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Draft Summary of Safety and Effectiveness Data

1. General Information

Device Generic Name: Endovascular Graft and Delivery System

Device Trade Name: Zenith[?] AAA Endovascular Graft and the H&L-B One-Shot[?] Introduction System

Applicant's Name and Address: Cook Incorporated
750 North Daniels Way
Bloomington, Indiana 47404

PMA Application Number: P020018

2. Indications and Usage

The Zenith[?] AAA Endovascular Graft with the H&L-B One-Shot[?] Introduction System and ancillary components is indicated for the endovascular treatment of patients with abdominal aortic, aorto-iliac or iliac aneurysms having morphology suitable for endovascular repair, including:

- ?? Adequate iliac/femoral access (?7.5 mm)
- ?? Non-aneurysmal infrarenal neck length of at least 15 mm
- ?? Neck diameter measured outer wall to outer wall of no greater than 28 mm and no less than 18 mm
- ?? Iliac artery distal fixation site greater than 10 mm in length and no greater than 20 mm in diameter (measured outer wall to outer wall)
- ?? One of the following:
 - ?? An abdominal aortic aneurysm with a diameter ?4 cm
 - ?? An iliac aneurysm with diameter ?3.5 cm
 - ?? Aortic, aorto-iliac, or iliac aneurysm with a history of growth ?0.5 cm per year

3. Contraindications

MRI use is contraindicated. MRI procedures should not be performed at any time after implantation of the Zenith[?] AAA Endovascular Graft.

4. Warnings and Precautions

See *Warnings and Precautions* in the labeling (Instructions for Use).

5. Device Description

The Cook Zenith[?] AAA Endovascular Graft (Zenith) is a modular system of components consisting of multiple endovascular graft configurations and additional ancillary pieces. All components in this system use common self-expanding Z-stents sewn to traditional, currently marketed Dacron graft material with currently marketed suture material.

A configuration of the main endovascular graft is selected based upon patient anatomy and implanted to exclude the aneurysmal chamber. The various ancillary components can be used to correct for inaccuracies in device size selection or to compensate for difficult anatomy encountered during the implant procedure. These ancillary components include aortic main body extenders, iliac leg extenders, converters, and occluders.

5.1. Zenith Main Endovascular Graft

The main endovascular graft (depicted in Figure 5.1-1) is a modular three component device (an aortic main body and two iliac legs), the sizes of which can be selected to match a variety of patient anatomies and specific treatment goals. These components are manufactured in a number of standard stock sizes and are supplied sterile, preloaded onto delivery systems, and ready for use with minimal pre-deployment preparation. Currently available main bodies are listed in Table 5.1-1. Currently available iliac legs are listed in Table 5.1-2.

The bifurcated main body component, comprised of an aortic section having an uncovered, barbed suprarenal stent at the proximal end and one long iliac limb and one short contralateral iliac limb at the distal end, is introduced via one iliac artery. An iliac leg is delivered via the contralateral iliac artery, and is docked with the short limb of the main body to form a continuous channel into the contralateral iliac artery. A second iliac leg is delivered via the ipsilateral iliac artery, and is docked with the long limb of the main body to form a continuous channel into the ipsilateral iliac artery.

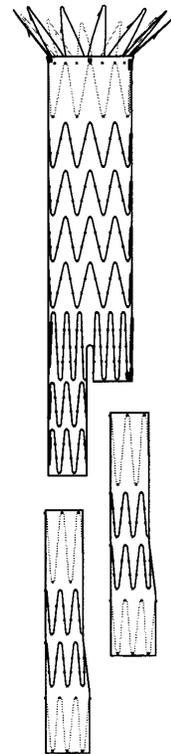


Figure 5.1-1. Zenith[?] AAA Endovascular Graft

Table 5.1-1. Catalog/reorder numbers for Zenith bifurcated main bodies

TFB-1 104 mm x diam.	TFB-2 118 mm x diam.	TFB-3 133 mm x diam.	TFB-4 147 mm x diam.	TFB-5 162 mm x diam.
TFB-1-22	TFB-2-22	TFB-3-22	TFB-4-22	TFB-5-22
TFB-1-24	TFB-2-24	TFB-3-24	TFB-4-24	TFB-5-24
TFB-1-26	TFB-2-26	TFB-3-26	TFB-4-26	TFB-5-26
TFB-1-28	TFB-2-28	TFB-3-28	TFB-4-28	TFB-5-28
TFB-1-30	TFB-2-30	TFB-3-30	TFB-4-30	TFB-5-30
TFB-1-32	TFB-2-32	TFB-3-32	TFB-4-32	TFB-5-32

Note: Catalog number indicates body length category (1-5) and diameter (mm).

Table 5.1-2. Catalog/reorder numbers for Zenith iliac legs

8 mm	10 mm	12 mm	14 mm	16 mm
TFLE-8-37	TFLE-10-37	TFLE-12-37	TFLE-14-37	TFLE-16-37
TFLE-8-54	TFLE-10-54	TFLE-12-54	TFLE-14-54	TFLE-16-54
TFLE-8-71	TFLE-10-71	TFLE-12-71	TFLE-14-71	TFLE-16-71
TFLE-8-88	TFLE-10-88	TFLE-12-88	TFLE-14-88	TFLE-16-88
TFLE-8-105	TFLE-10-105	TFLE-12-105		
TFLE-8-122	TFLE-10-122	TFLE-12-122		
18 mm	20 mm	22 mm	24 mm	none
TFLE-18-37	TFLE-20-37	TFLE-22-37	TFLE-24-37	
TFLE-18-54	TFLE-20-54	TFLE-22-54	TFLE-24-54	
TFLE-18-71	TFLE-20-71	TFLE-22-71	TFLE-24-71	
TFLE-18-88	TFLE-20-88	TFLE-22-88	TFLE-24-88	

Note: Catalog number indicates distal diameter (mm) x length (mm).

Zenith components are constructed using full-thickness woven Dacron graft material sewn to self-expanding stainless steel Cook-Z³ stents with standard surgical suture. Components are fully-stented, providing stability and the expansile force necessary to open the lumen of the graft during deployment. Additionally, they provide the necessary attachment and seal of the Zenith to the vessel wall. Cook-Z³ stents are located on the inside of the graft material at the locations of vessel seal sites and portions of the overlap joints, but are located on the outside of the remainder of the graft to allow the lumen to be as smooth as possible. There is an uncovered stent at the proximal end of the graft, shown in Figure 5.1-1, which features 10-12 barbs (depending upon graft diameter) for positive attachment to the vessel wall. This uncovered stent is securely attached with multiple sutures at each graft material/stent attachment site.

The Cook-Z³ stents offer excellent visibility during deployment. In addition, radiopaque markers are located on the most lateral aspect of the short limb of the main body to facilitate proper graft orientation with respect to the contralateral iliac artery. There are also radiopaque markers on the most proximal aspect of the graft material to allow proper longitudinal adjustment of the graft relative to the renal arteries.

5.2. Zenith Ancillary Components

The Zenith ancillary components consist of aortic main body extenders, iliac leg extenders, and a set of converters and occluders. The aortic main body extenders and iliac leg extenders can be used to provide additional length to their respective portions of the endovascular graft. The converters and occluders can be used to convert a bifurcated graft into an aorto-uni-iliac graft, if necessary. Examples of each ancillary component are shown in Figure 5.2-1.

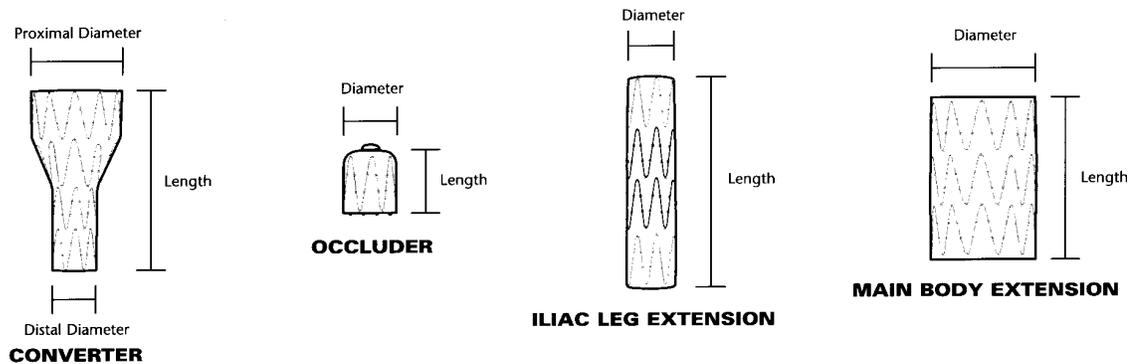


Figure 5.2-1. Zenith Ancillary Components

Ancillary components are manufactured in a number of standard stock sizes and are supplied sterile, preloaded onto their delivery systems, and ready for use with minimal pre-deployment preparation. Currently available ancillary components are listed in Table 5.2-1.

Table 5.2-1. Catalog/reorder numbers for Zenith ancillary components

Converters	Occluders	Iliac Leg Extenders	Main Body Extenders
ESC-24-12-80	ESP-14-20	ESLE-8-55	ESBE-22-36
ESC-28-12-80	ESP-16-20	ESLE-10-55	ESBE-24-36
ESC-32-12-80	ESP-20-20	ESLE-12-55	ESBE-26-36
	ESP-24-20	ESLE-14-55	ESBE-28-36
		ESLE-16-55	ESBE-30-36
		ESLE-18-55	ESBE-32-36
		ESLE-20-55	
		ESLE-22-55	
		ESLE-24-55	

Note: Catalog number for converters indicates proximal diameter (mm), distal diameter (mm), and length (mm). Catalog number for occluders and extenders indicates diameter (mm) x length (mm).

