9 metabolic activation.	In no case was there a 2-fold or greater increase in the mean number of revertants of tester strains TA98, TA100, TA1535, TA1537, and WP2uvrA.	In no case was there a 2-fold or greater increase in the mean number of revertants of tester strains TA98, TA100, and WP2uvrA or a 3-fold or greater increase in the number of	Y

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Test Description	Purpose	Results* (Medtronic Supplier 1)	Results* (Medtronic Supplier 2)	Results Acceptable (Y/N)
			revertants of tester strains TA1535 and TA1537.	
In vitro Chromosomal Aberration - ISO	To evaluate the potential of the test article to induce chromosome aberrations, structural or numerical, in Chinese Hamster Ovary (CHO) cells in the presence or absence of an exogenous mammalian metabolic activation system.	The test article extract was not considered genotoxic to CHO cells in the presence or absence of metabolic activation.	The test article extract was not considered genotoxic to CHO cells in the presence or absence of metabolic activation.	Y
In vivo Mouse Micronucleus - ISO	To evaluate the potential of the test article to induce damage to the chromosomes or mitotic apparatus in mouse bone marrow cells.	No statistically significant increase in the number of MN-RETs for either test extract group.	No statistically significant increase in the number of MN-RETs for either of the test extract groups.	Y
Sensitization - MHLW	To evaluate the potential for the test article to cause dermal sensitization.	1%, 10% and 100% test article extracts showed no evidence of causing sensitization. All Test Animals were graded 0.	100%, 50% and 25% test article extracts showed no evidence of causing sensitization. All Test Animals were graded 0.	Y
Intracutaneous Reactivity - ISO	To evaluate the test article for potential irritation effects as a result of an intracutaneous injection in rabbits.	Difference between test and control mean scores: Sodium Chloride: 0.0 Sesame Oil: 0.0	Difference between test and control mean scores: Sodium Chloride: 0.0 Sesame Oil: 0.0	Y
Acute Systemic Toxicity - MHLW	To evaluate the test article for the potential for toxic effects after a single-dose systemic injection into mice.	There was no mortality or evidence of systemic toxicity.	There was no mortality or evidence of systemic toxicity.	Y
In vitro Hemolysis - MHLW	To evaluate the hemolytic activity of the test article when in contact with rabbit blood.	1, 2, 4 hrs: all 0%	1, 2, 4 hrs: all 0%	Y
In vitro Hemolysis - ASTM	To determine whether the test article causes hemolysis in vitro by direct		Extraction Method Hemolytic Index = 0.2%	Y

Test Description	Purpose	Results* (Medtronic Supplier 1)	Results* (Medtronic Supplier 2)	Results Acceptable (Y/N)
	contact or extraction.		Direct Contact Method Hemolytic Index = 3.3%	
Complement Activation, C3a - ISO	To measure complement activation in human plasma as a result of exposure of the plasma to the test article.	Concentration of C3a in the test extract was not significantly higher than the activated NHS or the negative control.	Concentration of C3a in the test extract was not statistically higher than the activated NHS control or the negative control.	Y
Complement Activation, SC5b-9 - ISO	To measure complement activation in human plasma as a result of exposure of the plasma to the test article.		Concentration of SC5b-9 in the test extract was statistically higher than both the activated NHS control and the negative control. As a result, the SC5b-9 concentration of the test article was compared to historical data for the negative control and with the SC5b-9 concentration of the positive biomaterial reference control. Based on the level of activation as compared to the various controls and historical data, the test article results indicate a relatively low biological potential of activating the complement system.	Y
In vivo Thromboresistance -	To evaluate the potential of the test article to resist		Test article scored similarly as	Y

Test Description	Purpose	Results* (Medtronic Supplier 1)	Results* (Medtronic Supplier 2)	Results Acceptable (Y/N)
ISO	thrombus formation.		compared to sponsor-provided controls. Both demonstrated thromboresistance.	
4-wk Subchronic Toxicity (Subcutaneous Implantation) - ISO	To determine the systemic toxicity potential of the test article following subcutaneous implantation in rats for 4 weeks.	There was no evidence of systemic toxicity from the test article. Local macroscopic tissue reaction was not significant as compared to the negative control. Microscopically, the test article was considered a slight irritant. Based on the nature and shape of the test article implanted, it appeared that the local reaction noted and associated clinical pathology changes were due to skin penetration and not something inherently irritating or toxic associated with the test article.	There was no evidence of systemic toxicity from the test article. Local macroscopic tissue reaction was not significant as compared to the negative control. Microscopic evaluation indicated the test article as a non-irritant.	Y
12-wk Muscle Implantation - ISO	To evaluate the potential of the test article to induce local toxic effects after implantation in the muscle tissue of rabbits for 12 weeks.	Macroscopic reaction was not significant compared to the negative control. Microscopically, test article was	Macroscopic reaction was not significant compared to the negative control. Microscopically, test article was	Y

Test Description	Purpose	Results* (Medtronic Supplier 1)	Results* (Medtronic Supplier 2)	Results Acceptable (Y/N)
		classified as a non-irritant compared to the negative control.	classified as a slight irritant compared to the negative control.	

*The test lab's GLP protocol acceptance criteria changed between the time of testing at supplier 1 and supplier 2. Both studies were completed per the approved GLP protocol at the time of testing.

Table 9-2: Summary of Biocompatibility Testing of Captivia Delivery System

Test Description	Purpose	Results	Results Acceptable (Y/N)
Cytotoxicity - MHLW	To evaluate the toxicity of the test article when exposed to Chinese Hamster Lung (V79) cells by determining the potential of the test article to inhibit colony formation in V79 cells.	The test article was not cytotoxic. There was no IC_{50} value for the test extract since toxicity was not observed.	Y
Material Mediated Pyrogen Study – USP	To evaluate the test article for the potential of inducing a pyrogenic response in rabbits.	All animals <0.5°C increase.	Y
Maximization Sensitization – ISO	To evaluate the allergenic potential or sensitizing capacity of the test article upon exposure to guinea pigs.	All test and control animals were grade 0 (No visible change).	Y
Intracutaneous Reactivity – ISO	To evaluate the test article for potential irritation effects as a result of an intracutaneous injection into rabbits.	Difference between test and control mean scores: Sodium Chloride: 0.0 Sesame Oil: 0.0	Y
Acute Systemic Toxicity – MHLW	To evaluate the test article for the potential for toxic effects after a single-dose systemic injection into mice.	There was no mortality or evidence of systemic toxicity.	Y
In vitro Hemolysis - MHLW	To evaluate the hemolytic activity of the test article when in contact with rabbit blood.	1, 2, 4 hrs: all 0%	Y
Complement Activation, C3a - ISO	To measure complement activation in human plasma as a result of exposure of the plasma to the test article.	Concentration of C3a in the test extract was not statistically different than both negative control and sponsor provided control at all three time points.	Y
Complement Activation, SC5b-9 - ISO	To measure complement activation in human plasma as a result of exposure of the plasma to the test article.	Concentration of SC5b-9 in the test extract was lower than the negative control but similar to sponsor provided control at all three time points.	Y
In vivo Thromboresistance - ISO	To evaluate the potential of the test article to resist thrombus formation.	All test and sponsor provided control articles scored the same = 0 (No thrombosis).	Y

9.2 Sterilization/Packaging/Shelf Life

The Valiant Thoracic Stent Graft with the Captivia Delivery System is a single-use device that is provided sterile to the end user. The Valiant Thoracic Stent Graft with the Captivia Delivery System is sterilized using E-Beam sterilization and is validated to demonstrate a Sterility Assurance Level (SAL) of 10^{-6}.

Packaging performance and stability testing demonstrate that the packaging designs for the Valiant Thoracic Stent Graft with the Captivia Delivery System are sufficient to adequately protect the device and maintain the integrity of the Valiant Thoracic Stent Graft System package throughout its two-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 Valiant Thoracic Stent Graft with the Captivia Delivery System supports a 2-year shelf-life claim.

9.3 Laboratory Studies

Bench Testing

Medtronic conducted comprehensive preclinical, bench and analytical testing on the Valiant Thoracic Stent Graft with the Captivia Delivery System. The *in vitro* testing was intended to verify that the performance attributes of the Valiant Thoracic Stent Graft with the Captivia Delivery System are sufficient to minimize adverse events under anticipated clinical conditions. This testing included both the stent graft and the delivery system. All testing was conducted in accordance with national and international standards and guidance documents. The testing details include results from T=0 (baseline) as well as results using samples accelerated aged to 2 years (T=2). An asterisk (*) indicates testing was performed at both T=0 and T=2. Testing verified that the Valiant Thoracic Stent Graft with the Captivia Delivery System met its product performance and design specifications.

Results obtained from *in vitro* testing provided evidence supporting the safety and effectiveness of the Valiant Thoracic Stent Graft with the Captivia Delivery System.

Table 9-3: Summary of Tests Performed related to Functionality of the Valiant Thoracic Stent Graft with the Captivia Delivery System

Test	Test Purpose	Acceptance Criteria	Pass/Fail
Stent Graft Design Verification Testing			
Stent Graft Visual Expansion Integrity*	To evaluate any damage that occurs to the Valiant Thoracic Stent after deployment and demonstrate that the stent graft integrity meets the acceptance criteria.	No broken stents, minimum suture stitch density intact, support spring and RO markers attached, no graft tears, no graft holes larger than a diameter of 0.5 mm.	Pass
Stent Graft Recoil (Dimensional Verification)*	To confirm that the outer diameter of the Valiant Thoracic Stent Graft recovers within the specification after deployment, demonstrating that it meets the acceptance criteria.	The Valiant Thoracic Stent Graft must expand to a diameter that is $\geq$ 1 mm less than the labeled nominal diameter for aortic sections.	Pass

Test	Test Purpose	Acceptance Criteria	Pass/Fail
Spring Attachment Strength*	To measure the tensile strength of the attachment of the bare and body springs to the Valiant Thoracic Stent Graft and demonstrate spring attachment strength meets the acceptance criteria.	Spring Attachment Strength LTL > 32.0 lbf (142 N)	Pass
Stent Graft Burst*	To determine the burst strength of the Valiant Thoracic Stent Graft and demonstrate that it meets the acceptance criteria.	Stent Graft Burst Pressure LTL ≥ 18.8 psi (130 kPa)	Pass
Stent Graft Crimp Strength	To determine the strength of the bond between the crimp sleeve and the stent strut used on the Valiant Thoracic Stent Graft spring and demonstrate that it meets the acceptance criteria.	Ultimate Tensile Strength LTL > 6.4 lbf (28 N)	Pass
Radial Force	To determine the radial force exerted by the Valiant Thoracic Stent Graft in the proximal seal zone, distal seal zone and individual body stents and demonstrate that the stent graft radial force meets the acceptance criteria.	Radial Strength ≥ 8 mmHg (1.067 kPa)	Pass
Stent Graft Conformability	To determine the minimum radius of curvature that the stent graft can accommodate without kinking.	Valiant Stent Graft kink radius must show improved kink resistance in a simulated thoracic anatomy compared to the Talent Thoracic Stent Graft.	Pass
Stent Graft Migration	To quantify the peak migration force of the stent grafts in mock blood vessels and demonstrate that the migration force meets the acceptance criteria.	Stent Graft Migration Pressure LTL ≥ 300 mmHg (40.0 kPa)	Pass
Stent Graft Permeability	To determine the rate of water leakage through the entire stent-graft wall, or any areas where leakage is of concern, under a pressure of 120 mmHg.	Characterization Test; Samples characterized to be <700ml/min/cm².	Results Acceptable
Stent Graft Joint Strength	To evaluate the joint strength between components of Endovascular Stent Graft (ESG) Systems.	Valiant Thoracic Stent Graft joint strength ≥ Talent Thoracic Stent Graft joint strength	Pass
Simulated Use Testing	To evaluate the performance of the Valiant Thoracic Stent Graft with the Captivia Delivery System in an anatomically representative bench top model.	The Valiant Thoracic Stent Graft with the Captivia Delivery System must exhibit the ability to reach the target treatment site, deploy the stent graft, and be withdrawn from the model.	Pass
Stent Graft Corrosion Testing	To evaluate the breakdown potential for the 8-peak and 5-peak chemically etched springs, as well as the support spring.	Characterization Test; Results indicate acceptable corrosion resistance. Clinical performance with the Valiant Thoracic Stent Graft indicates acceptable corrosion resistance in clinical use.	Results Acceptable

Test	Test Purpose	Acceptance Criteria	Pass/Fail
Angulated Pulsatile Fatigue	To evaluate the device durability following 10 years simulated (400 million cycles) accelerated *in vitro* testing under clinically-relevant loading conditions.	Each test sample must complete 400 million cycles of pulsatile fatigue testing without a stent fracture. Graft material and suture durability characterized and compared to wear from clinically explanted specimens	Pass
Spring Component Fatigue	To evaluate the spring durability following 10 years simulated (400 million cycles) accelerated *in vitro* testing under clinically-relevant loading conditions.	Each test sample must complete 400 million test cycles of radial dilatation testing at physiologically challenging radial distension parameters without a stent fracture.	Pass
Overlap Radial Dilatation Fatigue	To evaluate the overlap fatigue interaction between a Valiant stent graft deployed within another Valiant Stent Graft in a vessel supported region during a 10 year simulation consisting of 400 Million cycles of accelerated in vitro testing.	Each test sample must complete 400 million test cycles of radial dilatation testing at physiologically challenging radial distension parameters without a stent fracture. Graft material and suture durability characterized and compared to wear from clinically explanted specimens.	Pass
Finite Element Analysis	To quantify the levels of strain of 8-peak and 5-peak springs when subjected to *in vivo* fatigue conditions.	Characterization Test; Fatigue safety factors characterized to be > 1 based on the endurance limit determined through endurance life testing.	Results Acceptable
Magnetic Resonance Compatibility	To ensure that the stent graft does not pose additional risk when the patient is subjected to a MR procedure.	1. No additional patient risk when subjected to 1.5T & 3.0T magnetic fields. 2. Characterize image artifact created by 1.5T & 3.0T magnetic fields.	Pass
Delivery System Verification Testing			
Graft Cover Working Length	To determine the working length of the graft cover of the Captivia delivery system and demonstrate that it meets the acceptance criteria.	Working Length = 83 ± 2 cm	Pass
Tapered Tip Length	To determine the working length of the Tapered Tip of the Captivia delivery system and demonstrate that it meets the acceptance criteria.	• 22 Fr 3.8 ± 0.1 cm • 24 Fr 4.6 ± 0.1 cm • 25 Fr 4.6 ± 0.1 cm	Pass
Hydrophilic Coating Length	To determine the Hydrophilic Coating Length on the Captivia delivery system and demonstrate that it meets the acceptance criteria.	Coating Length ≥ 60 cm	Pass
Hydrophilic Coating Drag Force*	To determine the drag force of the hydrophilic coating on the Captivia delivery system graft cover and demonstrate that it meets the acceptance criteria.	Average drag force on coated graft cover UTL < 3.00 lbf (13.3 N)	Pass
Delivery System Hemostasis (with and without tip)*	To determine the ability of the Captivia Delivery System to maintain an adequate hemostatic seal and demonstrate that seal meets the acceptance criteria.	Flow Rate < 2 cc/min	Pass

Test	Test Purpose	Acceptance Criteria	Pass/Fail
Tapered Tip Bond Strength*	To determine the tensile strength of the bond between the molded Tapered Tip and the inner member of the Captivia Delivery System and demonstrate that this bond meets the acceptance criteria.	Ultimate Tensile Strength LTL > 10.0 lbf (44.5 N)	Pass
Capture Fitting Tensile*	To measure the tensile strength of the connection between the Capture Fitting and the Capture Tube of the Captivia FreeFlo Delivery System and demonstrate that this connection meets the acceptance criteria.	Ultimate Tensile Strength LTL > 7.5 lbf (33 N)	Pass
Threaded Spindle to Tapered Tip Insert Tensile*	To measure the tensile strength of the connection between the Threaded Spindle and the Tapered Tip Insert of the Captivia FreeFlo Delivery System and demonstrate that the connection meets the acceptance criteria.	Ultimate Tensile Strength LTL > 10.0 lbf (44.5 N)	Pass
Tip Capture T-tube Tensile*	To measure the tensile strength of the connection between the Tip Capture T-Tube and the Capture Tube of the Captivia FreeFlo Delivery System and demonstrate that the connection meets the acceptance criteria.	Ultimate Tensile Strength LTL > 15.0 lbf (66.7 N)	Pass
Back End T-Tube Tensile*	To measure the tensile strength of the connection between the Back End T-Tube and the Inner Member of the Captivia Delivery System and demonstrate that the connection meets the acceptance criteria.	Ultimate Tensile Strength LTL > 10.0 lbf (44.5 N)	Pass
Middle Member – Flexible Stent Stop Bond Strength*	To measure the tensile strength of the bond between the Middle Member and Flexible Stent Stop of the Captivia Delivery System and demonstrate that the bond meets the acceptance criteria.	Ultimate Tensile Strength LTL > 10.0 lbf (44.5 N)	Pass
Middle Member Collar to Middle Member Tensile Strength*	To measure the tensile strength of the bond between the Middle Member Collar and the Middle Member of the Captivia Delivery System and demonstrate that the bond meets the acceptance criteria.	Ultimate Tensile Strength LTL > 8.0 lbf (36 N)	Pass
Middle Member to Screw Gear Interface*	To measure the force required to cause failure of the screw gear ribs that act as an interference for the middle member in the Captivia Delivery System.	Ultimate Tensile Strength LTL > 32.0 lbf (142 N)	Pass

Test	Test Purpose	Acceptance Criteria	Pass/Fail
Graft Cover Yield Strength*	To determine the graft cover yield strength of the Captivia Delivery System and demonstrate that it meets the acceptance criteria.	Graft Cover Yield Strength LTL > Deployment Force UTL	Pass
Radiopaque Marker Bond Strength*	To measure the tensile strength of the bond between the Radiopaque (RO) Marker Band and the Graft Cover of the Captivia Delivery System and demonstrate that the bond meets the acceptance criteria.	Radiopaque Marker Bond Strength LTL > 15.0 lbf (66.7 N)	Pass
Sideport Extension Bond Strength	To determine the bond strength of the Sideport Extension on the Captivia Delivery System and demonstrate that it meets the acceptance criteria.	Ultimate Tensile Strength LTL > 5.0 lbf (22 N)	Pass
Front Grip Tensile Strength*	To measure the force required to separate the Front Grip from the Screw Gear of the Captivia Delivery System and demonstrate that these components meet the acceptance criteria.	Ultimate Tensile Strength LTL > 32.0 lbf (142 N)	Pass
Hubcap Tensile Strength*	To measure the tensile strength of the bond between the Hubcap and T-Tube of the Captivia Delivery System and demonstrate that this bond meets the acceptance criteria.	Ultimate Tensile Strength LTL > 0.75 lbf (3.3 N)	Pass
Handle T-Tube Bond Strength*	To determine the ultimate tensile strength of the Handle T-Tube Assembly of the Captivia Delivery System and demonstrate that the bond meets the acceptance criteria.	Ultimate Tensile Strength LTL > 32.0 lbf (142 N)	Pass
Handle T-Tube Torque Strength	To measure the torsional forces created by the friction between the Handle T-Tube and graft cover of the Captivia Delivery System and demonstrate that the bond meets the acceptance criteria.	Ultimate Torque Strength LTL > 1.62 in-lb (18.3 N-cm)	Pass
End Seal – Hypotube Tensile Strength*	To measure the tensile strength of the bond between the End Seal and Hypotube of the Captivia Delivery System and demonstrate that the bond meets the acceptance criteria.	Ultimate Tensile Strength LTL > 5.0 lbf (22 N)	Pass
Endovascular Stent Graft System Verification Testing			

<table>
<tr><th>Test</th><th>Test Purpose</th><th>Acceptance Criteria</th><th>Pass/Fail</th></tr>
<tr><td>Crossing Profile*</td><td>To measure the outside diameter of the Captivia Delivery System and demonstrate that the crossing profile meets the acceptance criteria.</td><td>The appropriate ring gage diameter must pass over the loaded delivery system sizes per the table shown below:<table><tr><th>Catheter Size</th><th>Ring Gage Diameter</th></tr><tr><td>22 Fr</td><td>22.5 Fr</td></tr><tr><td>24 Fr</td><td>24.5 Fr</td></tr><tr><td>25 Fr</td><td>25.5 Fr</td></tr></table></td><td>Pass</td></tr>
<tr><td>Guidewire Acceptance*</td><td>To confirm that the Captivia Delivery System is compatible with a Ø0.035" (0.89 mm) guidewire and demonstrate that the guidewire acceptance meets the acceptance criteria.</td><td>A 0.035" (0.89 mm) diameter guidewire must pass through the guidewire lumen of the Captivia Delivery System with minimal resistance.</td><td>Pass</td></tr>
<tr><td>Trackability and Pushability*,**</td><td>To evaluate the Trackability and Pushability of the Captivia Delivery System.</td><td>The Captivia Delivery System must be advanced to and reach the target treatment site.</td><td>Pass</td></tr>
<tr><td>Deployment Force*</td><td>To determine the force required to deploy the Valiant Thoracic Stent Graft from the Captivia Delivery System and demonstrate that the deployment force meets the acceptance criteria.</td><td>Deployment Force UTL < LTL of Graft Cover Yield Strength</td><td>Pass</td></tr>
<tr><td>Capture Tube Retraction Force*</td><td>To determine the force required to retract the Capture Tube in the Valiant Thoracic Stent Graft with the Captivia FreeFlo Delivery System and demonstrate that the capture tube retraction force meets the acceptance criteria.</td><td>Capture Tube Retraction Force UTL < LTL of Tip Capture T-Tube Ultimate Tensile Strength</td><td>Pass</td></tr>
<tr><td colspan="4">* Indicates testing was performed at both T=0 and T=2
**Testing was conducted for characterization only at T=2</td></tr>
</table>

In vivo Animal Testing

Preclinical, *in vivo* animal testing, using prototypes of the final device design of the Valiant Thoracic Stent Graft with the Xcelerant Delivery System, was conducted for up to six months in 16 ovine test systems to evaluate acute technical success (deployment), stent graft integrity, and histopathological response of the Valiant Thoracic Stent Graft. The results demonstrated adequate handling and visualization of the Valiant Thoracic Stent Graft with the Xcelerant Delivery System, an adequate ability to access the target anatomical location, and adequate deployment accuracy. Although, the *in vivo* animal testing was conducted with the prior delivery system (i.e. Xcelerant), the vast majority of the testing evaluated the stent graft which remains unchanged. Stent graft 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 *in vivo* Studies conducted using the Valiant Thoracic Stent Graft with the Xcelerant Delivery System

Study	# of Animals	Objectives	Success Criteria	Objectives Met?
30 and 60 Day Safety Study FS154 (GLP): Evaluation of the Valiant Thoracic Stent Graft with the Xcelerant Delivery System in an Ovine Model	9	The objectives of the study were as follows: • Assess acute stent placement and any device related effects at the time of implant; • Evaluate the position of the implant at the time of explant; • Evaluate the structural integrity of the Valiant Thoracic Stent Graft at the time of explant; • Evaluate the histology and pathology of the explants and surrounding tissue.	• Test device mean evaluation scores for each acute performance characteristic of 'average' or greater. • Distal migration of the test devices of no more than 10 mm was considered acceptable. Position of the stent graft at implant and explant was compared using anatomical landmarks and aortograms and any change in position was documented. • Evaluation of the structural integrity of the Valiant Thoracic Stent Graft at explant before animal termination was evaluated using angiography and/or x-rays. Success was determined by the lack of evidence of stent fractures. • Comparable or superior histological indicators of vessel wall healing at 30 and 60 days for the Valiant Thoracic Stent Graft test devices as compared to the Talent Thoracic Stent Graft control data, including strut induced vessel wall injury, and inflammation. • Overall quantitative morphometric analysis of tissue sections from the test device indicating similar or better vascular response than the Talent control data.	Yes

Study	# of Animals	Objectives	Success Criteria	Objectives Met?
180 Day Safety Study FS159 (GLP): Evaluation of the Valiant Thoracic Stent Graft with the Xcelerant Delivery System in an Ovine Model	7	The objectives of the study were as follows: • Assess acute stent placement and any device related effects at the time of implant; • Evaluate the position of the implant at the time of explant; • Evaluate the structural integrity of the Valiant Thoracic Stent Graft at the time of Explant; • Evaluate the histology and pathology of the explants and surrounding tissue.	• Test device mean evaluation scores for each acute performance characteristic of 'average' or greater. • Distal migration of the test devices of no more than 10 mm was considered acceptable. Position of the stent graft at implant and explant was compared using anatomical landmarks and aortograms and any change in position was documented. • Evaluation of the structural integrity of the Valiant Thoracic Stent Graft at explant before animal termination was evaluated using angiography and/or x-rays. Success was determined by the lack of evidence of stent fractures. • Comparable or superior histological indicators of vessel wall healing at 180 days for the Valiant Thoracic Stent Graft test devices as compared to the Talent Thoracic Stent Graft control data, including strut induced vessel wall injury, and inflammation. • Overall quantitative morphometric analysis of tissue sections from the test device indicating similar or better vascular response than the Talent control data.	Yes[1]

[1] Please note that some degree of change in device position that may have exceeded 10 mm was noted in some cases upon angiographic measurement with respect to radiographic anatomic landmarks. However, these measurements are not necessarily reliable because of issues with parallax error that arose either from difficulties in reproducing the exact position of the animal on the table or due to some degree of animal body growth over the in-life period of the study.

10.0 Summary of Clinical Studies

The safety and effectiveness data supporting the Valiant Thoracic Stent Graft with the Captivia Delivery System included data from three multi-center studies conducted across the United States, European Union and Turkey. The aforementioned studies are summarized in **Table 10-1**. Please note that there were no prior feasibility studies performed using the Valiant Thoracic Stent Graft.

Table 10-1: Summary of Clinical Studies – Test Groups

Clinical Study	Study Design	Objective	Number of Sites	Number of Subjects Enrolled
VALOR II Study G050238	Prospective, multi-center, single arm study with comparison to a historical control on the primary safety endpoint	To evaluate the safety and effectiveness of the Valiant Thoracic Stent Graft with the Xcelerant Delivery System in the United States	24	160 subjects
Valiant Captivia OUS Registry	Post-market, non-interventional, single-arm, multicenter study	To evaluate the clinical performance of the Valiant Thoracic Stent Graft with the Captivia Delivery System in Europe and Turkey following market approval	13	50 subjects
Talent Captivia Study G980116	Prospective, non-randomized, multicenter study (Extension of the VALOR High Risk Arm)	To evaluate the acute clinical performance of the Talent Thoracic Stent Graft with the Captivia Delivery System	4	10 subjects

10.1 VALOR II Clinical Study Design

The clinical study that formed the basis for FDA's finding that the Valiant Thoracic Stent Graft System is safe and effective for its intended use was an open-label, non-randomized, prospective, multicenter, single arm study. Medtronic conducted the VALOR II clinical study to establish a reasonable assurance of safety and effectiveness of endovascular treatment of Descending Thoracic Aneurysms (DTA) with the Valiant Thoracic Stent Graft System.

10.1.1 Major Design Characteristics

The VALOR II clinical study ("Valiant Test Group") enrolled 160 subjects at 24 investigational sites across the United States under the same indications and similar study requirements as the VALOR clinical study ("Talent Control Group"). The Valiant Test Group enrolled patients diagnosed with a fusiform aneurysm and/or saccular aneurysm/penetrating atherosclerotic ulcer of the descending thoracic aorta who were considered candidates for elective surgical repair and who were low to moderate risk (SVS 0, 1, and 2) per the modified SVS/AAVS scoring system at the time of implant. A subject was

considered officially enrolled when an access site incision was made. After enrollment, subjects are required to return for follow-up visits at 30 days, 6 months, 12 months and annually thereafter for a total of five years. Assessments at these visits include a physical examination, CT/MR, chest X-ray, and adverse event evaluation. The enrolled subjects with evaluable data were used for analysis at the completion of the 30-day, 6-month and 12-month follow-up visits.

10.1.1.1 Level of Masking

The Valiant Test Group was enrolled in a single-arm open-label clinical study.

10.1.1.2 Type of Controls

The Valiant Test Group was compared to the Talent Control Group on the primary safety endpoint (**Table 10-2**). The Talent Control Group, which enrolled 195 subjects, was used as the pivotal study group to evaluate the safety and effectiveness of the Talent Thoracic Stent Graft System (refer to the Summary of Safety and Effectiveness Data for the Talent Thoracic Stent Graft System (P070007) for more information).

Table 10-2: Talent Thoracic Stent Graft System Clinical Study Summary – Control Group

Clinical Study	Study Design	Objective	Number of Sites	Number of Subjects
VALOR Study G980116	Prospective, non-randomized, multi-center study (Pivotal Test Group)	To evaluate the safety and effectiveness of the Talent Thoracic Stent Graft with the CoilTrac Delivery System in the United States	38	195 subjects

10.1.1.3 Duration of Study

The Talent Control Group was enrolled between March 2003 and June 2005, while the Valiant Test Group was enrolled between December 2006 and September 2009. The enrolled subjects with evaluable data were used for analyses at the completion of 30-day and 12 month follow-up visits. Long-term safety and effectiveness data on the Valiant Thoracic Stent Graft with the Xcelerant Delivery System will be collected by following enrolled subjects for a total of five years under the investigational plan.