5.3. H&L-B One-Shot? Introduction System Description

The Zenith[?] AAA Endovascular Graft is shipped preloaded onto the H&L-B One-Shot? Introduction System. This delivery system is designed for ease of use with minimal preparation. It has a simple sequential deployment method with built-in features to provide continuous control of the endovascular graft throughout the deployment procedure. The H&L-B One-Shot? Introduction System enables precise positioning and has the ability to readjust the final graft position before deploying the barbed suprarenal Z-stent.

Modular components of the Zenith[?] AAA Endovascular Graft are preloaded onto the H&L-B One-Shot? Introduction System. There are four sizes of delivery systems used for deployment (14, 16, 18, and 20 Fr). All sizes of each modular Zenith component (main bodies, main body extenders, iliac legs, iliac leg extenders, converters, and occluders) are deployed using one of these four delivery system sizes. All delivery systems are operated by retracting the sheath over the graft positioner to expose the preloaded, self-expanding component. Additional delivery system features are operated, as appropriate. All systems are compatible with an 0.035 inch wire guide.

5.3.1. 18 Fr and 20 Fr Delivery Systems Description

The 18 Fr and 20 Fr H&L-B One-Shot? Introduction Systems are used to deploy various sizes of main bodies, main body extenders, and converters in the Zenith family of modular components. Table 5.3.1-1 lists the catalog/reorder numbers of the main bodies deployed using these two sizes of H&L-B One-Shot? Introduction Systems. Zenith main bodies ranging in diameter from 22 - 26 mm are deployed using the 18 Fr system. Zenith main bodies ranging in diameter from 28 - 32 mm are deployed using the 20 Fr system.

Table 5.3.1-1. Zenith bifurcated main bodies deployed with 18 Fr and 20 Fr systems

H&L-B One-Shot? Introduction System	Main Body ¹				
	1 (104 mm)	2 (118 mm)	3 (133 mm)	4 (147 mm)	5 (162 mm)
18 Fr System	TFB-1-22	TFB-2-22	TFB-3-22	TFB-4-22	TFB-5-22
	TFB-1-24	TFB-2-24	TFB-3-24	TFB-4-24	TFB-5-24
	TFB-1-26	TFB-2-26	TFB-3-26	TFB-4-26	TFB-5-26
20 Fr System	TFB-1-28	TFB-2-28	TFB-3-28	TFB-4-28	TFB-5-28
	TFB-1-30	TFB-2-30	TFB-3-30	TFB-4-30	TFB-5-30
	TFB-1-32	TFB-2-32	TFB-3-32	TFB-4-32	TFB-5-32

1 Catalog number indicates body number and diameter (mm). The length of each body number is given in parentheses.

Table 5.3.1-2 lists the catalog/reorder numbers of the main body extenders and converters deployed using these two sizes of H&L-B One-Shot? Introduction Systems. Zenith main body extenders and converters ranging in diameter from 22 - 26 mm are deployed using the 18 Fr system. Zenith main body extenders and converters ranging in diameter from 28 - 32 mm are deployed using the 20 Fr system. In addition, Table 5.3.1-2 lists the iliac leg extenders deployed with the 18 Fr delivery system.

Table 5.3.1-2. Zenith ancillary components deployed with 18 Fr and 20 Fr systems

H&L-B One-Shot? Introduction System	Main Body Extender ¹	Converter ²	Iliac Leg Extender ¹
18 Fr System	ESBE-22-36 ESBE-24-36 ESBE-26-36	ESC-24-12-80	ESLE-22-55 ESLE-24-55
20 Fr System	ESBE-28-36 ESBE-30-36 ESBE-32-36	ESC-28-12-80 ESC-32-12-80	none

1 Catalog number for main body extender and iliac leg extender indicates diameter (mm) x length (mm).

2 Catalog number for converter indicates proximal diameter (mm), distal diameter (mm), and length (mm).

When configured for main body deployment, these systems contain dual trigger-wire release mechanisms with safety locks, a top cap assembly coupled with the dilator tip, and a bottom cap assembly. These features lock the Zenith main body onto the delivery system at both ends of the component, giving the physician both longitudinal and rotational control of the endovascular graft after sheath retraction. Therefore, accurate positioning relative to the renal arteries and appropriate orientation of the contralateral limb are possible.

Figure 5.3.1-1 depicts this configuration. The top cap assembly constrains the barbed, uncovered, suprarenal Z-stent until: 1) removal of its corresponding trigger-wire; and 2) release of the Z-stent from within the cap. The bottom cap assembly and trigger-wire constrain the ipsilateral limb of the main body until removal of its trigger-wire.

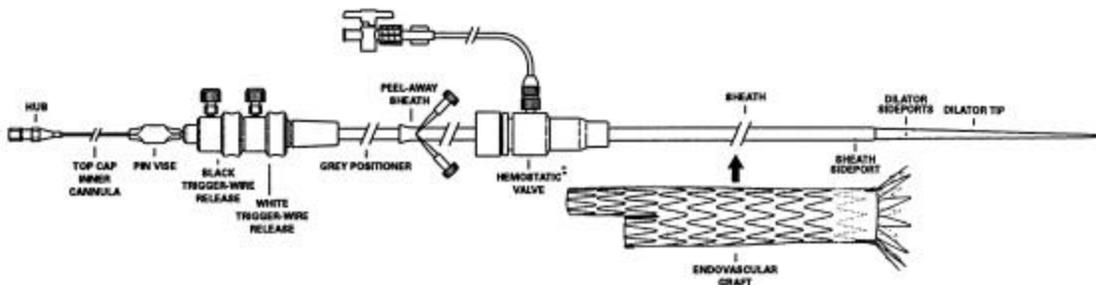


Figure 5.3.1-1. H&L-B One-Shot? Introduction System (Main Body)

When configured for main body extender deployment, these systems contain a single trigger-wire release mechanism with safety lock and bottom cap assembly. No top cap is included with the dilator tip because the main body extender component does not contain a barbed suprarenal Z-stent. After sheath retraction and exposure of the self-expanding component, the distal trigger-wire is removed freeing the body extender from the H&L-B One-Shot? Introduction System. Figure 5.3.1-2 depicts this configuration.

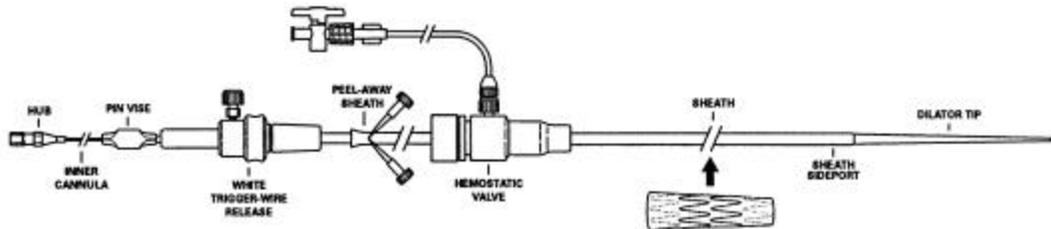


Figure 5.3.1-2. H&L-B One-Shot? Introduction System (Main Body Extender)

When configured for iliac leg (as well as converter and iliac leg extender) deployment, these systems have no trigger-wire release mechanisms, top cap, or bottom cap assemblies. Deployment is achieved by simple sheath retraction. Figure 5.3.1-3 depicts this configuration.

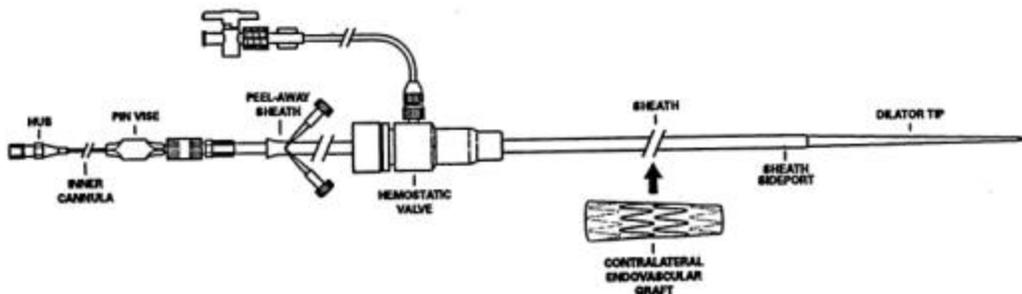


Figure 5.3.1-3. H&L-B One-Shot? Introduction System (Iliac Leg)

5.3.2. 14 Fr and 16 Fr delivery systems description

The 14 Fr and 16 Fr H&L-B One-Shot? Introduction Systems are used to deploy various sizes of the iliac legs and iliac leg extenders in the Zenith family of modular components. These delivery systems have no trigger-wire release mechanisms, top cap, or bottom cap assemblies. Deployment is achieved by simple sheath retraction.