10.1.1.4 Method of Allocation to Treatment Group

All subjects in the Valiant Test Group were enrolled to a single arm.

10.1.1.5 Treatment Arms

All subjects in the Valiant Test Group were enrolled to a single arm.

10.1.2 Clinical Endpoints

The analysis included clinically relevant endpoints for patients with thoracic aortic disease. The endpoints used by Medtronic to demonstrate the safety of the device were adequate to describe the adverse events resulting from using the Valiant Thoracic Stent Graft System. Similarly, the endpoints used by Medtronic to demonstrate the effectiveness of the device were adequate to demonstrate the treatment effect.

10.1.2.1 Safety

The **primary safety endpoint** was the demonstration of non-inferiority of the Valiant Test Group relative to the Talent Control Group of all-cause mortality within 12 months.

Hypothesis testing for the primary safety endpoint consisted of a comparison of the rates of all-cause mortality within 12 months for the Valiant Test Group and the Talent Control Group using an adjusted odds ratio. The primary analysis was performed on the null hypothesis of inferiority of the Valiant Test Group relative to the Talent Control Group using the Cochran-Mantel-Haenszel (CMH) to control for SVS scores. Rejection of the null hypothesis required the upper-endpoint of the exact 1-sided 95% confidence interval of the adjusted odds ratio to be less than a non-inferiority margin of 2.25. The primary analysis set for the primary safety endpoint was the intent-to-treat[1] (ITT) population.

10.1.2.2 Effectiveness

The **primary effectiveness endpoint** was Successful Aneurysm Treatment at 12 months which was defined as the absence of both:

- Aneurysm growth of more than 5 mm at the 12-month visit relative to the 1 month visit;
- Type I and/or Type III endoleak for which a secondary procedure was performed or recommended at or before the 12 month follow-up visit.

Hypothesis testing for the primary effectiveness endpoint consisted of a comparison to a fixed value of 80%. Rejection of the null hypothesis required the lower endpoint of an exact 1-sided 95% confidence interval to be greater than 80%. The primary analysis set for the primary effectiveness endpoint was the implanted population.

10.1.2.3 Secondary Endpoints

The **secondary endpoints** included the following acute and 12-month study endpoints:

- Within 30 days: successful delivery and deployment of the stent graft; peri-operative mortality; paraplegia; paraparesis; secondary procedures due to endoleak after discharge; and one or more major adverse event(s) (MAE);

[1] A subject was considered officially enrolled when an access site incision was made. This group of subjects is referred to as the intent-to-treat (ITT) population.

- Within 12 months: aneurysm-related mortality; secondary endovascular procedures due to endoleak after 30 days; conversion to open surgical repair; migration of the stent graft; loss of patency of the stent graft; aneurysm rupture; endoleak at 12 months; and one or more MAE.

Several additional descriptive statistics were calculated for complications including aortic dissection, stent graft integrity, changes in aneurysm diameter, additional secondary procedures, and stroke. Supplementary data included acute procedural data on the amount of blood loss, subjects requiring transfusion, duration of implant procedure, time in the intensive care unit, and overall hospital stay.

10.1.3 Success/Failure Criteria

The VALOR II US clinical study was considered successful if the null hypotheses for the tests of primary safety and effectiveness endpoints as described in **Section 10.1.2.1** and **Section 10.1.2.2** were rejected.

10.1.4 Pre-Specified Statistical Analysis Plan

10.1.4.1 Study Hypothesis

Analysis of the VALOR II clinical study results included hypothesis testing of the primary study endpoints and a presentation of descriptive statistics for the secondary and supplementary endpoints. The study was considered successful if the null hypotheses for the tests of primary safety and effectiveness endpoints, described in **Section 10.1.2.1** and **Section 10.1.2.2**, were both rejected. For the primary safety endpoint and primary effectiveness endpoint, analyses based on both the ITT and implanted populations were presented. Apart from any imaging-dependent endpoints, analyses for all secondary endpoints were based on the ITT population. Only patients who received adequate imaging and were at risk for the relevant events can be included in the evaluation of the imaging-dependent endpoints.

10.1.4.2 Comparator

The comparator for this study was the Talent Control Group. Although conducted over different periods of time, the Valiant Test and Talent Control Groups evaluated the same treatment indications and were conducted under similar study requirements. The design of both trials addressed sources of potential bias through the use of a physician screening committee to reduce potential selection bias and a core laboratory and clinical events committee (CEC) to reduce potential assessment bias. In addition, statistical testing was employed to control for differences in baseline risk factors. Nonetheless, there are several potential concerns associated with using a historical control. First, the control is non-concurrent so there is a temporal bias of unknown size that may affect the scientific validity of the study. Second, the historical control group may include a different subject population and/or outcomes than the contemporary study. There is no guarantee that the 2 groups are comparable, even with statistical techniques such as ANOVA or Cochran-Mantel-Haenszel analysis. In addition to the above concerns, protocol deviations occurred during this study and may have also introduced bias to the data.

10.1.4.3 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.

10.1.4.4 Sample Size Justification

The sample size was determined based on a goal of achieving 80% statistical power at a 1-sided significance level of 5% to demonstrate the primary safety and effectiveness objectives. These calculations yielded a minimum sample size of 150 subjects to evaluate the primary safety endpoint and a minimum sample size of 100 to evaluate the primary effectiveness endpoint. Taking into consideration expected performance on the primary endpoints and an expected attrition rate, a sample size of 160 enrolled subjects was considered to be sufficient.

10.1.4.5 Statistical Test

Hypothesis testing for the primary safety endpoint consisted of a comparison of the rates of all-cause mortality within 12 months for the Valiant Test Group and the Talent Control Group using an adjusted odds ratio. The primary analysis was performed on the null hypothesis of inferiority of the Valiant Test Group relative to the Talent Control Group using the Cochran-Mantel-Haenszel (CMH) to control for SVS scores. Rejection of the null hypothesis required the upper-endpoint of the exact 1-sided 95% confidence interval of the adjusted odds ratio to be less than a non-inferiority margin of 2.25.

10.1.4.6 Method for Accommodating Missing Data

Two sensitivity analyses, a tipping-point and worst-case scenario analysis, were also performed on each of the two primary endpoints to account for the impact of non-evaluable subjects.

10.1.4.7 Assumptions

The primary assumption made in this study was that, within the strata represented by the SVS scores, the subjects in the Valiant Test Group and in the Talent Control Group were interchangeable. That is, the probability of a subject meeting the primary safety endpoint was, other than the treatment effect, the same in the two groups. The validity of the statistical test used for the endpoint (CMH) depends on assumption that the treatment odds ratio is constant in all of the SVS strata, but this assumption was tested and validated before performing the CMH test.

10.1.5 External Evaluation Groups

- *Core laboratory.* In order to provide independent verification of imaging findings, images required by protocol were sent by investigational sites to a central imaging core laboratory with processes and systems that were GMP/GCP, HIPAA, and CFR 21 Part 11 compliant and were provided within an ISO 13485 certified facility which adhered to all applicable federal regulations.
- *Screening committee.* An independent screening committee reviewed the anatomic suitability of each potential subject prior to subject enrollment into the study. The screening committee reviewed three-dimensional reconstructions of computed tomography or magnetic resonance imaging (CT/MR) scans and measurements of the thoracic aorta to assess anatomic suitability. The committee was composed of a

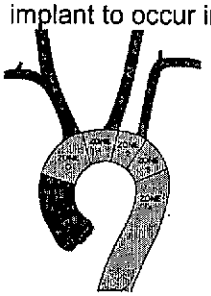
group of physicians with expertise and experience in the endovascular repair of thoracic aortic aneurysms.

- *Clinical Events Committee.* An independent Clinical Events Committee (CEC) adjudicated all deaths and MAEs for event type and device and procedure relatedness. The CEC was composed of a group of physicians independent of the clinical study with expertise and experience in the endovascular repair of thoracic aortic aneurysms.
- *Data monitoring committee.* An independent data monitoring committee (DMC) reviewed 30-day safety data at determined intervals during enrollment. Based on the safety data, the DMC could recommend that Medtronic Vascular continue, modify, or stop the study in accordance to previously agreed parameters. The committee was composed of three physicians with relevant training and one biostatistician, none of whom were directly involved in the conduct of the study.

10.1.6 Clinical Inclusion and Exclusion Criteria

Enrollment in the Valiant Test Group was limited to patients who met the following selection criteria as shown in **Table 10-3.**

Table 10-3: Inclusion/Exclusion Criteria for the Valiant Test Group – VALOR II

Inclusion	Exclusion
1) Subject is between the age of 18 and 85.	1. Planned placement of the COVERED portion of the stent graft requires implant to occur in zones 0 or 1.  Landing Zones of the Thoracic Aorta
2) Subject must be considered a candidate for elective surgical repair of the TAA (i.e., low to-moderate risk [categories 0, 1, and 2] per the modified SVS/AAVS scoring system at the time of implant).	2. Subject has a thoracic aneurysm with a contained rupture.
3) If subject is female of childbearing potential, she must have a negative pregnancy test within 7 days before the implant procedure.	3. Subject has a connective tissue disease (e.g., Marfan's syndrome, aortic medial degeneration).
4) Subject has a DTA that is: a) A fusiform aneurysm with a maximum diameter of ≥ 5 cm OR is > 2 times the diameter of the non-aneurysmal thoracic aorta; AND/OR b) Saccular aneurysm/penetrating atherosclerotic ulcer	4. Subject has a mycotic aneurysm or is suspected of having systemic infection.

5) Subject's anatomy must meet all of the following anatomical criteria: a) Subject's TAA must be ≥20 mm distal to the origin of the left common carotid artery and must be ≥20 mm proximal to the celiac artery; b) Proximal and distal non-aneurysmal neck diameter measurements must be between 20 mm and 42 mm; c) Proximal and distal non-aneurysmal neck must be ≥ 20 mm in length.	5. Subject has received a previous stent or stent graft or previous surgical repair in the DTA.
6) Thoracic aortic lesion is confirmed, at a minimum, by diagnostic contrast enhanced computerized tomography (CT) with optional 3-D reconstruction, and/or contrast enhanced magnetic resonance angiogram obtained within 4 months prior to the implant procedure.	6. Subject requires treatment of an infrarenal aneurysm at the time of implant.
7) Subject is able and willing to comply with the protocol and undergo follow-up requirements.	7. Subject has a history of bleeding diathesis, coagulopathy, or refuses blood transfusion.
8) Subject or subject's legal representative understands and has signed an informed consent approved by the sponsor and by the IRB for this study.	8. Subject has had or plans to have a major surgical procedure within 30 days before or after the Valiant Stent Graft procedure. This does not include planned procedures that are needed for the safe and effective placement of the stent graft (i.e., carotid/subclavian transposition, carotid/subclavian bypass procedure).
9) Subject has patent iliac or femoral arteries or can tolerate a vascular conduit that allows endovascular access to the aneurysmal site with the delivery system of the appropriate size device chosen for treatment.	9. Subject has had an MI or cerebral vascular accident (CVA) within 3 months.
	10. Subject is currently participating in an investigational drug or device clinical trial.
	11. Subject has a known allergy or intolerance to the device components.
	12. Subject has a known hypersensitivity or contraindication to anticoagulants or contrast media, which is not amenable to pre-treatment.
	13. Subject has significant and/or circumferential aortic mural thrombus at either the proximal or distal attachment sites that would compromise fixation and seal of the device.
	14. Subject has other medical, social, or psychological problems that, in the opinion of the investigator, preclude him or her from receiving this treatment and the procedures and evaluations pre- and post-treatment, or a limited life expectancy of less than 1 year.

A comparison of the inclusion and exclusion criteria for the Valiant Test Group and the Talent Control Group is described in **Table 10-4.** These minor differences in inclusion and exclusion criteria exist to accommodate the modifications in the study designs (institution of

a physician screening committee to assess eligibility of subjects) and to reflect current medical practices (use of conduits).

Table 10-4: Comparison of Clinical Inclusion and Exclusion Criteria – Valiant Test Group and Talent Control Group – VALOR II

	Valiant Test Group	Talent Control Group
Inclusion Criteria		
	Subject's anatomy must meet all of the following anatomical criteria: a. Subject's thoracic aortic aneurysm must be at least 20 mm distal to the origin of the left common carotid artery and must be at least 20 mm proximal to the celiac artery; b. Proximal and distal non-aneurysmal neck diameter measurements must be of a range between 20 mm and 42 mm; c. Proximal and distal non-aneurysmal neck must be 20 mm or greater in length.	Subject's anatomy must meet all of the following anatomical criteria: a. Subject's thoracic aortic aneurysm must be at least 20 mm distal to the origin of the left common carotid artery and must be at least 20 mm proximal to the celiac artery; b. Proximal and distal non-aneurysmal neck diameter measurements must be of a range between 18 mm and 42 mm; c. Proximal and distal non-aneurysmal neck must be 20 mm or greater in length.
	Thoracic aortic lesion is confirmed, at a minimum, by diagnostic contrast enhanced computerized tomography (CT) with optional 3-D reconstruction, and/or contrast enhanced magnetic resonance angiogram obtained within four months prior to the implant procedure.	Thoracic aortic lesion is confirmed, at a minimum, by diagnostic contrast enhanced computerized tomography (CT) with optional 3-D reconstruction, and/or contrast enhanced magnetic resonance angiogram obtained within the previous three months prior to screening.
	Subject or subject's legal representative understands and has signed an informed consent approved by the sponsor and by the IRB for this study.	*Not an inclusion criterion.*
	Subject has patent iliac or femoral arteries or can tolerate a vascular conduit that allows endovascular access to the aneurysmal site with the delivery system of the appropriate size device chosen for treatment.	*Adequacy of access vessels addressed in exclusion criteria. Use of conduits was not allowed.*
Exclusion Criteria		
	Adequacy of access vessels addressed in inclusion criteria. Use of conduits was allowed.	The subject's access vessel (as determined by the treating physician) precludes safe insertion of the delivery system. Patient requires a planned aortic conduit.
	Subject requires treatment of an infrarenal aneurysm at the time of implant.	Subject requires treatment of an infrarenal aneurysm at the time of implant or has had a previous surgical or endovascular treatment of an infrarenal aortic aneurysm.
	Subject has had a recent MI or cerebral vascular accident (CVA) (within 3 months).	Subject has had a recent (within three 3 months) cerebral vascular accident (CVA).

10.1.6.1 Follow-up Schedule and Evaluations

Treatment and follow-up protocols were identical for the Valiant Test Group and Talent Control Group. Clinical assessments occur at one, six, and 12 months and annually for five years post implant at which time a physical exam and CT/MR and x-ray imaging were or will be performed. All imaging-based measures through the 12-month visit were assessed by a core laboratory. Magnetic resonance imaging was recommended in patients with impaired renal function or intolerance to contrast media.

10.1.6.2 Prospectively Defined Subgroup Evaluations

Potential differences based on lesion type were tested through a subgroup analysis of the primary safety endpoint of all-cause mortality within 12 months, in which fusiform aneurysms and saccular aneurysms/penetrating aortic ulcers were examined separately. Potential gender-based differences in treatment outcomes were also explored for both the primary safety and primary effectiveness endpoints.

10.1.7 Accountability of PMA Cohort

One hundred-and-sixty (160) subjects were enrolled at 24 investigational sites in the Valiant Test Group. At the time of database lock, 151 of 160 enrolled subjects were available for evaluation of the primary safety endpoint and 115 CT/MR images were available for the evaluation of primary effectiveness endpoint. Subject compliance is presented in **Table 10-5.** The number of data points evaluable for each endpoint is reported in the results sections. In the Talent Control Group, 195 subjects were enrolled across 38 sites with 192 being available for the evaluation of the primary safety endpoint. Additional information on the Talent Control Group patient accountability and follow-up can be found in the Summary of Safety and Effectiveness for P070007.

Table 10-5: Subject Accountability and Core Lab Imaging Compliance within 12 Months[1] – Valiant Test Group – VALOR II

	Subject follow-up # (%)			Subjects with Imaging (at each time interval) # (%)		Subjects with adequate imaging to assess the parameter # (%)					Subject events occurring before next visit #					
Treatment / Follow-up Interval	Eligible[1]	Treatment or Clinical f/u	Imaging f/u	CT/MR Imaging	Chest X-Ray	Max ANR Diameter	Change in ANR diameter (from 1 month)	Endoleak	Migration (from 1 month)	Integrity	Intent to Treat but Not Implanted	Con-version to Surgery	Death	Withdrawal	LTF	Not due for next visit
Originally Enrolled	160	100% (160/160)														
Events between implant and 1 month follow-up visit											3	0	1[3]	0	0	0
1 month (0-122 Days)	156	100.0% (156/156)	98.7% (154/156)	97.4% (152/156)	96.8% (151/156)	96.2% (150/156)		89.1% (139/156)		95.5% (149/156)						
Events between 1 month and 6 months follow-up visit												0	9	0	0	0
6 month (123-336 Days)[2]	147	75.5% (111/147)	93.2% (137/147)	92.5% (136/147)	77.6% (114/147)	89.8% (132/147)		83.0% (122/147)	85.7% (126/147)	76.9% (113/147)						
Events between 6 months and 12 months follow-up visit												0	7	0	0	7
12 month (337-480 Days)	133	87.2% (116/133)	91.0% (121/133)	87.2% (116/133)	84.2% (112/133)	86.5% (115/133)	85.7% (114/133)	75.2% (100/133)	78.9% (105/133)	82.7% (110/133)						
										Totals	3	0	17[4]	0	0	

Death post conversion to surgery	0
Total Deaths	17

[1] The number of subjects eligible for each interval is determined by how many subjects completed a physical exam less those who converted to surgery, died, withdrew, or were lost to follow-up in the previous interval.

[2] "Treatment or Clinical f/u" at six months and "Events between 6 months 12 months follow-up visit" are based on the protocol-defined follow-up window. "Evaluable core lab imaging" is based on the analysis window of 123-366 days.

[3] Four of 5 subjects who died within 30 days completed a physical exam at discharge and were therefore recorded as having completed the 1-month interval.

[4] Two of 19 subjects who died within 365 days completed a physical exam prior to expiring and were therefore recorded as having completed the 12-month interval.

10.1.8 Subject Population Demographics and Baseline Parameters

Table 10-6 through **Table 10-8** provide the demographics, baseline medical history, and SVS risk classification of the Valiant Test Group and the Talent Control Group.

Table 10-9 through **Table 10-14** provide baseline aneurysm characteristics and distribution of Valiant Thoracic Stent Grafts implanted at the initial procedure.

As shown in **Table 10-6,** the mean age in the Valiant Test Group was 72.2 years ± 9.1 (36-85 years) and males composed 59.4% of the study population. These and other demographic variables were similar between the Valiant Test Group and Talent Control Group.

Table 10-6: Subject Demographics – Valiant Test Group and Talent Control Group - VALOR II

	Valiant Test Group	Talent Control Group	p-value
Age (years)			
Total Population			
n	160	195	
Mean ± SD	72.2 ± 9.1	70.2 ± 11.1	0.459
Median	74.0	73.0	
Min, max	36, 85	27, 86	
Sex/Gender % (m/n)			
Males	59.4% (95/160)	59% (115/195)	0.769
Females	40.6% (65/160)	41% (80/195)	
Race % (m/n)			
American Indian or Alaska Native	0% (0/160)	0% (0/190)	0.787
Asian/Native Hawaiian/Pacific Islander	2.5% (4/160)	1.1% (2/190)	
Black	10% (16/160)	13.2% (25/190)	
White	86.3% (138/160)	85.3% (162/190)	
Subject refuses to answer	0% (0/160)	0% (0/190)	
Multi-racial / other	1.3% (2/160)	0.5% (1/190)	

As shown in **Table 10-7,** the medical history of subjects in the Valiant Test Group and Talent Control Group were similar although a number of factors contributed to a higher level of risk among the Valiant Test Group. Subjects in the Valiant Test Group have a higher rate of abdominal aortic aneurysm (AAA), prior AAA repair, carotid artery disease, percutaneous coronary intervention and hyperlipidemia while subjects in the Talent Control Group had a higher rate of gastrointestinal medical history. Additionally, a history of ascending thoracic aneurysm and the use of an abdominal aortic conduit for vascular access, both of which were exclusion criteria in the Talent Control Group, likely added to an increase in baseline risk factors for the Valiant Test Group.

Table 10-7: Baseline Medical History - Valiant Test Group and Talent Control Group - VALOR II

Medical History	Valiant Test Group % (m/n) (N = 160)	Talent Control Group % (m/n) (N = 195)	p-value
Cardiovascular			
Abdominal aortic aneurysm (AAA)	38.8% (62/160)	19% (37/195)	<0.001
Previous AAA repair	20.6% (33/160)	2.1% (4/195)	<0.001
Ascending thoracic aneurysm[1]	8.1% (13/160)		
Angina	9.4% (15/160)	14.4% (28/195)	0.094
Arrhythmia	31.3% (50/160)	26.7% (52/195)	0.602
Carotid artery disease	28.1% (45/160)	5.6% (11/195)	<0.001
Congestive heart failure	11.9% (19/160)	8.7% (17/195)	0.546
Coronary artery disease	44.4% (71/160)	40.5% (79/195)	0.928
Coronary artery bypass grafting	13.8% (22/160)	10.3% (20/195)	0.466
Hypertension	93.8% (150/160)	87.2% (170/195)	0.186
Myocardial infarction	21.3% (34/160)	13.8% (27/195)	0.117
Percutaneous coronary intervention	16.9% (27/160)	5.6% (11/195)	0.002
Peripheral vascular disease	25% (40/160)	16.4% (32/195)	0.091
Pulmonary			
Chronic obstructive pulmonary disorder	35% (56/160)	36.9% (72/195)	0.426
Renal			
Renal insufficiency	16.3% (26/160)	17.4% (34/195)	0.479
Cerebrovascular / Neurological			
Transient ischemic attack	11.3% (18/160)	7.7% (15/195)	0.471
Cerebral vascular accident	10.6% (17/160)	9.7% (19/195)	0.958
Paraplegia	0% (0/160)	1% (2/195)	0.388
Paraparesis	0.6% (1/160)	0.5% (1/195)	0.984
Other Abnormal Body Systems			
Bleeding disorder	2.5% (4/160)	2.6% (5/195)	0.994
Diabetes	21.3% (34/160)	15.9% (31/195)	0.426
Gastrointestinal complications	40.6% (65/160)	53.8% (105/195)	0.006
Hyperlipidemia	73.8% (118/160)	43.6% (85/195)	<0.001
Tobacco use in last ten years[2]	44.4% (71/160)	50.3% (98/195)	0.333

[1] Data point was not collected in Talent Control Group.
[2] For Talent Control Group, subjects who answered 'Yes' to 'Tobacco Use' and whose resolution date was more than 10 years prior to implant were considered as 'No' to the question of 'Tobacco Use in the last 10 years'.

The baseline modified SVS classifications for the Valiant Test Group and Talent Control Group subjects are shown in **Table 10-8**. Of the 160 subjects enrolled in the Valiant Test Group, one subject (0.6%) was in SVS class 0, 17 subjects (10.6%) were in SVS class 1 and 140 subjects (87.5%) were in SVS class 2 categories. Two subjects were classified in SVS class 3 (1.3%) and constituted protocol deviations. The distribution of SVS score was statistically different between the two groups with a greater percentage of high severity scores in the Valiant Test Group.

Table 10-8: Baseline Modified SVS/AAVS Classification - Valiant Test Group and Talent Control Group - VALOR II

SVS/AAVS Score[1]	Valiant Test Group % (m/n) (N = 160)	Talent Control Group % (m/n) (N = 195)	p-value[2]
0	0.6% (1/160)	4.1% (8/195)	0.002
1	10.6% (17/160)	21% (41/195)	
2	87.5% (140/160)	72.8% (142/195)	
3	1.3% (2/160)	2.1% (4/195)	

[1] Modified SVS/AAVS Medical Comorbidity Grading System modified for age, hypertension, cardiac, pulmonary and renal, as described in the Valiant Test Group clinical study protocol
[2] p-value is calculated using one-way ANOVA with SVS score being the dependent variable.

Table 10-9 provides the treated anatomic lesion type for both the Valiant Test Group and the Talent Control Group.

Table 10-9: Anatomic Lesion Type - Valiant Test Group and Talent Control Group – VALOR II

Etiology	Valiant Test Group % (m/n) (N = 160)	Talent Control Group % (m/n) (N = 195)
Thoracic Aortic Aneurysm (Fusiform)	64.4% (103/160)	57.4% (112/195)
Thoracic Aortic Aneurysm (Saccular / Penetrating ulcer)	35.6% (57/160)	35.9% (70/195)
Both	0.0% (0/160)	6.7% (13/195)

Table 10-10 and **Table 10-11** provide the baseline anatomical and aneurysm measurements of the Valiant Test Group and Talent Control Group.

Table 10-10: Baseline Vessel Dimensions - Core Laboratory Reported - Valiant Test Group and Talent Control Group - VALOR II

Baseline Vessel Dimension	Valiant Test Group (N = 160)	Talent Control Group (N = 195)	p-value[1]
Proximal Neck Diameter (mm)			
n[2]	157	187	
Mean ± SD	32.47 ± 5.17	31.20 ± 4.93	0.074
Median	32.00	31.50	
Min, Max	21.0, 51.5	18.5, 43.5	
Max Aneurysm Diameter (mm)			
n[2]	160	187	
Mean ± SD	57.00 ± 11.03	55.51 ± 11.60	0.363
Median	56.10	56.00	
Min, Max	31.4, 97.7	26.2, 88.8	
Distal Neck Diameter (mm)			
n[2]	157	184	
Mean ± SD	31.23 ± 5.78	29.72 ± 5.00	0.050
Median	30.50	29.50	

Min, Max	19.0, 51.0	17.0, 42.5	
Proximal Centerline Neck Length (mm)			
n[2]	157	187	
Mean ± SD	83.03 ± 51.05	80.02 ± 52.09	0.882
Median	80.00	77.90	
Min, Max	14.0, 246.5	10.0, 234.0	
Aneurysm Length (mm)			
n[2]	154	180	
Mean ± SD	123.25 ± 73.02	121.38 ± 72.69	0.861
Median	108.55	107.65	
Min, Max	17.0, 316.0	8.0, 297.5	
Distal Neck Length (mm)			
n[2]	158	184	
Mean ± SD	90.62 ± 58.52	90.00 ± 62.90	0.711
Median	79.05	73.50	
Min, Max	0.0, 285.0	9.0, 255.0	
Right External Iliac Minimum Diameter (mm)			
n[2]	120	122	
Mean ± SD	7.07 ± 1.96	6.49 ± 1.53	0.011
Median	7.00	6.50	
Min, Max	3.5, 13.5	2.9, 11.0	
Left External Iliac Minimum Diameter (mm)			
n[2]	120	124	
Mean ± SD	7.04 ± 1.93	6.59 ± 1.55	0.046
Median	7.00	6.50	
Min, Max	3.5, 13.0	3.3, 10.9	

[1] Each variable will be assessed for balance between the treatment groups. This assessment is also adjusted for SVS score of (0, 1) versus (2, 3).
[2] n = number of known values.

Table 10-11: Baseline Maximum Aneurysm Diameters - Core Laboratory Reported - Valiant Test Group and Talent Control Group - VALOR II

Diameter (mm)	Valiant Test Group % (m/n)[1]	Talent Control Group % (m/n)[1]
10-17	0.0% (0/160)	0.0% (0/187)
18-29	0.0% (0/160)	0.5% (1/187)
30-39	4.4% (7/160)	7.5% (14/187)
40-49	15.6% (25/160)	20.3% (38/187)
50-59	45.0% (72/160)	34.8% (65/187)
60-69	24.4% (39/160)	24.6% (46/187)
70-79	7.5% (12/160)	10.2% (19/187)
80-89	1.3% (2/160)	2.1% (4/187)
90-99	1.9% (3/160)	0.0% (0/187)
100-109	0.0% (0/160)	0.0% (0/187)
110-119	0.0% (0/160)	0.0% (0/187)
120+	0.0% (0/160)	0.0% (0/187)
Aneurysm diameter < 50 mm (%m/n)	20.0% (32/160)	28.3% (53/187)
Aneurysm diameter > 50 mm (% m/n)	80.0% (128/160)	71.7% (134/187)

[1] m = numbers in category, n = number of known values.

A total of 288 stent grafts and an average of 1.8 stent grafts per subject were implanted in the Valiant Test Group. **Table 10-12** provides the distribution of the number of Valiant Thoracic Stent Grafts implanted per subject at the initial procedure.