Table 5.3.2-1 lists the catalog/reorder numbers of the iliac legs deployed using these two sizes of H&L-B One-Shot? Introduction Systems. Zenith iliac legs ranging in diameter from 8 - 16 mm are deployed using the 14 Fr system. Zenith iliac legs ranging in diameter from 18 - 24 mm are deployed using the 16 Fr system.

Table 5.3.2-1. Zenith iliac legs deployed with 14 Fr and 16 Fr systems

H&L-B One-Shot? Introduction System	Iliac Legs ¹				
14 Fr System	TFLE-8-37	TFLE-10-37	TFLE-12-37	TFLE-14-37	TFLE-16-37
	TFLE-8-54	TFLE-10-54	TFLE-12-54	TFLE-14-54	TFLE-16-54
	TFLE-8-71	TFLE-10-71	TFLE-12-71	TFLE-14-71	TFLE-16-71
	TFLE-8-88	TFLE-10-88	TFLE-12-88	TFLE-14-88	TFLE-16-88
	TFLE-8-105	TFLE-10-105	TFLE-12-105		
	TFLE-8-122	TFLE-10-122	TFLE-12-122		
16 Fr System	TFLE-18-37	TFLE-20-37	TFLE-22-37	TFLE-24-37	none
	TFLE-18-54	TFLE-20-54	TFLE-22-54	TFLE-24-54	
	TFLE-18-71	TFLE-20-71	TFLE-22-71	TFLE-24-71	
	TFLE-18-88	TFLE-20-88	TFLE-22-88	TFLE-24-88	

¹ Catalog number indicates distal diameter (mm) x length (mm).

Table 5.3.2-2 lists the catalog/reorder numbers of the iliac leg extenders deployed using these two sizes of H&L-B One-Shot? Introduction Systems. Zenith iliac leg extenders ranging in diameter from 8 - 16 mm are deployed using the 14 Fr system. Zenith iliac leg extenders ranging in diameter from 18 - 20 mm are deployed using the 16 Fr system.

Table 5.3.2-2. Zenith ancillary components deployed with 14 Fr and 16 Fr systems

H&L-B One-Shot Introduction System	Iliac Leg Extenders ¹
14 Fr System	ESLE-8-55
	ESLE-10-55
	ESLE-12-55
	ESLE-14-55
	ESLE-16-55
16 Fr System	ESLE-18-55
	ESLE-20-55

¹ Catalog number indicates diameter (mm) x length (mm).

5.3.3. Occluder Cartridge Description

The H&L-B One-Shot? Introduction System is used together with a preloaded cartridge (transfer capsule) for occluder deployment. Table 5.3.3-1 lists the catalog/reorder numbers of the occluders deployed using the H&L-B One-Shot? Introduction System. Zenith occluders ranging in diameter from 14 - 16 mm are deployed using the 16 Fr system. Zenith occluders ranging in diameter from 20 - 24 mm are deployed using the 18 Fr system.

Table 5.3.3-1. Zenith occluder plugs deployed with 18 Fr and 16 Fr systems

H&L-B One-Shot Introduction System	Occluders ¹
16 Fr System	ESP-14-20 ESP-16-20
18 Fr System	ESP-20-20 ESP-24-20

¹ Catalog number for occluders indicates diameter (mm) x length (mm).

To deploy the occluder, the preloaded cartridge containing the occluder is docked with the back of the hemostatic valve on the end of the sheath, after the sheath has been placed within the iliac artery. A blunt positioner included with the occluder cartridge kit is then used to push the occluder plug out of the cartridge and into the sheath, transferring it to the H&L-B One-Shot? Introduction System. Once transferred, the plug is then advanced with the blunt positioner through the sheath to the location of deployment within the artery. The occluder cartridge, blunt positioner, and H&L-B One-Shot? Introduction System are depicted in Figure 5.3.3-1.

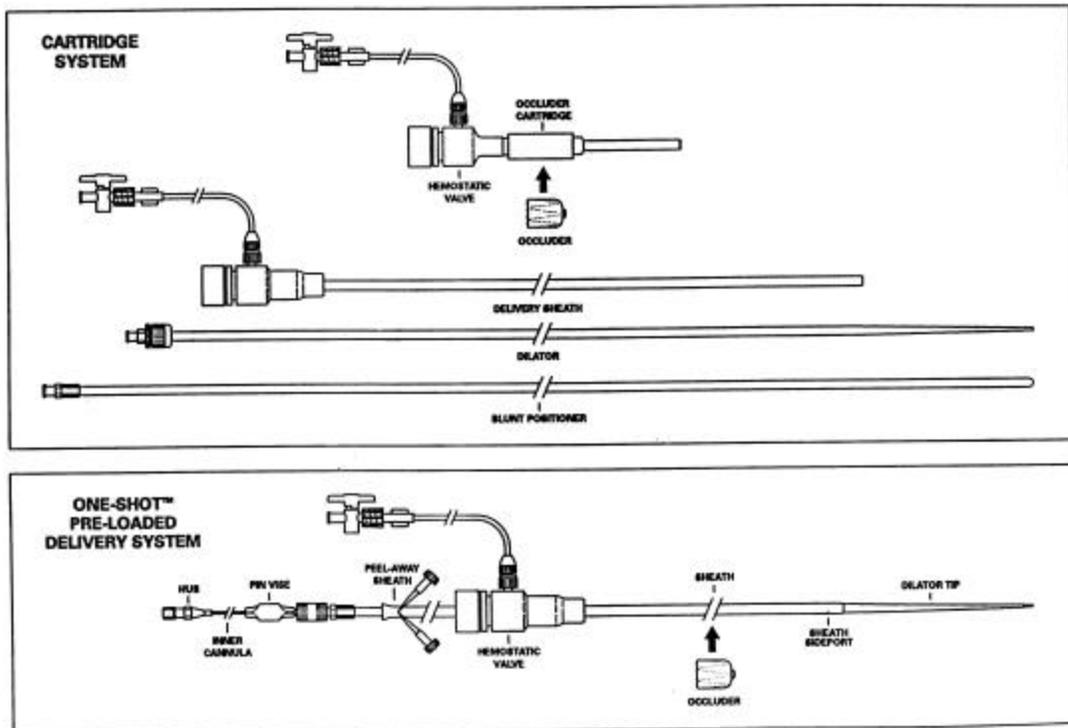


Figure 5.3.3-1. Zenith[®] AAA Endovascular Graft Occluder Cartridge System

6. Alternate Practices and Procedures

The currently accepted standard of care for treatment of abdominal aortic aneurysms is surgical implantation of a synthetic graft within the diseased vessel. Surgical repair of AAA is indicated when the risk of rupture is judged to be greater than the risks of the procedure.

7. Marketing History

The Zenith[®] AAA Endovascular Graft is commercially available in many countries throughout the world including Europe (Germany, Sweden, Belgium, Italy, France, Spain, Switzerland, and the United Kingdom), Australia, New Zealand, Brazil, Argentina, South Africa, Israel, Singapore, Malaysia, Hong Kong, India and Canada. The Zenith[®] AAA Endovascular Graft has not been withdrawn from marketing for any reason relating to safety and effectiveness.

8. Adverse Events

Adverse events are summarized from the U.S. study of the Zenith⁷ AAA Endovascular Graft. In this study, endovascular study patients (standard risk group) were compared to open surgery (control group). Two additional study groups were established to account for patients that were felt to be physiologically challenged with respect to an open surgical approach (high risk group), and to allow for centers to achieve a level of device familiarity prior to patient accrual in the pivotal arms (roll-in group).

8.1. Observed Adverse Events

Table 8.1-1 lists adverse events observed in the U.S. clinical study.

Table 8.1-1. Adverse events

Death and rupture	Standard Risk	Control	High Risk	Roll-in
All death (0-30 days) ²	0.5% (1/199) ¹	2.5% (2/80)	2.0% (2/100)	1.9% (1/52)
All death (0-365 days) ^{2,3}	3.5% (7/199)	3.8% (3/80)	9.0% (9/100)	11.5% (6/52)
AAA-related	0.5% (1/199)	3.8% (3/80)	5.0% (5/100)	1.9% (1/52)
Non-AAA-related	3.0% (6/199)	0.0% (0/80)	4.0% (4/100)	9.6% (5/52)
Rupture (0-30 days)	0.0% (0/199)	0.0% (0/80)	0.0% (0/100)	0.0% (0/52)
Rupture (0-365 days)	0.0% (0/199)	0.0% (0/80)	1.0% (1/100)	0.0% (0/52)
Other adverse events³	Standard Risk	Control	High Risk	Roll-in
Cardiovascular ³	3.0% (6/200)	11% (9/80)	14% (14/100)	1.9% (1/52)
Pulmonary ³	1.0% (2/200)	15% (12/80)	2.0% (2/100)	0.0% (0/52)
Renal ³	2.5% (5/200)	10% (8/80)	6.0% (6/100)	5.8% (3/52)
Bowel	1.0% (2/200)	3.8% (3/80)	1.0% (1/100)	1.9% (1/52)
Wound	4.5% (9/200)	7.5% (6/80)	2.0% (2/100)	3.8% (2/52)
Neurologic	0.0% (0/200)	2.5% (2/80)	0.0% (0/100)	0.0% (0/52)
Vascular ³	11% (21/200)	31% (25/80)	20% (20/100)	19% (10/52)
Other ³	15% (30/200)	38% (30/80)	16% (16/100)	31% (16/52)

1 Denominator of 199 because one standard risk patient did not receive a device

2 All deaths (0-30 days) were considered AAA procedure related.

3 Of the deaths (0-365 days), ten were considered AAA related: 1 standard risk (cardiac failure), 3 surgical (massive hemorrhage, mesenteric ischemia, and septic shock from ischemic colitis), 5 high risk (respiratory failure, cardiac failure with pulmonary embolism, pancreatitis with renal failure and sepsis, hemorrhage from upper abdominal aneurysm [not treated AAA], and multiple system failure) and 1 roll-in (suspected cardiac failure).