Table 10-12: Number of Devices Implanted at Initial Procedure - Valiant Test Group and Talent Control Group - VALOR II

Number of Devices Implanted	Valiant Test Group % (m/n)[1] N = 160	Talent Control Group % (m/n)[1] N = 195
0[2]	1.9% (3/160)	0.5% (1/195)
1	38.8% (62/160)	19.5% (38/195)
2	40.0% (64/160)	28.7% (56/195)
3	16.3% (26/160)	24.6% (48/195)
4	3.1% (5/160)	17.4% (34/195)
5	0.0% (0/160)	7.2% (14/195)
6	0.0% (0/160)	1.5% (3/195)
7+	0.0% (0/160)	0.5% (1/195)

[1] n is the number of enrolled subjects.
[2] Three enrolled subjects did not receive a stent graft due to a failure to achieve access.

Table 10-13 provides the distribution of the proximal diameter of Valiant Thoracic Stent Grafts implanted per subject at the initial procedure.

Table 10-13: Devices Implanted by Proximal Diameter – VALOR II

Proximal Diameter	Number of Devices % (m/n)[1]
24	0.3% (1/288)
26	0.7% (2/288)
28	1.4% (4/288)
30	2.1% (6/288)
32	11.5% (33/288)
34	8.3% (24/288)
36	13.9% (40/288)
38	12.2% (35/288)
40	16.7% (48/288)
42	9% (26/288)
44	11.5% (33/288)
46	12.5% (36/288)

[1] m is the number of devices of that proximal diameter implanted and n is the total number of devices implanted.

Table 10-14 provides the distribution of the type of Valiant Thoracic Stent Grafts implanted per subject at the initial procedure. Since multiple stent graft configurations could have been used in a single subject, the number of total devices implanted exceeded the number of subjects enrolled. One subject was implanted with a distal device in the proximal position due to an adjustment in size made at the time of procedure. This event was noted as a deviation from the protocol.

Table 10-14: Type of Devices Implanted - Valiant Test Group only – VALOR II

Device Type	% (m/n)[1]
Proximal FreeFlo straight	99.4% (156/157)[2]
Distal closed web straight	29.3% (46/157)
Distal closed web tapered	24.2% (38/157)
Distal bare spring straight	5.1% (8/157)

[1] m = numbers in subjects who are implanted with the corresponding device, n = number of implanted subjects.
[2] One subject was implanted with a Closed Web device in the proximal position due to an adjustment in size made at the time of procedure.

10.1.9 Acute Procedural Data

Acute procedural data are presented in **Table 10-15.**

Table 10-15: Acute Procedural Details - Valiant Test Group only – VALOR II

Procedure Details	% (m/n)
Left Subclavian Artery (LSA) Revascularization Pre-Implant or at Initial Procedure	13.8% (22/160)
Left subclavian transposition	1.3% (2/160)
Carotid to subclavian bypass	12.5% (20/160)
Arterial Access[2]	
Abdominal aortic conduit	1.9% (3/160)

Procedure Details	% (m/n)[1]
Iliac conduit	13.1% (21/160)
Femoral/Iliac artery	85.6% (137/160)
Anesthesia[2]	
General	88.1% (141/160)
Epidural	0% (0/160)
Spinal	8.1% (13/160)
Local	5.6% (9/160)
Spinal Protection	
Spinal CSF drainage	53.8% (86/160)
Implantation Zone of Proximal Component	
Zone 0	0% (0/157)
Zone 1	0% (0/157)
Zone 2	31.2% (53/157)
Zone 3	46.5% (73/157)
Zone 4	22.3% (35/157)
LSA Coverage	
Complete	27.4% (43/157)
Partial	5.1% (8/157)
None	67.5% (106/157)

[1] m = numbers in category, n = number of known values.
[2] Not mutually exclusive.

10.1.10 Safety and Effectiveness Results

Table 10-16 presents the key outcomes of the Valiant Test Group and the Talent Control Group; detailed analyses may be found in the following sections.

Table 10-16: Summary of Key Outcomes - Valiant Test Group and Talent Control Group – VALOR II

	Total Number of Subjects Reaching Follow-up		Aneurysm Rupture		Conversion to Surgical Repair		Death		Aneurysm Related Mortality[1]		Major Adverse Event[2]	
	Test N	Control N	Test N	Control N	Test N	Control N	Test N (%)	Control N (%)	Test N (%)	Control N (%)	Test N (%)	Control N (%)
Intra-operative	160	195	0	0	0	0	1 (0.6%)	0	1 (0.6%)	0	29 (18.1%)	55 (28.2%)
≤30 Days[3]	160	195	0	0	0	0	5 (3.1%)	4 (2.1%)	5 (3.1%)	4 (2.1%)	61 (38.1%)	80 (41.0%)
≥ 31 to 365 Days	151	192	0	1 (0.5%)	0	1 (0.5%)	14 (9.6%)	27 (14.4%)	0	2 (1.1%)	34 (23.3%)	62 (33.2%)
0 to 365 Days	151	192	0	1 (0.5%)	0	1 (0.5%)	19 (12.6%)	31 (16.1%)	5 (3.3%)	6 (3.1%)	75 (48.7%)	103 (53.6%)
Kaplan-Meier Summaries			Freedom from Aneurysm Rupture		Freedom from Conversion		Probability of Survival		Freedom from Aneurysm Related Death		Freedom from Major Adverse Event	
12 Month Kaplan-Meier			100%	99.4%	100%	99.4%	87.7%	83.9%	96.9%	96.9%	52.8%	46.8%

Test = Valiant Thoracic

Control = Talent Thoracic

[1] For the Valiant Test Group, ARM is defined as any death occurring within 30 days from initial implantation or occurring as a consequence of an aneurysm rupture, a conversion to open repair, or any other secondary endovascular procedure relative to the aneurysm that is being treated by the Valiant Thoracic Stent Graft System as evidenced by CT, angiography, or direct observation at surgery or autopsy. Ultimate adjudication of relatedness of death was made by the Clinical Event Committee (CEC). Excluded are aneurysms in anatomic areas other than the targeted segment treated by the Valiant Thoracic Stent Graft System.

[2] For Major Adverse Events, m is the number of subjects experiencing a MAE within the interval, n is the number of subjects who either experienced at least one MAE or secondary procedure in the interval or were followed for at least 337 days (Test) or 335 days (Control).

[3] Subjects who experienced events at the time of the procedure were also included in the interval ≤ 30 days post implantation.

10.1.11 Safety Results

10.1.11.1 Primary Safety Objective

The primary safety objective for the Valiant Test Group was achieved. The analysis of safety was based on the ITT cohort of 151 patients available for the 12 month evaluation. Important safety outcomes for this study are presented below in **Table 10-17** to **Table 10-19**. The upper endpoint of the calculated adjusted odds ratio of all-cause mortality within 12 months was 1.18, which was less than the non-inferiority margin of 2.25; therefore, the null hypothesis was rejected and the primary safety objective was achieved.

Table 10-17: Summary of Primary Safety Endpoint – ITT Population - VALOR II

Primary Safety Endpoint: All-Cause Mortality at 12 Months	% (m/n)[1] (upper endpoint of 1-sided 95% CI)	Odds Ratio (upper endpoint of 1-sided 95% CI)[2]	p-value for non-homogeneity
Valiant Test Group	12.6% (19/151) (17.9%)	0.70 (1.18)	0.719
Talent Control Group	16.1% (31/192) (21.2%)		

[1] The numerator m is the number of ITT subjects who died within 365 days; the denominator n is the number of ITT subjects followed through at least 337 days.

[2] The non-inferiority test was performed using the Cochran-Mantel-Haenszel (CMH) test to adjust for SVS scores of (0,1) versus (2, 3). The required assumption of homogeneity among the odds ratios defined by the SVS score strata was statistically tested using the Breslow-Day test.

A survival analysis was performed on the rate of all-cause mortality within 12 months for both the Valiant Test Group and the Talent Control Group. The results are presented in **Figure 10-1** and **Table 10-18**.

Figure 10-1: Kaplan-Meier Curve of Freedom from All-Cause Mortality at 12 Months - VALOR II

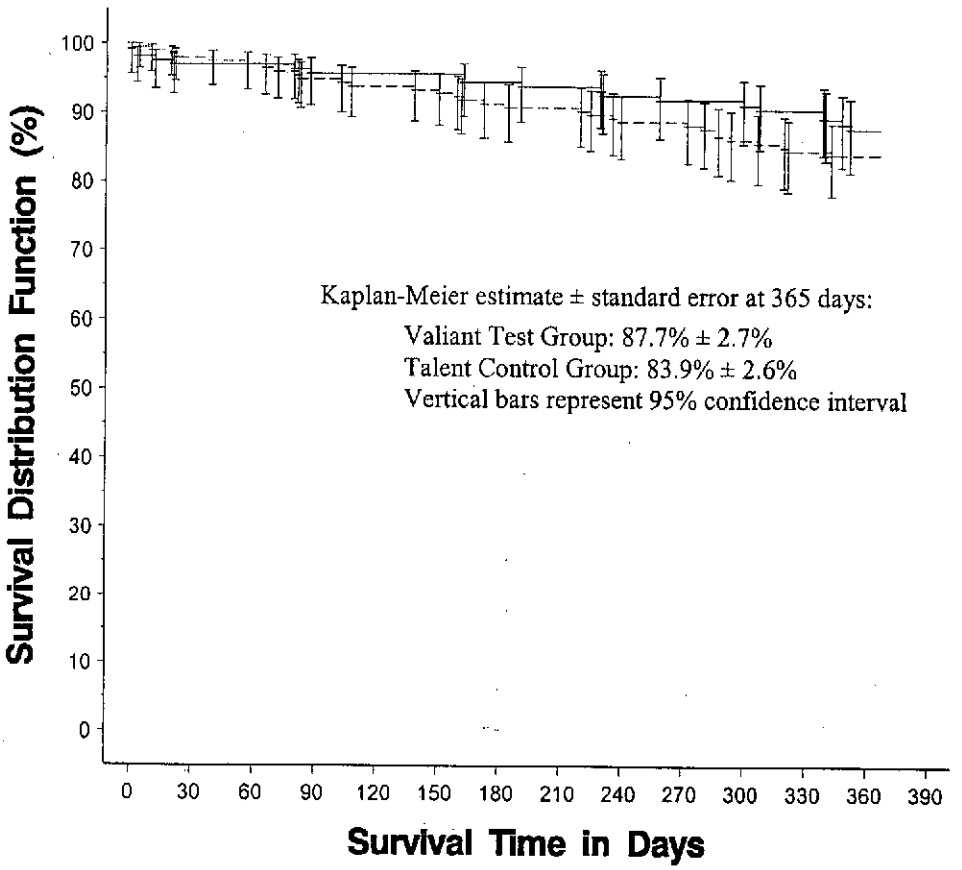


Table 10-18: Kaplan-Meier Estimates of Freedom from All-Cause Mortality within 12 Months - Valiant Test Group and Talent Control Group – VALOR II

	Valiant Test Group			Talent Control Group		
Days	**0 to 30**	**31 to 183**	**184 to 365**	**0 to 30**	**31 to 183**	**184 to 365**
No. at Risk[1]	160	155	150	195	190	176
No. of Events	5	4	10	4	13	14
No. Censored[2]	0	1	22	1	1	1
Kaplan-Meier Estimate[3]	96.9%	94.4%	87.7%	97.9%	91.2%	83.9%
(2-sided 95% CI)[3]	(92.7%, 98.7%)	(89.5%, 97%)	(81.3%, 92%)	(94.6%, 99.2%)	(86.3%, 94.5%)	(78%, 88.4%)
Standard Error[3]	1.4%	1.8%	2.7%	1%	2%	2.6%

[1] Number of subjects at risk at the beginning of an interval.
[2] Subjects are censored because their last follow-up has not reached the end of the time interval. Censored subjects will include those who withdraw or are lost to follow-up.
[3] Kaplan-Meier estimate and standard error, and 95% confidence interval were calculated at the end of a time interval.

10.1.11.2 Aneurysm-Related Mortality (ARM) within 12 Months

Five deaths within 365 days were adjudicated by the CEC to be aneurysm-related (5/151, 3.3%). All five aneurysm-related deaths occurred within the first 30 days and were classified as aneurysm-related per protocol. There were no additional aneurysm-related deaths after 30 days. A survival analysis revealed freedom from ARM within 12 months was 96.9% with a standard error of 1.4% (**Figure 10-2** and **Table 10-19**).

Figure 10-2: Kaplan-Meier Curve of Freedom from Aneurysm-Related Mortality within 12 Months - VALOR II

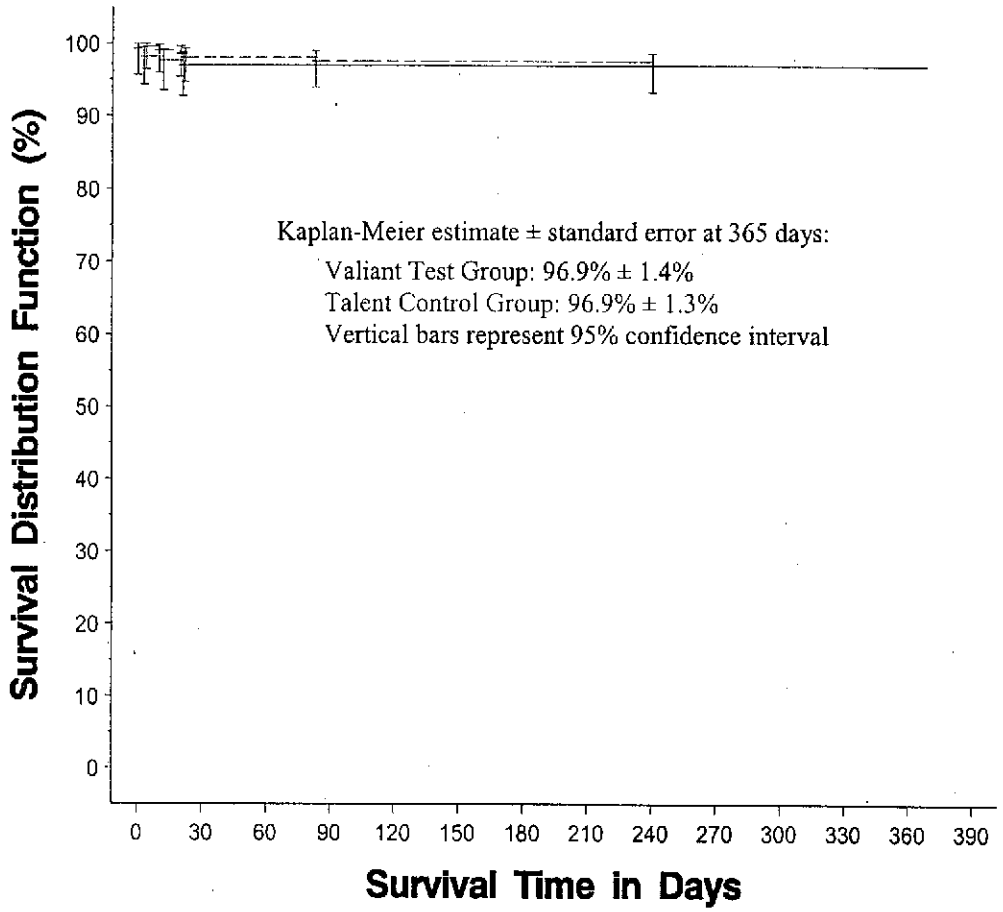


Table 10-19: Kaplan-Meier Estimates of Freedom from Aneurysm-Related Mortality within 12 Months - Valiant Test Group and Talent Control Group – VALOR II

	Valiant Test Group			Talent Control Group		
Days	**0 to 30**	**31 to 183**	**184 to 365**	**0 to 30**	**31 to 183**	**184 to 365**
No. at Risk[1]	160	155	150	195	190	176
No. of Events	5	0	0	4	1	1
No. Censored[2]	0	5	32	1	13	14
Kaplan-Meier Estimate[3]	96.9%	96.9%	96.9%	97.9%	97.4%	96.8%
(2-sided 95% CI)[3]	(92.7%, 98.7%)	(92.7%, 98.7%)	(92.7%, 98.7%)	(94.6%, 99.2%)	(93.9%, 98.9%)	(93.1%, 98.6%)
Standard Error[3]	1.4%	1.4%	1.4%	1%	1.1%	1.3%

[1] Number of subjects at risk at the beginning of an interval.
[2] Subjects are censored because their last follow-up has not reached the end of the time interval. Censored subjects will include those who withdraw, are lost to follow-up or die from causes adjudicated to be unrelated to the aneurysm.
[3] Kaplan-Meier estimate and standard error, and 95% confidence interval were calculated at the end of a time interval.

10.1.11.3 Secondary Safety Endpoints

A summary of secondary safety endpoints is presented in **Table 10-20.**

Table 10-20: Summary of Secondary Safety Endpoints

Secondary Endpoints	Valiant Test Group % (m/n)	Talent Control Group % (m/n)
Within 30 days:		
Perioperative mortality[1]	3.1% (5/160)	2.1% (4/195)
Paraplegia[1]	0.6% (1/160)	1.5% (3/195)
Paraparesis[1]	1.9% (3/160)	7.2% (14/195)
One or more Major Adverse Events (MAE)[1]	38.1% (61/160)	41% (80/195)
Within 12 months:		
Aneurysm-related mortality[1]	3.3% (5/151)	3.1% (6/192)
Aneurysm rupture[1]	0% (0/154)	0.5% (1/192)
Conversion to open surgical repair[2]	0% (0/154)	0.5% (1/192)
One or more Major Adverse Events (MAE)[1]	48.7% (75/154)	53.6% (103/192)
[1]CEC reported [2]Site reported		

Perioperative mortality

One subject died due to an aortic rupture at the time of procedure. The rupture occurred at the paradiaphramatic aorta, distal to the aneurysm, during advancement of the stent graft system in a subject with severe tortuosity of the thoracic aorta. One subject died following an acute dissection of the ascending aorta 3 days post procedure. An autopsy revealed a dissection extending from a point 1-2 cm proximal to the stent graft to the heart. Three other subjects expired due to pneumonia, respiratory failure, and multisystem organ failure.

Paraplegia

One subject (1/160, 0.6%) experienced paraplegia 1 day following implant. The subject continues to be active in the trial albeit with permanent adverse sequelae.

Paraparesis

Three subjects (3/160, 1.9%) experienced paraparesis within 30 days of implant. Two of the 3 subjects continue to be active in the study, one with ongoing paraparesis and the other with paraparesis resolved 5 days post surgery. The third subject died 21 days post-procedure due to respiratory failure and had continuing paraparesis at time of death.

Major Adverse Events (MAEs)

Please see **Section 10.1.11.4** for information regarding MAEs.

Aneurysm Related Mortality (ARM)

See **Section 10.1.11.2** for information regarding ARM.

10.1.11.4 Major Adverse Events (MAEs)

Adverse events in the Valiant Test Group and the Talent Control Group were categorized by severity as Major Adverse Events (MAEs). MAEs were defined as the occurrence of any of the following:

- Death:
  - due to complications of the procedure, including bleeding, vascular repair, transfusion reaction, or conversion to open surgical TAA repair
  - within 30 days of the baseline implant or surgical procedure
- Respiratory complications (atelectasis / pneumonia, pulmonary embolism, pulmonary edema, respiratory failure)
- Renal complications (renal failure, renal insufficiency)
- Cardiac: MI, unstable angina, new arrhythmia, exacerbation of congestive heart failure (CHF)
- Neurological: new CVA / embolic events, paraplegia / paraparesis
- Gastrointestinal: bowel ischemia
- Major bleeding complication
- Vascular Complications

Table 10-21 below presents a summary of the CEC reported MAEs through 12 months.

Table 10-21: Summary of MAEs within 12 Months - CEC Reported - Valiant Test Group and Talent Control Group - VALOR II

	0-30 days % (m/n)[1]		0-365 days % (m/n)[2]	
Category	VALIANT TEST GROUP	TALENT CONTROL GROUP	VALIANT TEST GROUP	TALENT CONTROL GROUP
Mortality	3.1% (5/160)	2.1% (4/195)	12.6% (19/151)	16.1% (31/192)
Respiratory Complications	9.4% (15/160)	13.3% (26/195)	14.9% (23/154)	24.0% (46/192)
Renal Complications	5.0% (8/160)	6.2% (12/195)	8.4% (13/154)	10.4% (20/192)
Cardiac Complications	15.0% (24/160)	12.3% (24/195)	20.1% (31/154)	21.9% (42/192)
Neurological Complications	5.0% (8/160)	11.8% (23/195)	10.4% (16/154)	16.1% (31/192)
Gastrointestinal Complications	1.3% (2/160)	1.0% (2/195)	2.6% (4/154)	1.6% (3/192)
Major Bleeding Complications	6.9% (11/160)	15.4% (30/195)	7.8% (12/154)	16.7% (32/192)
Vascular Complications	20.6% (33/160)	21.0% (41/195)	24.0% (37/154)	24.5% (47/192)
Any MAE	38.1% (61/160)	41.0% (80/195)	48.7% (75/154)	53.6% (103/192)

[1] m is the number of subjects experiencing a certain event within 30 days, n is the number of ITT subjects.
[2] m is the number of subjects experiencing a certain event at the interval of 0-365 days, n is the number of subjects who either experienced at least one MAE or secondary procedure in the interval or are followed for at least 337 days.

10.1.11.5 Serious Adverse Events (SAEs)

A serious adverse event was defined in conformance with ISO 14155 as any adverse event that led to a death, resulted in a medical or surgical intervention to prevent permanent impairment to a body structure or a body function, or led to a serious deterioration in the health status of a subject that either: resulted in a life-threatening illness or injury; resulted in a permanent impairment of a body structure or body function; required inpatient hospitalization or prolongation of an existing hospitalization. Serious Adverse Events for the Valiant Test Group are described in **Table 10-22**.

Table 10-22: Serious Adverse Events – Valiant Test Group – VALOR II

Category	All SAEs % (m/n)[1]	Procedure-Related SAEs % (m/n)[1]	Device-Related SAEs % (m/n)[1]
Respiratory events			
Pulmonary Complications (General)	17.5% (28/160)	7.5% (12/160)	0.0% (0/160)
Renal events			
Renal Complications (General)	5.6% (9/160)	1.9% (3/160)	0.0% (0/160)
Cardiac events			
Cardiac and Hemodynamic (General)	12.5% (20/160)	1.9% (3/160)	0.0% (0/160)
Cardiac Arrhythmia	1.9% (3/160)	0.0% (0/160)	0.0% (0/160)
Congestive Heart Failure	5.0% (8/160)	0.0% (0/160)	0.0% (0/160)
Myocardial Infarction	2.5% (4/160)	0.6% (1/160)	0.0% (0/160)
Neurological events			
Neurologic(General)	8.1% (13/160)	5.0% (8/160)	0.0% (0/160)
Paraplegia and Paraparesis	1.3% (2/160)	0.6% (1/160)	0.0% (0/160)
Stroke/CVA	2.5% (4/160)	0.6% (1/160)	0.0% (0/160)
TIA	2.5% (4/160)	0.0% (0/160)	0.0% (0/160)
Gastrointestinal events			
Bowel Obstruction	1.9% (3/160)	1.3% (2/160)	0.0% (0/160)
Gastrointestinal (General)	8.8% (14/160)	0.6% (1/160)	0.0% (0/160)
Mesenteric Ischemia	1.3% (2/160)	0.6% (1/160)	0.6% (1/160)
Bleeding events			
Bleeding and Hematogenic	14.4% (23/160)	8.8% (14/160)	0.6% (1/160)
Gastrointestinal Bleed	3.1% (5/160)	0.6% (1/160)	0.0% (0/160)
Vascular events			
Arterial	15.0% (24/160)	6.3% (10/160)	0.6% (1/160)
Arterial Embolism	2.5% (4/160)	1.3% (2/160)	0.0% (0/160)
Arterial Insertion Trauma	2.5% (4/160)	2.5% (4/160)	0.6% (1/160)
Arterial Thrombosis	0.6% (1/160)	0.6% (1/160)	0.0% (0/160)

TAA Rupture	0.0% (0/160)	0.0% (0/160)	0.0% (0/160)
Venous	1.9% (3/160)	1.3% (2/160)	0.0% (0/160)
Device-related events			
Graft Complications (General)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Graft Deployment or Placement Issues	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Graft Endoleak	2.5% (4/157)	0.6% (1/157)	1.9% (3/157)
Graft Infection	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Graft Limb Thrombosis	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Graft Migration	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Graft Stenosis, Occlusion	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Other			
Cancer	3.1% (5/160)	0.0% (0/160)	0.0% (0/160)
Edema (General)	0.0% (0/160)	0.0% (0/160)	0.0% (0/160)
Infection (General)	5.0% (8/160)	1.3% (2/160)	0.0% (0/160)
Sexual Dysfunction(General)	0.0% (0/160)	0.0% (0/160)	0.0% (0/160)
Urologic	3.8% (6/160)	1.3% (2/160)	0.0% (0/160)
Wound Complication (General)	3.8% (6/160)	1.3% (2/160)	0.0% (0/160)
Other	8.8% (14/160)	1.3% (2/160)	0.0% (0/160)
Subjects with One or More Serious Adverse Events	61.9% (99/160)	28.1% (45/160)	5.0% (8/160)

[1] m is the number of subjects experiencing the corresponding event and n is the number of all ITT subjects for all categories except device-related events in which case n is the number of all implanted subjects.

10.1.12 Effectiveness Results

10.1.12.1 Primary Effectiveness Endpoint

Based on an evaluation of the primary effectiveness endpoint, the primary effectiveness objective of the Valiant Test Group study was achieved. The analysis of effectiveness was based on 115 evaluable subjects at the 12-month time point. Important effectiveness outcomes are presented in **Table 10-23** and **Table 10-24**.

The rate of Successful Aneurysm Treatment at 12 months was 97.4%. The lower endpoint of the 1-sided 95% confidence interval was 93.4%, exceeding the performance goal of 80% (**Table 10-23**). There were three subjects considered treatment failures in the Valiant Test Group. Two subjects were found to have aneurysm growth of more than 5 mm and had secondary procedures after 365 days (**Table 10-24**). One subject had a distal type Ib endoleak for which a secondary procedure was recommended at the 12-month visit and subsequently performed after 365 days.

Table 10-23: Primary Effectiveness Endpoint Analysis – Implanted population - VALOR II

Primary Effectiveness Endpoint	Within Expanded Analysis Window % (m/n)[1] (lower endpoint of 1-sided 95% CI)
Successful Aneurysm Treatment at 12 months	97.4% (112/115) (93.4%)

[1] m is the number of subjects confirmed with Successful Aneurysm Treatment; n is the total implanted subjects.

Table 10-24: Change in maximum aneurysm diameter from one month

Change in maximum aneurysm diameter from one month[1]	VALIANT TEST GROUP % (m/n)	TALENT CONTROL GROUP % (m/n)
Increase more than 5 mm[2]	1.7% (2/115)	8.5% (11/129)
Stable (within ±5 mm)	71.3% (82/115)	67.4% (87/129)
Decrease more than 5 mm	27% (31/115)	24% (31/129)

[1] Eligible subjects required CT/MR 1-month and 12-month images depicting location at the proximal and distal end of the stent graft.
[2] One subject had type II endoleak, had two additional endovascular procedures after 365 days, and was alive at the 24-month visit. The other subject had no endoleak per core laboratory at 12 months; a secondary endovascular procedure was performed to reline the graft when the investigational site reported continued aneurysm growth without radiographic evidence of endoleak at the 24-month visit.