8.2. Potential Adverse Events

Potential adverse events include, but are not limited to:

- ?? Death
- ?? Emboli and subsequent tissue damage and/or loss
- ?? Perforation of aorta
- ?? Hypotension/hypertension
- ?? Pseudoaneurysm
- ?? Infection and pain at the vascular access site, hematoma
- ?? Contrast reactions, which may include renal failure or require permanent or transient hemodialysis
- ?? Vessel damage
- ?? Graft or native vessel occlusion
- ?? Wound dehiscence
- ?? Anesthetic complications
- ?? Myocardial infarction
- ?? Gastrointestinal complications and subsequent attending problems
- ?? Renal complications and subsequent attending problems
- ?? Lymphatic complications
- ?? Claudication
- ?? Impotence
- ?? Paralysis
- ?? Transient fever and pain
- ?? Arrhythmia
- ?? Bleeding or coagulopathy
- ?? Deep vein thrombosis (DVT)
- ?? Pulmonary/respiratory complications
- ?? Device failures due to:
 - Migration
 - Dilation
 - Endoleak
 - Rupture
 - Suture break
 - Stent break
 - Barb separation
 - Erosion with fistula or pseudoaneurysm

9. Summary of Pre-Clinical Results

9.1. Biocompatibility

Appropriate compliance with the criteria specified for material and biocompatibility toxicity testing was undertaken in accordance with the recommendations in the *Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices*, May 1994, as well as the *ISO 10993-1 Biological Evaluation of Medical Devices standard* dated June 1998. The tests performed to establish biocompatibility were conducted on both the Zenith[?] AAA Endovascular Graft and the H&L-B One-Shot[?] Introduction System by an independent laboratory (NAMSA, Northwood, OH). The device met the requirements of all tests providing reasonable assurance of device biocompatibility. Table 9.1-1 summarizes biocompatibility testing for the implant. Table 9.1-2 summarizes biocompatibility testing for the delivery system.

Table 9.1-1. Summary of Biocompatibility Test Results for the Zenith AAA Endovascular Graft

Biocompatibility Test	Result
Physicochemical Study (Nonaqueous Extract)	Pass
Cytotoxicity Study Using the ISO Elution Method (1X MEM Extract)	Pass
ISO Sensitization Study in the Guinea Pig (Maximization Method)	Pass
ISO Acute Intracutaneous Reactivity Study in the Rabbit (Extracts)	Pass
ISO Acute Systemic Toxicity Study in the Mouse (Extracts)	Pass
ISO Rabbit Pyrogen Study (Material Mediated)	Pass
Genotoxicity: Bacterial Reverse Mutation Study (Saline Extract)	Pass
Genotoxicity: Bacterial Reverse Mutation Study (DMSO Extract)	Pass
Genotoxicity: <i>In Vitro</i> Chromosomal Aberration Study in Mammalian Cells (Extract)	Pass
Mouse Bone Marrow Micronucleus Study	Pass
<i>In Vitro</i> Hemolysis Study (Modified ASTM – Extraction Method)	Pass
Plasma Recalcification Time Coagulation Study	Pass
C3a Complement Activation Assay	Pass
Subchronic Intravenous Toxicity Study in the Rat (14 Day, Saline Extract)	Pass
ISO Muscle Implantation Study in the Rabbit with Histopathology (4 Weeks)	Pass
ISO Muscle Implantation Study in the Rabbit with Histopathology (12 Weeks)	Pass
ISO Muscle Implantation Study in the Rabbit with Histopathology (26 Weeks)	Pass

Table 9.1-2. Summary of Biocompatibility Test Results for the H&L-B One-Shot? Delivery System.

Biocompatibility Test	Result
USP Physicochemical Study	Pass
Physicochemical Study (Nonaqueous Extract)	Pass
Cytotoxicity Study using the ISO Elution Method (1X MEM Extract)	Pass
ISO Sensitization Study in the Guinea Pig (Maximization Method)	Pass
ISO Acute Intracutaneous Reactivity Study in the Rabbit (Extracts)	Pass
ISO Acute Systemic Toxicity Study in the Mouse (Extracts)	Pass
<i>In Vitro</i> Hemolysis Study (Modified ASTM – Extraction Method)	Pass
Rabbit Pyrogen Study (Material Mediated)	Pass

9.2. Product Testing

Cook conducted comprehensive non-clinical bench and analytical testing on the Zenith[?] AAA Endovascular Graft and the H&L-B One-Shot? Introduction System. The testing and approval plan for the Zenith[?] AAA Endovascular Graft and the H&L-B One-Shot? Introduction System considered methodology from multiple national and international standards and guidances. Compilation and cross-referencing of guidance methodology from these documents in light of the Zenith design is the basis for tests presented in this summary. Documents considered include the following:

Table 9.2-1. International Standards and Guidances Considered in the Zenith Testing Plan

Document	Title
ANSI/AAMI 10993-1-1994	Biological Evaluation of Medical Devices
ANSI/AAMI VP20-1994	Cardiovascular Implants - Vascular Prostheses
AAMI/CDV-1 14971-1998	Medical devices - Risk management - Application of risk management to medical devices (committee draft for vote)
ISO/DIS 7198-1-1990	Cardiovascular Implants - Tubular Vascular Prostheses (draft standard)
ISO/CD 15539-1998	Cardiovascular implants - Endovascular devices (committee draft for comment)
FDA Guidance-1993	Guidance for the Preparation of Research and Marketing Applications for Vascular Graft Prostheses (draft guidance)
FDA Guidance-1994	Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices: PTCA Catheters, Atherectomy Catheters, Lasers, Intravascular Stents
prEN 12006-2-1995	Vascular Prostheses and Cardiovascular Patches (European draft standard)
prEN 12006-3-1998	Non-active surgical implants; particular requirements for cardiac and vascular implants Part 3: Endovascular devices (European draft standard)

The express intent of this *in vitro* testing was to verify that the performance attributes of the Zenith system are sufficient to minimize adverse events under anticipated clinical conditions. Results of this testing support the safety and effectiveness of the Zenith[?]

AAA Endovascular Graft and the H&L-B One-Shot? Introduction System which are expected to perform as intended when used in accordance with the Instructions for Use.

9.2.1. Implant Test Results Summary

The following table summarizes testing performed to assess the implant's deployment accuracy, fixation effectiveness, durability, ability to exclude the aneurysm, modularity, sizing, patency, and MRI compatibility.

Table 9.2.1-1. Summary of Test Results Related to Zenith[?] AAA Endovascular Graft Functionality

<i>In Vitro</i> Test	Relevant Functional Requirement	Summary of Test Result
Graft Material Mechanical Properties Test	?? Testing of the modularity of the endovascular system ?? Appropriate sizing of the implant ?? Durability and integrity of the implanted device	The full thickness Dacron graft material used in Zenith construction is a currently-marketed device (cleared for marketing by FDA in 1993). Base graft porosity, longitudinal tensile strength, circumferential tensile strength, probe burst strength, suture retention strength, kink radius, and wall thickness data obtained are consistent with vascular grafts successfully used in aortic applications.
Stainless Steel Material Analysis Test	?? Durability and integrity of the implanted device	All sizes of stainless steel wire used in Zenith construction were chemically analyzed and quantified. The material analysis meets the material specification required.
Stainless Steel Mechanical Properties Test	?? Durability and integrity of the implanted device	Tensile testing was performed on all three stent wire sizes to characterize the mechanical properties of the material. These properties include modulus of elasticity, yield strength, and ultimate strength. In addition, rotary beam fatigue testing was conducted on all three stent wire sizes (at three different stress levels) to characterize wire fatigue parameters. Results indicate the wire used in Zenith construction is expected to be sufficient for clinical use.
Solder Material Analysis	?? Durability and integrity of the implanted device	The solder used in Zenith construction was chemically analyzed and quantified. The material analysis meets the material specification required.
Time-Accelerated Corrosion Test	?? Durability and integrity of the implanted device	The resistance of the stainless steel wire, solder, and gold markers to general, pitting, crevice, and galvanic corrosion was evaluated. Some loss of solder was observed, but device fixation is not expected to be compromised. Results demonstrate no apparent corrosion of the stainless steel wire and gold markers after 12 years of simulated implant time.
Barb Attachment Strength Test (after corrosion test)	?? Durability and integrity of the implanted device	Mean barb attachment (shear) strength met the acceptance criterion after 12 years of simulated implant (corrosion) time. Therefore, barb attachment strength is expected to be adequate for clinical use.
Cannula Tensile Test (after corrosion test)	?? Durability and integrity of the implanted device	Minimum cannula tensile strength met the acceptance criterion after 12 years of simulated implant (corrosion) time. Therefore, cannula tensile strength is expected to be adequate for clinical use.