10.1.12.2 Secondary Effectiveness Endpoints

The results of the secondary effectiveness endpoint analysis are provided in **Table 10-25.**

Table 10-25: Summary of Secondary Effectiveness Endpoints

Secondary Endpoints	VALIANT TEST GROUP % (m/n)	TALENT CONTROL GROUP % (m/n)
Successful deployment and delivery of the stent graft at implant[1,9]	96.3% (154/160)	99.5% (194/195)
Within 30 days:		
Secondary procedure due to endoleak after discharge[1]	0.6% (1/157)	0% (0/194)
Within 12 months:		
Endoleak at 12 months[2,3]	*13% (13/100)*	*12.2% (15/123)*
Type I	3% (3/100)[4]	4.9% (6/123)
Type II	7% (7/100)[5]	4.9% (6/123)
Type III	1% (1/100)[6]	0% (0/123)
Type IV	0% (0/100)	0% (0/123)
Type V / unknown	2% (2/100)[7]	2.4% (3/123)
Secondary endovascular procedure due to endoleak after 30 days and within 365 days[1]	*0% (0/143)*	*6.5% (12/186)*
Migration of the stent graft at 12 months relative to 1 month[2,3]	*2.9% (3/105)*	*3.9% (4/103)*
Proximal stent graft migration >10 mm proximally	0% (0/105)	0% (0/103)
Proximal stent graft migration >10 mm distally	0% (0/105)	1.9% (2/103)
Distal stent graft migration >10 mm proximally	2.8% (3/105)[8]	1.9% (2/103)
Distal stent graft migration >10 mm distally	0% (0/105)	0% (0/103)
Loss of patency of the stent graft[2, 3]	0% (0/100)	0% (0/107)

[1]Site reported.
[2]Core laboratory reported.
[3]The follow-up windows for these endpoints are similar.
[4]Three subjects had distal type Ib endoleak; 1 subject had a secondary procedure after 365 days, a second subject withdrew consent at day 609 post index procedure, and a third subject had no additional clinical sequelae related to endoleak. Of the 2 active subjects, both were alive at the most recent follow-up visit.
[5]One subject had 2 additional endovascular procedures and was alive at the 24-month visit; 1 subject died of lung cancer at day 593 post index procedure; 1 subject died in a motor vehicle accident at day 679 post index procedure. The other 4 subjects had no clinical sequelae related to endoleak and were alive at the most recent study visit.
[6]One subject had type III endoleak reported by the core laboratory at the 12-month interval. No endoleak was reported by the investigational site though the 24-month visit and the subject had no clinical sequelae related to endoleak. There was no separation of stent graft components. No loss of stent graft integrity was reported by core laboratory, though the 6- and 12-month x-ray images could not be evaluated for stent graft integrity. There was no site-reported loss of stent graft integrity through the 24-month visit.
[7]One subject had endoleak of unknown type resolved at the 24-month visit following reduction of antiplatelet therapy; endoleak of unknown type again noted at the 36-month visit. Another subject had no clinical sequelae related to endoleak of unknown type.
[8]None of these 3 subjects had clinical sequelae related to stent graft migration. Two of the 3 subjects had limited or no remaining stent graft coverage of the distal nonaneurysmal neck.
[9]Defined as attaining vessel access, to insert the delivery catheter and deployment of the graft to the intended treatment site. If the thoracic treatment site cannot be accessed with the delivery catheter, it is considered a technical failure. Six subjects had unsuccessful deployment or delivery. Three of these six subjects did not receive a Valiant device due to access failure. Two other subjects had misaligned deployment, and one subject had an aortic rupture.

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

Table 10-26 below summarizes site-reported device-specific events.

Table 10-26: Device-Specific Adverse Events – Valiant Test Group - VALOR II

Event	Through 1 Month visit % (m/n)[1]	> 1 Month visit to 12 Month visit % (m/n)[1]
Endoleak[2]	17.1% (25/146)	6.9% (9/131)
Type I	3.4% (5/146)	2.3% (3/131)
Type Ia (proximal)	0.7% (1/146)	0.8% (1/131)
Type Ib (distal)	2.7% (4/146)	1.5% (2/131)
Type II	10.3% (15/146)	4.6% (6/131)
Type III[3]	0.7% (1/146)	0.0% (0/131)
Type IV	1.4% (2/146)	0.0% (0/131)
Type V / Unknown	1.4% (2/146)	0.8% (1/131)
Aneurysm enlargement[4]	N/A	3.5% (4/115)
Loss of patency	0.0% (0/146)	0.0% (0/131)
Migration > 10mm from 1 month image	N/A	0.0% (0/143)
Loss of stent graft integrity	0.0% (0/152)	0.0% (0/136)
Lumen obstruction	0.0% (0/146)	0.0% (0/131)
Aneurysm rupture	0.0% (0/157)	0.0% (0/156)

[1] m = number in category; n = number of known values. Time intervals are not mutually exclusive.
[2]Total subjects with endoleak within the interval; site-reported endoleak at 365 days was 3.8% (4/104).
[3]Endoleak noted at discharge, resolved without treatment at 1 month visit. No loss of stent graft integrity was reported by the investigational site.
[4]At 12 month visit relative to 1 month visit.

10.1.13 Sub-Group Analyses

10.1.13.1 By Lesion Type

There was not a statistically significant difference in the primary safety endpoint when results were sorted by lesion type. In the subjects with fusiform aneurysms all-cause mortality within 12 months was 16.3% (16/98) with the upper endpoint of the 1-sided 95% confidence interval being 23.7%. Among subjects with saccular aneurysms/PAU aneurysms, all-cause mortality was 5.7% (3/53) with the upper endpoint of the 1-sided 95% confidence interval being 14.0% (p=0.073). The results of the primary effectiveness endpoint, Successful Aneurysm Treatment at 12 months, were similar when sorted by lesion type. Among those subjects who did not meet the primary effectiveness endpoint, two subjects had a fusiform aneurysm and one subject had a saccular aneurysm/PAU.

10.1.13.2 By Sex/Gender

The study accrued a total of 65 (40.6%) female and 95 (59.4%) male subjects. Information on the gender distribution of thoracic aortic aneurysm (TAA) in the general population was estimated based on a publication by Orandi et al in the Journal of Vascular Surgery.[2] The authors presented the demographics for patients treated with open and endovascular repair of their TAAs from a national administrative database. The percentage of females in this article was 33.1% of the total, 33.9% for open repair, and 30.8% for endovascular repair. The distribution in this study compares favorably. Additionally, the percentage of female subjects enrolled in the VALOR II study was comparable those enrolled in previous endovascular graft studies for treatment of TAA.

The prevalence of fusiform TAA was 62% in the study female population, 66% in males, and 64% in both groups combined. The prevalence of saccular TAA/penetrating ulcer was 38% in the study female population, 34% in males, and 36% 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.

A prospectively defined covariate analysis detected that female gender is a significant predictor of both MAEs (odds ratio 2.94, p = 0.007) and serious MAEs (odds ratio 3.47, p = 0.002) within 12 months. To more carefully evaluate the possible gender-based differences, several sex/gender subset analyses were performed for the safety and effectiveness endpoints.

A total of 61 (40.4%) female and 90 (59.6%) male subjects were evaluable for the primary safety endpoint of all-cause mortality at 12 months. Female and male subjects had similar mortality rates (16.4% and 10.0%, respectively; p=0.32 for difference in rates) with an overall rate of 12.6%. A Kaplan-Meier analysis is presented in **Figure 10-3** and **Table 10-28**.

[2] J Vasc Surg 2009;49:1112-6

Figure 10-3: Kaplan-Meier Curve of Freedom from All-Cause Mortality within 12 Months by Gender – VALOR II

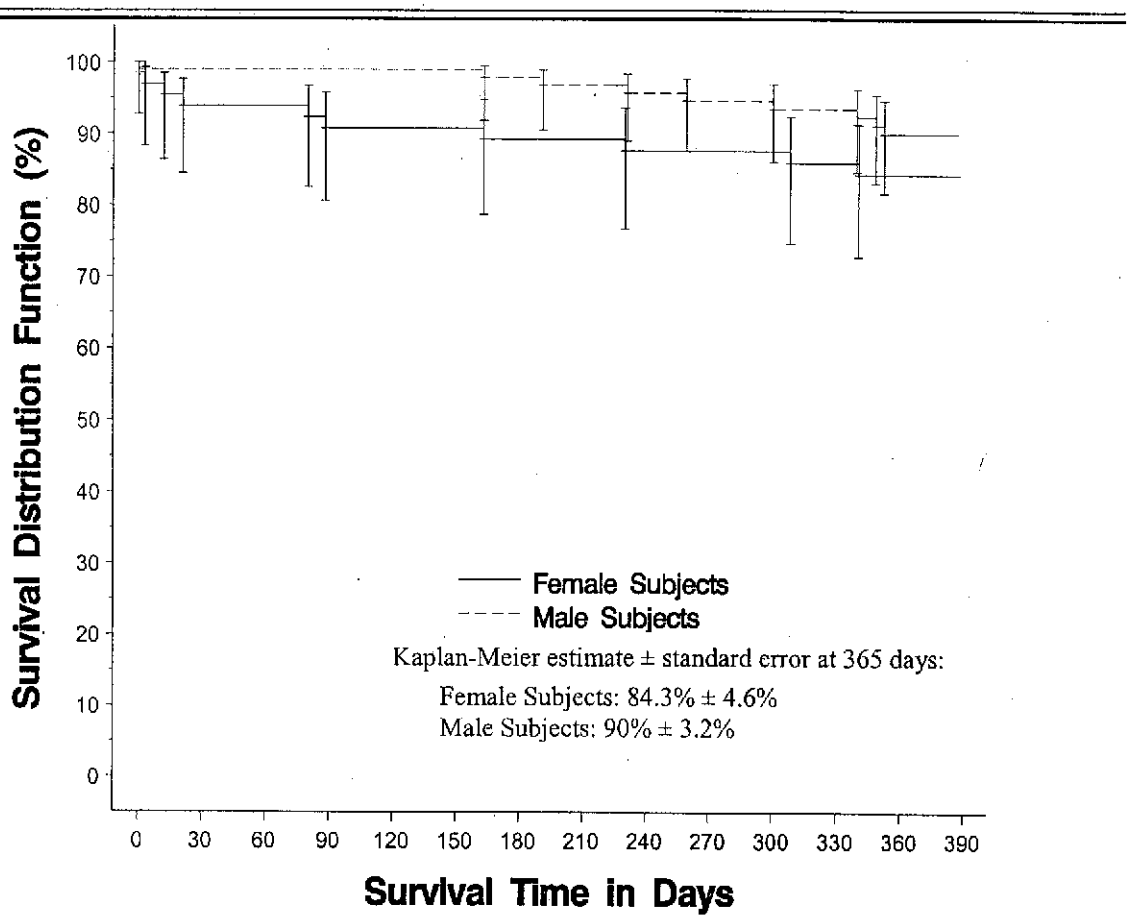


Table 10-28: Kaplan-Meier Estimates of Freedom from All-Cause Mortality within 12 Months by Gender – VALOR II

	Female			Male		
Days	**0 to 30**	**31 to 183**	**184 to 365**	**0 to 30**	**31 to 183**	**184 to 365**
No. at Risk[1]	65	61	58	95	94	92
No. of Events	4	3	3	1	1	7
No. Censored[2]	0	0	10	0	1	12
Kaplan-Meier Estimate[3]	93.9%	89.2%	84.3%	99.0%	97.9%	90.0%
Standard Error[3]	3.0%	1.8%	4.6%	1.1%	1.5%	3.2%

[1] Number of subjects at risk at the beginning of an interval.
[2] Subjects are censored because their last follow-up has not reached the end of the time interval. Censored subjects will include those who withdraw or are lost to follow-up.
[3] Kaplan-Meier estimate and standard error were calculated at the end of a time interval.

A post hoc analysis of primary safety endpoint data was also conducted to assess for homogeneity of treatment effect across sex/gender (using Breslow-Day test). The results

indicated no statistically significant interaction between treatment and sex/gender for the primary safety endpoint. This analysis suggests that it is valid to pool data for males and females, and that the overall results of this study can be generalized to both sexes.

In addition, 44 (38.3%) female and 71 (61.7%) male subjects were evaluable for the primary effectiveness endpoint of successful aneurysm treatment at 12 months. Successful aneurysm treatment rate was 97.7% in females and 97.2% in males (p>0.50 for difference in rates) for an overall rate of 97.4%. These findings indicate similar safety and effectiveness outcomes for males and females.

Finally, endovascular graft specific outcomes were presented separately for male and female subjects, as summarized in Table 10-29.

Table 10-29: Endpoints by Gender - Valiant Test Group - VALOR II[1]

Endpoint	Male % (m/n)[2]	Female % (m/n)[2]
Primary Safety: All-Cause Mortality at 12-Months	10.0% (9/90)	16.4% (10/61)
Primary Effectiveness: Successful aneurysm treatment[3] at 12 months	97.2% (69/71)	97.7% (43/44)
Secondary		
Successful deployment and delivery of the stent graft at implant	95.8% (91/95)	96.9% (63/65)
Within 30 days:		
Perioperative mortality	1.1% (1/95)	6.2% (4/65)
Paraplegia[4]	0.0% (0/95)	1.5% (1/65)
Paraparesis[4]	1.1% (1/95)	3.1% (2/65)
Secondary procedure due to endoleak after discharge[5]	1.1% (1/93)	0.0% (0/64)
One or more Major Adverse Events (MAE)[4]	30.5% (29/95)	49.2% (32/65)
Within 12 months:		
Aneurysm-related mortality[4]	1.1% (1/90)	6.6% (4/61)
Aneurysm rupture[4]	0.0% (0/92)	0.0% (0/62)
Conversion to open surgical repair	0.0% (0/92)	0.0% (0/62)
Endoleak at 12 months[6]	9.7% (6/62)	18.4% (7/38)
Secondary endovascular procedure due to endoleak after 30 days[5]	0.0% (0/87	0.0% (0/56)
Migration of the stent graft at 12 months relative to 1 month[6]	3.1% (2/65)	2.5% (1/40)
Loss of patency of the stent graft[6]	0.0% (0/62)	0.0% (0/38)
One or more Major Adverse Events (MAE)[4]	41.3% (38/92)	59.7% (37/62)

[1] Table resulted from post hoc analysis requested by the FDA
[2] m = numbers in category, n = number of known values
[3] Successful aneurysm treatment is defined as the absence of the following two conditions in subjects who are implanted with a device:
- Aneurysm growth > 5 mm at the 12-month visit relative to the 1-month visit
- Type I and/or Type III endoleak for which a secondary procedure was performed or recommended at or before the 12-month follow-up visit

[4] CEC reported
[5] Site reported
[6] Core lab reported

In summary, women were reasonably represented in the VALOR II study given the prevalence of TAAs in women in the general population and the expected enrollment of female subjects in an endovascular graft study. The results of the prospective and retrospective analyses showed that there may be some differences in the expected event rates for women as compared to men, but critical endovascular graft specific outcomes were comparable for the two genders/sexes. Given these similar outcomes and the expected relatively high rate of major adverse events with open surgical repair, the information provided in the PMA was found adequate to support approval of the device for treatment of fusiform TAA and saccular TAA/penetration ulcers both men and women.

10.1.14 Clinical Utility Data

Clinical utility measures in the Valiant Test Group are presented in **Table 10-27**.

Table 10-27: Clinical Utility Data

Parameter	Valiant Test Group N	Valiant Test Group	Talent Control Group N	Talent Control Group
Subjects requiring transfusion % (m/n)[1]	160	10% (16/160)	194	22.7% (44/194)
Blood loss during procedure (cc) Mean ± SD	153	277.0 ± 468.8	189	371.2 ± 514.4
Duration of procedure (min) Mean ± SD	160	119.7 ± 54.8	194	154.2 ± 76.0
Time in ICU (hours) Mean ± SD	160	66.5 ± 112.3	193	46.8 ± 114.3
Overall hospital stay (days) Mean ± SD	160	6.1 ± 8.9	195	6.4 ± 11.5

[1] m = numbers in category, n = number of known values

10.2 Summary of Supplemental Clinical Information

As the VALOR II clinical study evaluated the Valiant Thoracic Stent Graft with the Xcelerant Delivery System, Medtronic conducted the Valiant Captivia OUS Registry and the Talent Captivia Study to evaluate the Captivia Delivery System. The results of these studies are discussed in **Section 10.2.2** and **Section 10.2.3**.