<i>In Vitro</i> Test	Relevant Functional Requirement	Summary of Test Result
Stent Free-Area Percentage	?? Patency of the implant	Stent free-area percentages were calculated for the stent configurations used in the suprarenal stent position. Free-area percentages for these Z-stents are 82% and 84% respectively, for the worst case (smallest aorta) conditions and are expected to be suitable for clinical use.
Radial Force Test	?? Fixation effectiveness of the implant ?? Appropriate sizing of the implant ?? Patency of the implant	Radial force testing was performed on Z-stent configurations used in the entire Zenith product line. Results demonstrate the ability of the Z-stent to exert an outward non-zero radial force on the graft material even under worst case (largest resting diameter) conditions allowing the Z-stents to expand and maintain an open lumen in a variety of patient anatomies. Radial force is expected to be adequate for clinical use.
Time-Accelerated Pulsatile Fatigue Test (Three-piece bifurcated graft)	?? Durability and integrity of the implanted device	Time-accelerated pulsatile fatigue testing was conducted to an equivalent of 10 years. At 10 years, there was no loss of device function, fragmentation, barb separation, suprarenal stent breaks, or cannula separations. No component separations, migrations, graft kinks, or graft twists were observed and all grafts were patent. A single Z-stent vertex break (1/6530) was observed. This test was not designed to assess suture and graft material abrasion, although it was noted. Binomial statistics demonstrate with at least 95% confidence that 99% of the Zenith stents will not fracture after 10 years of implant time meeting the acceptance criteria for this test.
Time-Accelerated Longitudinal Fatigue Test (Suprarenal Attachment) ¹	?? Durability and integrity of the implanted device ?? Fixation effectiveness of the implant	Time-accelerated longitudinal fatigue testing of the double-sutured suprarenal stent attachment site was conducted to an equivalent of 10 years. At 10 years, there were no failures of the suprarenal attachment sutures or graft material at the suprarenal attachment sites. Attachment site durability and fixation of the graft are expected to be adequate for clinical use.
Finite Element Analysis	?? Durability and integrity of the implanted device	Force versus diameter curves and maximum stress (in the loop or eye of the stent points) versus diameter curves were generated demonstrating the ability of the Z-stent to self-expand the graft during deployment. Fatigue analysis of the Z-stents and their barbs demonstrated that fatigue failure is unlikely to occur during the expected implant life of the Zenith.
Magnetic Resonance Imaging Test	?? MRI compatibility	As specified by FDA, the acceptance criteria for a claim of 'MR safe' with respect to force and torque is a magnetically induced force less than the weight of the device and a magnetically induced torque less than that encountered by the device during normal daily activities outside a large magnetic field. Based upon these acceptance criteria, the current design of the Zenith does not meet FDA's criteria for 'MR Safe' labeling. MRI procedures are contraindicated for patients receiving the Zenith.
Dimensional Verification	?? Ability to accurately deploy ?? Appropriate sizing of the implant	Records from work orders indicate that production processes are outlined sufficiently to enable repeatable dimensional characteristics from lot-to-lot of manufacturing.

<i>In Vitro</i> Test	Relevant Functional Requirement	Summary of Test Result
Water Permeability Test	?? Ability to exclude the aneurysm ?? Testing of the modularity of the endovascular system	Permeability of the Zenith was tested using the methods defined in ANSI/AAMI VP:20 – 1994. Results of this test demonstrate that the addition of sutures, during Zenith manufacturing, does not significantly increase the mean permeability of the Zenith above that of the virgin graft material. Zenith samples met the acceptance criterion for this test.
Graft to Stent Attachment Strength Test	?? Durability and integrity of the implanted device	Mean attachment strength of the sutures met the acceptance criterion for tensile strength. Results indicate that detachment of the graft material from the Z-stents due to inadequate graft to stent attachment strength is unlikely.
Kink Radius Test	?? Ability to accurately deploy ?? Fixation effectiveness of the implant ?? Patency of the implant	Acceptance criteria for the main body components are based upon the anatomical restrictions established for angulation between the aortic neck and the longitudinal axis of the aneurysm. Kink radius test results demonstrate the Zenith is expected to resist kinking when implanted within aortas having a degree of angulation ? 60°.
Migration Resistance Test	?? Fixation effectiveness of the implant ?? Testing of the modularity of the endovascular system	Migration resistance of the main body, ipsilateral leg, contralateral leg, main body extender, iliac leg extender, and occluder met the acceptance criteria established for this test. The main body design prevents distal migration of the converter, therefore the converter is expected to remain in its location of deployment. Based upon these results, component migration appears unlikely.

1 Submitted to, but not yet reviewed by, FDA

9.2.2. Delivery System Test Results Summary

The following table summarizes testing performed to assess the delivery system's ability to access the implant location, accurately deploy the implant, safely withdraw, and maintain hemostasis.

Table 9.2.2-1. Summary of Results Related to H&L-B One-Shot? Introduction System Functionality

<i>In Vitro</i> Test	Relevant Functional Requirement	Summary of Test Result
Tensile/Bond Strength	?? Ability to access the intended location ?? Ability to deploy the implant ?? Ability to withdraw the delivery system	The tensile strengths of the bonds and joints of the H&L-B One-Shot? Introduction System were determined. A total of 220 catheter bonds were tested. Results indicate that there is at least a 95% confidence level that the minimum tensile strength of each catheter junction will exceed the established acceptance criterion.
Torsional Bond Strength	?? Ability to access the intended location ?? Ability to deploy the implant	The torsional strengths of the bonds and joints of the H&L-B One-Shot? Introduction System were determined. A total of 130 catheter bonds were tested. Mean bond strength met the acceptance criterion for each joint tested.
Dimensional Verification	?? Ability to access the intended location ?? Ability to deploy the implant	Dimensional checks are part of internal QC records verifying conformance to design specifications for each device.

<i>In Vitro</i> Test	Relevant Functional Requirement	Summary of Test Result
Crossing Profile	<p>?? Ability to access the intended location</p> <p>?? Ability to deploy the implant</p> <p>?? Ability to withdraw the delivery system</p> <p>?? Hemostasis of the delivery system</p>	Crossing profile was analyzed for all four delivery system sizes (14, 16, 18, and 20 Fr). All delivery systems passed the established acceptance criterion, demonstrating the delivery systems are capable of being inserted into the vasculature during clinical use.
Top Cap Microscopic Inspection	<p>?? Ability to deploy the implant</p> <p>?? Ability to withdraw the delivery system</p>	Microscopic examination revealed only slight surface scratches which could be attributed to manufacturing, loading, or deployment. There was no evidence of pitting or gouging of the top cap material by the suprarenal stent barbs. Results of microscopic examination demonstrate that the top cap of the H&L-B One-Shot? Introduction System is unlikely to pit or gouge during deployment of the barbed suprarenal Z-stent.
Deployment Test	<p>?? Ability to access the intended location</p> <p>?? Ability to deploy the implant</p> <p>?? Ability to withdraw the delivery system</p>	Comprehensive evaluation of <i>in vitro</i> deployment was conducted in a clinically relevant model. A total of 113 finished sterilized devices were tested with 100% deployment success. Results of deployment testing demonstrate the ability of all four sizes (14, 16, 18, and 20 Fr) of the H&L-B One-Shot? Introduction System to deliver the Zenith in a safe, consistent and accurate manner. Delivery systems are capable of deploying all modular components (main bodies, main body extenders, iliac legs, iliac leg extenders, converters, and occluders) in the entire product line. The deployment mechanisms of the delivery systems functioned to release the pre-loaded endovascular graft components. After release, each component expanded in the intended deployment location, and the delivery system was withdrawn successfully.
Minimum Bend Radius Test	<p>?? Ability to access the intended location</p> <p>?? Ability to deploy the implant</p> <p>?? Ability to withdraw the delivery system</p>	A total of 108 delivery systems (all four sizes: 14, 16, 18, and 20 Fr) containing the largest and smallest diameters of main bodies, main body extenders, iliac legs, iliac leg extenders, converters and occluders were passed through a clinically-relevant model and then deployed. 100% successful deployment was achieved for all components. All delivery systems passed the established acceptance criterion, demonstrating the Zenith components may be deployed after worst case (percutaneous introduction) insertion into patient vasculature.
Catheter Body Maximum Pressure Test	<p>?? Ability to deploy accurately</p>	The lower bound of catheter body maximum pressure was calculated to be much higher than that expected from a typical power contrast injector. Therefore, the H&L-B One-Shot? Introduction System is considered suitable for contrast injection.
Contrast Media Flow Rate Test	<p>?? Ability to deploy accurately</p>	Clinical experience with the H&L-B One-Shot? Introduction System (both international and domestic) has demonstrated that rapid contrast (power) injection into the aorta through the cannula may be done successfully.

The results of *in vitro* testing demonstrate that the Zenith? AAA Endovascular Graft has met the physical and mechanical design goals and provide evidence of the safety and effectiveness of the device for treatment of abdominal aortic aneurysms.

9.3. Shelf Life Testing

Results demonstrate that the H&L-B One-Shot[?] Introduction System is capable of deploying the Zenith[?] AAA Endovascular Graft after three years of simulated aging. The endovascular graft has been shown to self-expand and the delivery system components have been shown to function satisfactorily. Tensile and torque test results demonstrate the delivery system retains adequate component and bond strength. Dimensional measurements indicate the endovascular graft retains dimensional stability. Therefore, based upon these test results, a three year expiration date has been established for all sizes of every component in the Zenith family (main bodies, main body extenders, iliac legs, iliac leg extenders, converters, and occluders).

9.4. Animal Studies

Throughout development, the Zenith[?] AAA Endovascular Graft was evaluated in multiple animal studies. Eight studies involving 85 animals evaluated device placement accuracy, device deployment, aneurysm exclusion, potential for adverse events, histology and survival. These studies demonstrated that the delivery system is capable of accessing the aneurysm site, accurately deploying the Zenith in an infrarenal position with good visibility and ease of operation, and can be withdrawn effectively, all with minimal blood loss during the procedure. The implant was shown to be capable of self-expanding into its deployed position. It successfully excluded the aneurysm while remaining patent and in position after implant, demonstrating the effectiveness of the design and appropriateness of the device sizing method. In these studies, there was a low incidence of adverse events. Histological and pathological analyses demonstrated implantation of the Zenith to be minimally traumatic and non-reactive in these early studies.

In addition, a definitive animal study performed under U.S. FDA Good Laboratory Practice regulations was conducted on the final design for the U.S. clinical trial to provide histopathology and gross anatomical observations to demonstrate device safety before clinical approval and to provide controlled histology not available from clinical studies. Study results demonstrate the safety of the Zenith device. Table 9.4-1 summarizes the results of the definitive animal study.

Table 9.4-1. Summary of non-clinical *in vivo* study

Animal Study	# / Type of Animal	Test Article	Methods	Results/Conclusions
Sub-Chronic and Chronic Study of Tapered Endoprosthesis	15 Canines	Human-Sized Zenith Components and H&L-B One-Shot? Introduction System	Catheter delivery and device functionality were assessed sub-chronically and chronically in 15 animals. Four canines were maintained for one month, five canines were maintained for three months and six canines were maintained for six months.	All acceptance criteria were met. 100% successful deployment of the Zenith in an infrarenal position was achieved and 100% device patency at 1, 3, and 6 months was evidenced by angiography. There was no thrombosis, aortic rupture, or death observed in the animal study. Qualitative histopathologic evaluation performed by an independent board-certified pathologist demonstrates minimal injury and inflammation confirming that implantation of the Zenith is minimally traumatic, non-reactive, and biocompatible.

10. Summary of Clinical Studies

10.1. Objectives

The objective of the clinical study was to investigate the safety and effectiveness of the Zenith® AAA Endovascular Graft as an alternative to open surgical repair in the primary treatment of infrarenal abdominal aortic, aorto-iliac, or iliac aneurysms through assessment of device safety as measured by the incidence of adverse events and factors related to morbidity and device effectiveness as measured by technical, procedural, and treatment success, and rupture-free survival at 12 months. Additionally, measures related to the procedure, patient recovery, clinical utility, and quality of life were assessed.

10.2. Zenith Study Design

The clinical study was a multicenter, concurrently controlled study comparing standard risk endovascular patients having anatomy suitable for the Zenith device to a control group comprised of standard risk surgical patients. Two additional endovascular treatment groups, one which allowed high medical risk patients to be treated with the Zenith device, and the other a roll-in treatment group of initial cases. Fifteen centers enrolled 200 standard risk, 80 surgical control, 100 high risk, and 52 roll-in patients. Clinical and imaging follow-up were scheduled for post-procedure and 1 month, 6 months, 12 months, and annually thereafter. Data provided in this summary are based on findings from an independent core lab that reviewed CT scans, abdominal x-rays, and ultrasound scans to assess aneurysm changes, device position and integrity, and endoleaks.

The rate of patient follow-up (patient flow) was tracked with respect to patients who received no device, reached an endpoint, were withdrawn, were eligible for follow-up, refused follow-up, or were outstanding at follow-up time points. Also calculated were the rate of follow-up of eligible patients and the rate of follow-up of total patients at follow-up time points. Table 10.2-1 provides the definitions for categories used to classify patients with respect to follow-up. Table 10.2-2 presents patient clinical and imaging follow-up for the standard risk and surgical groups. Table 10.2-3 presents the patient clinical and imaging follow-up for the high risk and roll-in groups.

Table 10.2-1. Categories used to classify a patient with respect to follow-up

Item	Definition
No device	Device was not deployed
Endpoints	Patient expired or was converted prior to the required follow-up period
Withdrawn	Patient withdrew from study prior to completing the required follow-up exam(s)
Eligible for follow-up	Patient eligible for follow-up in which a device was deployed, did not reach an endpoint or did not withdraw from the study $\frac{[(\# \text{ of patients enrolled}) - (\text{No device}) - (\text{Endpoints}) - (\text{Withdrawn})]}{[\# \text{ of patients enrolled}]}$
Refused	Patient refused to undergo the required follow-up exam(s) but did not withdraw from the study
Outstanding	Patient for whom imaging is not available for analysis by the core lab at this time; patient who did not withdraw from the study or who has not yet refused follow-up
Follow-up of eligible	Portion of eligible patients for whom we have follow-up data $\frac{[(\text{Eligible for Follow-up}) - (\text{Refused}) - (\text{Outstanding})]}{[\text{Eligible for Follow-up}]}$
Follow-up of total	Portion of all patients for whom we have follow-up data or who are not eligible for follow-up $\frac{[(\text{Follow-up of Eligible}) + (\text{No device}) + (\text{Endpoints}) + (\text{Withdrawn})]}{[\# \text{ of patients enrolled}]}$

Table 10.2-2. Follow-up rates: standard risk and surgical patients

Item	Zenith Standard Risk (N=200)				Surgical Standard Risk (N=80)			
	Clinical		Imaging		Clinical		Imaging	
Pre-discharge								
No device	0.5%	(1/200)	0.5%	(1/200)	0.0%	(0/80)	0.0%	(0/80)
Endpoints	0.0%	(0/200)	0.0%	(0/200)	2.5%	(2/80)	n/a	
Withdrawn	0.0%	(0/200)	0.0%	(0/200)	0.0%	(0/80)	n/a	
Eligible for follow-up	99%	(199/200)	99%	(199/200)	98%	(78/80)	n/a	
Refused	9.0%	(18/199)	6.0%	(12/199)	9.0%	(7/78)	n/a	
Outstanding	0.0%	(0/199)	0.0%	(0/199)	0.0%	(0/80)	n/a	
Follow-up of eligible	91%	(181/199)	94%	(187/199)	91%	(71/78)	n/a	
Follow-up of total	91%	(182/200)	94%	(188/200)	91%	(73/80)	n/a	
30 day								
No device	0.5%	(1/200)	0.5%	(1/200)	0.0%	(0/80)	0.0%	(0/80)
Endpoints	0.5%	(1/200)	0.0%	(0/200)	2.5%	(2/80)	2.5%	(2/80)
Withdrawn	0.0%	(0/200)	0.0%	(0/200)	0.0%	(0/80)	0.0%	(0/80)
Eligible for follow-up	99%	(198/200)	99%	(199/200)	98%	(78/80)	98%	(78/80)
Refused	1.0%	(2/198)	4.0%	(8/199)	1.3%	(1/78)	11.5%	(9/78)
Outstanding	0.0%	(0/198)	0.5%	(1/199)	0.0%	(0/78)	0.0%	(0/78)
Follow-up of eligible	99%	(196/198)	95%	(190/199)	99%	(77/78)	88%	(69/78)
Follow-up of total	99%	(198/200)	96%	(191/200)	99%	(79/80)	89%	(71/80)
6 month								
No device	0.5%	(1/200)	0.5%	(1/200)	0.0%	(0/80)	0.0%	(0/80)
Endpoints	2.5%	(5/200)	2.5%	(5/200)	n/a		n/a	
Withdrawn	0.0%	(0/200)	0.0%	(0/200)	n/a		n/a	
Eligible for follow-up	97%	(194/200)	97%	(194/200)	n/a		n/a	
Refused	2.6%	(5/194)	3.6%	(7/194)	n/a		n/a	
Outstanding	0.0%	(0/194)	0.5%	(1/194)	n/a		n/a	
Follow-up of eligible	97%	(189/194)	96%	(186/194)	n/a		n/a	
Follow-up of total	98%	(195/200)	96%	(192/200)	n/a		n/a	
12 month								
No device	0.5%	(1/200)	0.5%	(1/200)	0.0%	(0/80)	0.0%	(0/80)
Endpoints	4.5%	(9/200)	4.5%	(9/200)	3.8%	(3/80)	3.8%	(3/80)
Withdrawn	0.0%	(0/200)	0.0%	(0/200)	5.0%	(4/80)	5.0%	(4/80)
Eligible for follow-up	95%	(190/200)	95%	(190/200)	9.1%	(73/80)	9.1%	(73/80)
Refused	1.6%	(3/190)	2.1%	(4/190)	14%	(10/73)	14%	(10/73)
Outstanding	7.9%	(15/190)	7.9%	(15/190)	5.5%	(4/73)	5.5%	(4/73)
Follow-up of eligible	90.5%	(172/190)	90%	(171/190)	81%	(59/73)	81%	(59/73)
Follow-up of total	90.5%	(181/200)	90%	(180/200)	83%	(66/80)	83%	(66/80)