10.2.1 Comparison of Xcelerant and Captivia Delivery Systems

Subsequent to the enrollment in the pivotal stent graft study presented above, the delivery system was updated from the Xcelerant to the Captivia Delivery System. The Captivia Delivery System is a design iteration of the Xcelerant Delivery System. The primary difference between the two delivery systems is the incorporation of a tip capture mechanism designed to constrain the proximal bare springs of the FreeFlo stent graft until proper positioning has been obtained. The following two studies were conducted to provide confirmatory clinical information to support the engineering evaluation of the modified delivery system.

10.2.2 Valiant Captivia OUS Registry Summary

The Valiant Thoracic Stent Graft with the Captivia Delivery System received CE mark in September 2009. The objective of this ongoing registry is to gather pertinent post-approval clinical data to assess that the Valiant Thoracic Stent Graft with the Captivia Delivery System ("Valiant Captivia") can be used safely and effectively to treat diseases of the descending thoracic aorta in both surgical and non-surgical candidates. Subjects diagnosed with a variety of thoracic aortic diseases were considered candidates for the registry. Subjects who enrolled in the study will be followed for up to three years post-implantation. A 30-day interim analysis was conducted on 50 subjects to assess acute performance of the Captivia Delivery System.

10.2.2.1 Study Population and Subject Accountability

These 50 subjects, hereafter referred to as the Registry Study Group, were enrolled in Europe and Turkey to participate in the Valiant Captivia OUS Registry. Only the 30-day analysis for the Registry Study Group is included. Of the 50 subjects who underwent repair using the Valiant Thoracic Stent Graft with the Captivia Delivery System, 25 (50%) were indicated for thoracic aortic aneurysm (TAA), 20 (40%) were indicated for Type B aortic dissection, and 8 (16%) were classified as "Other". Three of the subjects who are included in the "Other" category also had a concurrent thoracic aortic aneurysm or Type B aortic dissection, and are therefore included in more than one category. Since the acute deliverability of the delivery system is less dependent upon the type of aortic etiology, subjects with dissection and other etiologies were also considered relevant to the assessment.

Three subjects died and one subject was converted to open surgical repair within 30 days. No subjects were lost to follow-up or withdrew consent. Thirty-four of the 45 eligible subjects had a follow-up visit at 30 days post-implant. All of the remaining 11 eligible subjects were alive and underwent clinical evaluations at subsequent follow-up visits.

10.2.2.2 Successful Delivery and Deployment

Delivery and deployment of Valiant Captivia was evaluated at 30-days for the Valiant Captivia OUS Registry. Successful delivery and deployment was defined by deployment of the Valiant Thoracic Stent Graft in the planned location with no unintentional coverage of the left subclavian artery, left common carotid artery and/or brachiocephalic artery and with the removal of the delivery system. Successful delivery and deployment was achieved in all 50 subjects in the Registry Study Group, yielding a rate of 100% (95% CI 92.9%-100%) (**Table 10-28**).

Table 10-28: Successful Delivery and Deployment - Valiant Captivia OUS Registry

Primary Endpoint	% (m/n) [95% CI]
Successful delivery and deployment at implant	100% (50/50) [92.9%-100%]

10.2.2.3 Secondary Study Endpoints

The secondary endpoints for the 30-day analysis included both procedural complications and clinical outcomes. A summary of secondary endpoints is presented in **Table 10-29.**

Three subjects died within 30 days of the index procedure. The CEC adjudicated two of the three deaths as due to causes other than cardiac or neurological. The first subject was treated for a symptomatic TAA and died from multi-organ failure. The second subject was treated for a TAA and subsequently died from a ruptured abdominal aortic aneurysm (AAA). This subject, who had risk factors for neurologic complications, also experienced paraplegia that resolved two days later after placement of a lumbar drain. A third death occurred in a subject with a history of Marfan's syndrome and previous thoracic aortic dissection. The death was adjudicated as being related to the lesion in an acute complicated type B dissection.

One subject required a conversion to open surgery following aneurysm rupture at the index procedure. The subject became unstable after the first stent graft was successfully delivered and deployed. The subject underwent a thoracotomy and a second stent graft was placed, successfully sealing off the rupture site. The subject was alive at 30 days.

Two subjects, including the subject with Marfan's syndrome noted above, experienced aortic dissection within 30 days of the index procedure. Both events occurred in subjects treated for Type B aortic dissection.

Table 10-29: Secondary Endpoints - Valiant Captivia OUS Registry

Secondary Endpoints	% (m/n)
Misaligned Deployment at Index Procedure (Site reported)	0% (0/50)
Aortic Perforation at Index Procedure	0% (0/50)
Death	
All Cause Mortality Within 30 Days	6% (3/50)
Paraplegia/Paraparesis	
Paraplegia Within 30 Days post-implantation	2% (1/50)
Paraparesis Within 30 Days post-implantation	0% (0/50)
Secondary Endovascular Procedure due to Endoleak	
Within 30 days post-implantation	0% (0/50)

One or more Major Adverse Events (MAE)	
Any MAEs within 30 days post-implantation	24% (12/50)
One or more Serious Major Adverse Events (SMAE)[2]	
Any serious MAEs within 30 days post-implantation	22% (11/50)

[1]Death and rupture were adjudicated by CEC. All other categories were reported by the investigational sites.
[2]A serious MAE is defined as a MAE that was identified as a Serious Adverse Event (SAE) by the Investigator.

10.2.3 Talent Captivia Study Summary

In another study of the Captivia Delivery System, 10 subjects were enrolled in an open arm of the US IDE evaluation of the Talent Thoracic Stent Graft System in the treatment of patients with thoracic aortic disease (G980116/S270). Disease etiologies included fusiform aneurysms and saccular aneurysms/penetrating ulcers of the descending thoracic aorta. A 30-day analysis was conducted on 10 subjects to assess acute performance of the Captivia Delivery System. The data collected from this evaluation was considered relevant because the delivery systems for use with Talent and Valiant stent grafts are essentially identical in design and possess the same principles of operations.

10.2.3.1 Study Population and Subject Accountability

These 10 subjects with descending aortic aneurysms were enrolled at 4 sites in the United States to participate in the Talent Captivia Study. Of the 10 enrolled subjects, 1 subject died and another failed to receive a stent graft. No subject was lost to follow-up or withdrew consent.

10.2.3.2 Successful Delivery and Deployment

Delivery and deployment of the Talent Thoracic Stent Graft with the Captivia Delivery System was assessed. Implantation of the device was successful in 9 of 10 enrolled subjects, yielding a rate of 90% (95% CI 55.5%-99.7%). Successful delivery and deployment was defined as attaining vessel access to insert the delivery catheter and deployment of the graft to the intended treatment site. One enrolled subject did not receive a Talent Thoracic Stent Graft, as the Captivia Delivery System could not reach the targeted lesion due to severe angulation of the thoracic aortic arch. This subject was converted to an open surgical repair.

10.2.3.3 Secondary Study Endpoints

The secondary endpoints for the 30-day analysis included both procedural complications and clinical outcomes. A summary of secondary endpoints is presented in **Table 10-30.**

One subject died within 30 days of the index procedure and was considered an aneurysm related death. The CEC adjudicated the death as due to cardiac causes. This subject and one other experienced paraplegia within 30 days. Both subjects who experienced paraplegia had significant risk factors for spinal cord ischemia.

Table 10-30: Secondary Endpoints - Talent Captivia Study

Secondary Endpoints	% (m/n)
Misaligned deployment at index procedure[2]	0% (0/9)
Aortic perforation at index procedure[2]	0% (0/9)
Death	
All-cause mortality within 30 days[1]	10% (1/10)
Paraplegia/Paraparesis	
Paraplegia within 30 days[1] Paraparesis within 30 days[1]	20% (2/10) 0% (0/10)
Secondary endovascular procedure due to Endoleak	
within 30 days post-implantation[2]	0% (0/10)
One or more Major Adverse Events (MAE)	
within 30 days post-implantation[1]	40% (4/10)
One or more serious Major Adverse Events (serious MAE)	
within 30 days post-implantation[1]	40% (4/10)

[1]Clinical Events Committee reported
[2]Site reported

11.0 Overall Conclusions Drawn from Pre-Clinical and Clinical Studies

Comprehensive pre-clinical bench testing was performed on the Valiant Thoracic Stent Graft with the Captivia Delivery System in accordance with national and international standards and guidance documents. The testing demonstrated that the Valiant Thoracic Stent Graft with the Captivia Delivery System met its performance and design specifications.

Preclinical *in vivo* animal testing was conducted on 16 animals in order to evaluate the acute and chronic performance of the Valiant Thoracic Stent Graft with the Xcelerant Delivery System. The studies were performed to evaluate deployment, stent graft integrity, and histopathological response in ovine test systems for up to six months. The results support the expected safety and performance of the Valiant Thoracic Stent Graft.

Biocompatibility testing was performed on the Valiant Thoracic Stent Graft with the Captivia Delivery System in accordance with applicable standards. All testing met the requirements as specified in the applicable standard, ensuring the finished device was biocompatible.

Sterilization, packaging, and shelf life testing were performed on the Valiant Thoracic Stent Graft with the Captivia Delivery System. The sterilization testing demonstrated that the Valiant Thoracic Stent Graft with the Captivia Delivery System maintains a Sterility Assurance Level of 10^{-6}. The results of shelf life testing confirmed that the Valiant Thoracic Stent Graft with the Captivia Delivery System maintained functionality throughout its 2-year shelf life, and the packaging testing demonstrated that the packaging adequately protected the device throughout its 2-year shelf life.

The primary safety and effectiveness objectives were achieved in the VALOR II clinical study. The primary safety data from the VALOR II study showed that all cause mortality within 12 months for the Valiant Test Group was similar to that for the Talent Control Group. Aneurysm-related mortality was limited to five subjects within 30 days of the procedure.

Effectiveness of aneurysm treatment using the Valiant Thoracic Stent Graft at 12 months, which was included the absence of aneurysm growth or a significant Type I and/or Type III endoleak was 97.4%. There were no losses of device integrity or patency, ruptures or conversions to open surgical repair within 12 months. Three patients had distal stent graft migration and three had distal Type I endoleaks reported by the Core Lab. One patient had a Type III endoleak reported by the Core Lab. These results compared favorably to those for the Talent Control Group.

Confirmatory clinical information on the Captivia Delivery System was provided by two separate clinical studies, the Valiant Captivia OUS Registry and the Talent Captivia Study. The Valiant Thoracic Stent Graft was successfully delivered and deployed using the Captivia Delivery System in all 50 patients included in the report for the Valiant Captivia OUS Registry. Additionally, the Talent Thoracic Stent Graft was successfully delivered and deployed using the Captivia Delivery System in 9 of the 10 patients included in the report for the Talent Captivia Study. Both studies provide collective evidence in support of the Captivia Delivery System.

Based on the data presented, the Valiant Thoracic Stent Graft with the Captivia Delivery System has been demonstrated to be safe and effective in the treatment of subjects with fusiform aneurysms and saccular aneurysms/penetrating ulcers of the descending thoracic aorta who are candidates for endovascular repair. However, the Valiant Thoracic Stent Graft System is contraindicated in patients who have a condition that threatens to infect the graft and in patients who are sensitive to or have allergies to the device materials.

The safety and effectiveness of the Valiant Thoracic Stent Graft with the Captivia Delivery System has not been evaluated in the following patient situations or populations:

- The patient requires planned placement of the *covered* proximal end of the stent graft requires implant to occur in Zone 0 or Zone 1. See Figure 3.

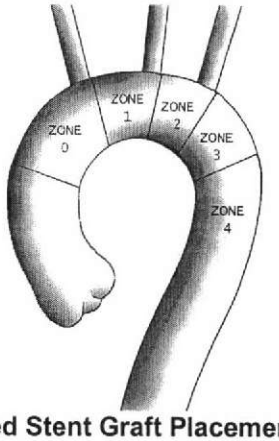


Figure 11-1: Covered Stent Graft Placement Zones

- The patient's access vessel, as determined by treating physician, precludes safe insertion of the delivery system.

  Note: Iliac conduits may be used to ensure the safe insertion of the delivery system.
- The patient has a thoracic aneurysm with a contained rupture.
- The patient has connective tissue disease (for example, Marfan syndrome or medial degeneration).
- The patient has received a previous stent or stent graft or previous surgical repair in the descending thoracic aortic area.
- The patient will be undergoing a concommitant surgical or endovascular treatment of an infrarenal aortic aneurysm.
- The patient has a history of bleeding diathesis or coagulopathy, or refuses blood transfusions.
- The patient has had a cerebrovascular accident (CVA) within 3 months of the procedure.
- The patient has a known hypersensitivity or contraindication to anticoagulants or contrast media, which is not amenable to pretreatment.
- The patient has a significant or circumferential aortic mural thrombus, which could compromise fixation and seal of the implanted stent graft.
- The patient is a pregnant female.
- The patient is less than 18 years old.
- The patient has a dissection or transection of the thoracic aorta.

12.0 Panel Recommendation

In accordance with 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 System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

13.0 CDRH Decision

FDA issued an approval order on April 1, 2011. The final conditions of approval cited in the approval order are described below.

1. You will provide a clinical update to physician users at least annually. At a minimum, this update will include, for your 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. The clinical updates for physician users and the information supporting the updates must be provided in the ODE annual report.

2. In addition to the Annual Report requirements outlined above, you will provide the following data in a separate post-approval study report. You will perform a post-approval study to evaluate the longer-term safety and effectiveness of the Valiant Thoracic Stent Graft with the Captivia Delivery System through five years of implantation. The primary endpoint for this study is freedom from aneurysm-related mortality at 5 years. Aneurysm-related mortality is defined as:

   > Death from rupture of the fusiform aneurysm or saccular aneurysm/penetrating ulcer or from any procedure intended to treat the fusiform aneurysm or saccular aneurysm/penetrating ulcer. If a death occurred within 30 days of any procedure intended to treat the fusiform aneurysm or saccular aneurysm/penetrating ulcer, then it is presumed to be aneurysm related.

   This study is expected to include the 160 patients enrolled in the VALOR II clinical study. At 1 month, 12 months, and, at each annual visit to five (5) years, a chest x-ray, CT scan with and without contrast, and 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.

   Upon completion of this post-approval study, you must provide a supplement with revised labeling that reflects the study findings.

The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

14.0 Approval Specifications

Directions for Use: See labeling.

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

Post Approval Requirements and Restrictions: See approval order.