Table 10.2-3. Follow-up rates: high risk and roll-in patients

Item	Zenith High Risk (N=100)				Zenith Roll-in (N=52)			
	Clinical		Imaging		Clinical		Imaging	
Pre-discharge								
No Device	0.0%	(0/100)	0.0%	(0/100)	0.0%	(0/52)	0.0%	(0/52)
Endpoints	1.0%	(1/100)	0.0%	(0/100)	1.9%	(1/52)	1.9%	(1/52)
Withdrawn	0.0%	(0/100)	0.0%	(0/100)	0.0%	(0/52)	0.0%	(0/52)
Eligible for follow-up	99%	(99/100)	100%	(100/100)	98%	(51/52)	98%	(51/52)
Refused	6.1%	(6/99)	6.0%	(6/100)	7.8%	(4/51)	9.8%	(5/51)
Outstanding	0.0%	(0/99)	1.0%	(1/100)	0.0%	(0/51)	5.9%	(3/51)
Follow-up of eligible	94%	(93/99)	93%	(93/100)	92%	(47/51)	84%	(43/51)
Follow-up of total	94%	(94/100)	93%	(93/100)	92%	(48/52)	85%	(44/52)
30 day								
No device	0.0%	(0/100)	0.0%	(0/100)	0.0%	(0/52)	0.0%	(0/52)
Endpoints	2.0%	(2/100)	2.0%	(2/100)	1.9%	(1/52)	1.9%	(1/52)
Withdrawn	0.0%	(0/100)	0.0%	(0/100)	0.0%	(0/52)	0.0%	(0/52)
Eligible for follow-up	98%	(98/100)	98%	(98/100)	98%	(51/52)	98%	(51/52)
Refused	2.0%	(2/98)	3.1%	(3/98)	2.0%	(1/51)	3.9%	(2/51)
Outstanding	0.0%	(0/98)	0.0%	(0/98)	0.0%	(0/51)	2.0%	(1/51)
Follow-up of eligible	98%	(96/98)	97%	(95/98)	98%	(50/51)	94%	(48/51)
Follow-up of total	98%	(98/100)	97%	(97/100)	98%	(51/52)	94%	(49/52)
6 month								
No device	0.0%	(0/100)	0.0%	(0/100)	0.0%	(0/52)	0.0%	(0/52)
Endpoints	9.0%	(9/100)	9.0%	(9/100)	5.8%	(3/52)	5.8%	(3/52)
Withdrawn	0.0%	(0/100)	0.0%	(0/100)	3.8%	(2/52)	3.8%	(2/52)
Eligible for follow-up	91%	(91/100)	91%	(91/100)	90%	(47/52)	90%	(47/52)
Refused	6.6%	(6/91)	8.8%	(8/91)	4.3%	(2/47)	8.5%	(4/47)
Outstanding	0.0%	(0/91)	0.0%	(0/91)	0.0%	(0/47)	2.1%	(1/47)
Follow-up of eligible	93%	(85/91)	91%	(83/91)	96%	(45/47)	89%	(42/47)
Follow-up of total	94%	(94/100)	92%	(92/100)	96%	(50/52)	90%	(47/52)
12 month								
No Device	0.0%	(0/100)	0.0%	(0/100)	0.0%	(0/52)	0.0%	(0/52)
Endpoints	10%	(10/100)	10%	(10/100)	12%	(6/52)	12%	(6/52)
Withdrawn	1.0%	(1/100)	1.0%	(1/100)	3.8%	(2/52)	3.8%	(2/52)
Eligible for follow-up	89%	(89/100)	89%	(89/100)	85%	(44/52)	85%	(44/52)
Refused	6.7%	(6/89)	10%	(9/89)	6.8%	(3/44)	6.8%	(3/44)
Outstanding	7.9%	(7/89)	8.0%	(8/89)	14%	(6/44)	16%	(7/44)
Follow-up of eligible	85%	(76/89)	81%	(72/89)	80%	(35/44)	77%	(34/44)
Follow-up of total	87%	(87/100)	83%	(83/100)	83%	(43/52)	81%	(42/52)

10.3. Patient Demographics

Table 10.3-1 and Figure 10.3-1 tabulate patient demographics and comorbid conditions and present the distribution of initial aneurysm diameters for the four study groups.

Table 10.3-1. Patient demographics and comorbid conditions

Item	Zenith Standard Risk	Surgical Standard Risk	Zenith High Risk	Zenith Roll-in
Age (years)	71 ± 7	69 ± 7	77 ± 7	74 ± 8
Gender male	94% (187/200)	89% (71/80)	92% (92/100)	90% (47/52)
Current medical conditions				
Peripheral vasc. disease	16% (31/195)	25% (19/76)	24% (23/96)	9.6% (5/52)
Hypertension	64% (127/200)	83% (65/78)	68% (67/99)	67% (35/52)
Renal failure	0.0% (0/197)	0.0% (0/79)	5.2% (5/97)	1.9% (1/52)
COPD	20% (39/199)	18% (14/78)	34% (33/98)	22% (11/51)
Thromboembolic event	4.5% (9/199)	7.7% (6/78)	7.1% (7/99)	1.9% (1/52)
Liver disease	2.1% (4/192)	5.1% (4/79)	1.0% (1/99)	1.9% (1/52)
Diabetes Mellitus	12% (24/199)	15% (12/79)	17% (17/99)	14% (7/51)
Insulin-dependent	17% (4/24)	8.3% (1/12)	24% (4/17)	43% (3/7)
Previous medical conditions				
MI	39% (74/192)	29% (23/80)	35% (34/98)	35% (18/52)
Congestive heart failure	5.0% (10/199)	12% (9/78)	16% (16/100)	10% (5/50)
Angina	49% (98/198)	39% (31/79)	45% (44/98)	44% (23/52)
Arrhythmia	20% (40/197)	22% (17/78)	28% (27/98)	24% (12/51)
Cerebrovascular disease	9.5% (19/199)	16% (13/79)	20% (20/99)	9.8% (5/51)
Systemic infection	1.0% (2/196)	0.0% (0/78)	3.1% (3/97)	0.0% (0/49)
Cancer	22% (43/200)	19% (15/80)	31% (31/99)	29% (15/51)
Family history of aneurysmal disease	16% (24/150)	27% (17/63)	14% (11/77)	26% (10/38)
Previous surgery at site	10% (20/200)	15% (12/79)	10% (10/99)	14% (7/51)
Previous radiation at site	0.5% (1/197)	0.0% (0/79)	2.0% (2/100)	2.0% (1/51)

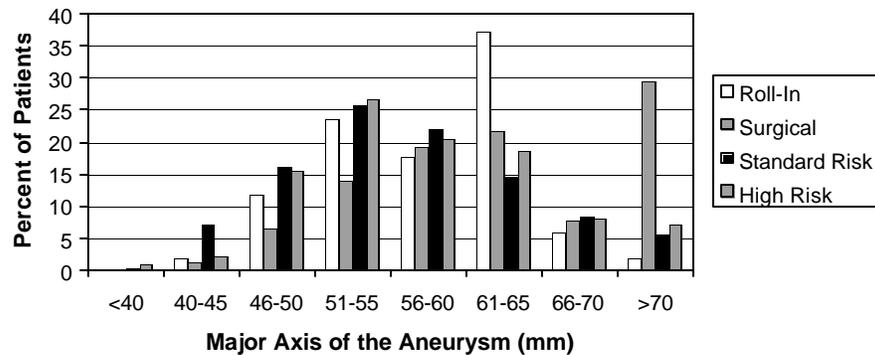


Figure 10.3-1. Pre-Procedure Aneurysm Diameter Distribution

10.4. Results

10.4.1. Devices Implanted

Table 10.4-1 lists the sizes of Zenith main bodies and iliac legs, as well as the ancillary components (main body extenders, iliac leg extenders, occluders and converters) implanted in the U.S. pivotal trial.

Table 10.4.1-1. Devices implanted in the U.S. pivotal study

Main Body TFB-X-YY

	1	2	3	4	5	Subtotal
22	0	2	1	0	0	3
24	9	13	10	2	0	34
26	13	28	28	12	2	83
28	1	29	33	18	5	86
30	7	27	33	10	6	83
32	3	12	31	14	1	61
Subtotal	33	111	136	56	14	350

Iliac Leg TFLE-XX-YY

	37	54	71	88	105	122	Subtotal
8	0	0	2	0	0	1	3
10	2	1	7	3	1	1	15
12	30	21	33	9	0	0	93
14	32	60	61	6	0	0	159
16	46	79	61	4	0	0	190
18	15	40	36	2	0	0	93
20	18	38	28	0	0	0	84
22	11	19	11	2	0	0	43
24	4	6	5	2	0	0	17
Subtotal	158	264	244	28	1	2	697

Iliac Leg Extenders ESLE-XX-55

	55
8	0
10	5
12	18
14	15
16	14
18	6
20	4
22	3
24	3
Subtotal	68

Main Body Extenders

	ESBE-XX-36
8	0
10	36
12	0
14	0
16	0
18	3
20	4
22	1
24	1
Subtotal	8

Plus one TFLE-14-88, one TFLE-24-88,

and one TFLE-20-54 used as leg extenders.

Occluders ESP-XX-20

	20
14	0
16	0
20	0
24	0
Subtotal	0

Converters ESC-XX-80

	80
24	0
28	0
32	1
Subtotal	1

10.4.2. Principal Safety Results

Measures of mortality, rupture, conversion and secondary intervention are presented in Table 10.4.2-1. Figure 10.4.2-1 shows the Kaplan-Meier survival plots for all treatment groups depicting AAA-related survival with time expressed in months.

Table 10.4.2-1. Principal safety results

Item	Zenith Standard Risk ¹	Surgical Standard Risk	Zenith High Risk	Zenith Roll-in
All death (0-30 days)	0.5% (1/199)	2.5% (2/80)	2.0% (2/100)	1.9% (1/52)
All death (0-365 days)	3.5% (7/199)	3.8% (3/80)	9.0% (9/100)	11.5% (6/52)
AAA-related	0.5% (1/199)	3.8% (3/80)	5.0% (5/100)	1.9% (1/52)
Non-AAA-related	3.0% (6/199)	0.0% (0/80)	4.0% (4/100)	9.6% (5/52)
Rupture (0-30 days)	0.0% (0/199)	0.0% (0/80) ²	0.0% (0/100)	0.0% (0/52)
Rupture (0-365 days)	0.0% (0/199)	0.0% (0/80) ²	1.0% (1/100)	0.0% (0/52)
Conversion (0-30 days)	0.0% (0/199)	n/a	0.0% (0/100)	0.0% (0/52)
Conversion (0-365 days)	1.0% (2/199)	n/a	1.0% (1/100)	0.0% (0/52)
Secondary interventions (0-30 days)	3.0% (6/199)	2.5% (2/80)	3.0% (3/100)	3.8% (3/52)
Secondary interventions (0-365 days)	11% (21/199)	2.5% (2/80)	12% (12/100)	5.8% (3/52)

1 Although enrolled, one standard risk patient did not receive a device.

2 Three surgical patients had massive hemorrhages; two required re-operation and one died.

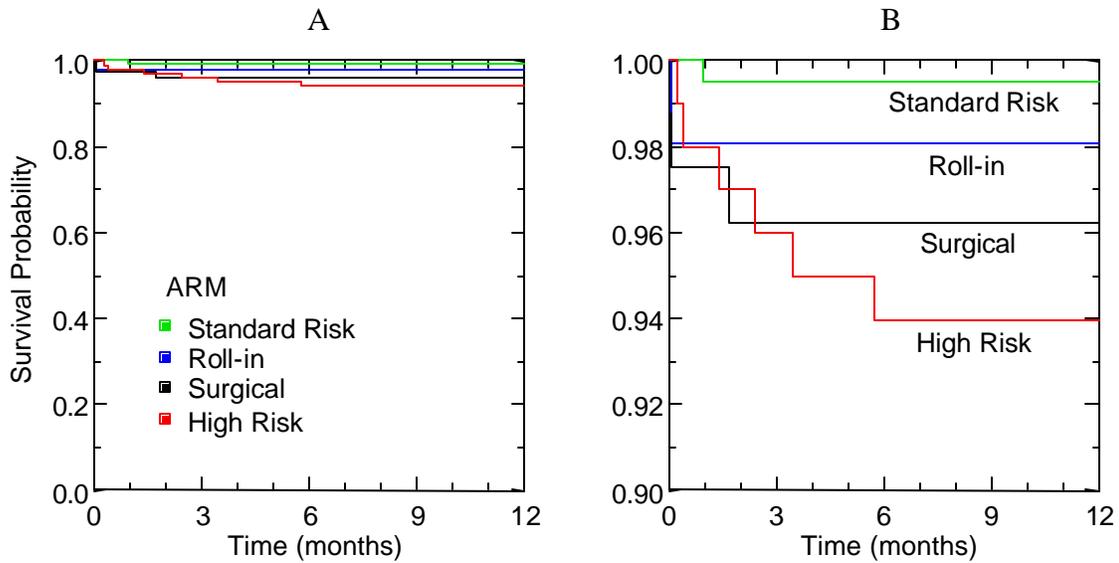


Figure 10.4.2-1. (A) Kaplan-Meier plot of AAA-related survival. (B) Same plot with expanded y-axis to clarify survival rates in the four treatment groups.

10.4.3 Principal Effectiveness Results

Principal effectiveness results including deployment success, presence of endoleaks, graft patency, migration and device integrity measures are presented in table 10.4.3-1.

Table 10.4.3-1. Principal effectiveness results

Item	Zenith Standard Risk	Zenith High Risk	Zenith Roll-In
Deployment success	99.5% (199/200)	100% (100/100)	100% (52/52)
Early endoleaks (identified within 30 days)			
Proximal Type I	2.8% (5/179)	2.3% (2/88)	0.0% (0/36)
Distal Type I	1.7% (3/179)	1.1% (1/88)	0.0% (0/36)
Type II	9.5% (17/179)	9.1% (8/88)	5.6% (2/36)
Type III	1.1% (2/179)	0.0% (0/88)	2.8% (1/36)
Type IV	0.0% (0/179)	0.0% (0/88)	0.0% (0/36)
Multiple	1.1% (2/179)	4.5% (4/88)	0.0% (0/36)
Unknown	1.1% (2/179)	1.1% (1/88)	2.8% (1/36)
Late endoleaks (identified at 6 or 12 months)			
Proximal Type I	0.0% (0/184)	0.0% (0/80)	0.0% (0/38)
Distal Type I	0.5% (1/184)	0.0% (0/80)	0.0% (0/38)
Type II	3.3% (6/184)	2.5% (2/80)	2.6% (1/38)
Type III	0.5% (1/184)	2.5% (2/80)	0.0% (0/38)
Type IV	0.0% (0/184)	0.0% (0/80)	0.0% (0/38)
Unknown	0.5% (1/184)	0.0% (0/80)	0.0% (0/38)

Item		Zenith Standard Risk	Zenith High Risk	Zenith Roll-In
Graft patency	30 day	100% (185/185)	99% (85/86)	100% (47/47)
	6 month	99% (183/184)	100% (74/74)	100% (39/39)
	12 month	99% (153/155)	100% (62/62)	100% (30/30)
Graft migration	with clinical sequelae ¹	0.0% (0/162)	0.0% (0/71)	0.0% (0/34)
	without clinical sequelae	2.5% (4/162)	2.8% (2/71)	0.0% (0/34)
Barb separation ²	Pre-discharge	0.0% (0/176)	0.0% (0/86)	0.0% (0/39)
	30 day	0.0% (0/178)	0.0% (0/86)	0.0% (0/43)
	6 month	1.2% (2/167)	2.5% (2/80)	0.0% (0/35)
	12 month	2.0% (3/149)	1.7% (1/60)	0.0% (0/28)
Stent fractures ³	Pre-discharge	0.0% (0/172)	0.0% (0/81)	0.0% (0/39)
	30 day	0.0% (0/172)	0.0% (0/83)	0.0% (0/43)
	6 month	0.0% (0/166)	0.0% (0/78)	0.0% (0/35)
	12 month	0.0% (0/148)	0.0% (0/60)	0.0% (0/28)
Limb separation	Pre-discharge	0.0% (0/176)	0.0% (0/86)	0.0% (0/39)
	30 day	0.0% (0/178)	0.0% (0/86)	0.0% (0/43)
	6 month	0.0% (0/167)	0.0% (0/80)	0.0% (0/35)
	12 month	0.0% (0/149)	0.0% (0/60)	0.0% (0/28)
Graft material rupture	Pre-discharge	0.0% (0/176)	0.0% (0/86)	0.0% (0/39)
	30 day	0.0% (0/178)	0.0% (0/86)	0.0% (0/43)
	6 month	0.0% (0/167)	0.0% (0/80)	0.0% (0/35)
	12 month	0.0% (0/149)	0.0% (0/60)	0.0% (0/28)

1 Migration with clinical sequelae would include endoleak, conversion, rupture or AAA-related death

2 Patients with separation of 1 or 2 barbs (of 10 or 12 total); no adverse clinical sequelae

3 Stent fracture percentages are for main body. There were also no right iliac leg, left iliac leg, occluder, converter, left iliac extension, right iliac extension, or main body extension fractures observed by the core lab.

10.4.4. Change in Aneurysm Size

Aneurysm size was determined by the core lab as the major axis diameter of the aneurysm from CT images. Table 10.4.4-1. shows the percent of patients with a change in major axis of the aneurysm for the categories defined as decrease >5 mm, unchanged, and increase >5 mm.

Table 10.4.4-1. Changes of major axis of the aneurysm diameter from CT by the core lab

Item	Zenith Standard Risk	Zenith High Risk	Zenith Roll-In
From pre-discharge			
30-day			
Decrease >5 mm	1.7% (3/180)	4.8% (4/84)	0.0% (0/40)
Unchanged	97% (174/180)	94% (79/84)	97.5% (39/40)
Increase >5 mm	1.7% (3/180)	1.2% (1/84)	2.5% (1/40)
Change from pre-discharge			
6-month			
Decrease >5 mm	36% (63/173)	41% (30/73)	49% (18/37)
Unchanged	62% (108/173)	59% (43/73)	51% (19/37)
Increase >5 mm	1.2% (2/173)	0.0% (0/73)	0.0% (0/37)
Change from pre-discharge			
12-month			
Decrease >5 mm	68% (102/151)	63% (39/62)	67% 20/30
Unchanged	31% (47/151)	35% (22/62)	33% 10/30
Increase >5 mm	1.3% (2/151)	1.6% (1/62)	0.0% 0/30

10.4.5. Secondary Endpoints

Secondary endpoints included anesthesia time, procedure time, blood bank products received and blood loss. In addition, clinical utility was assessed through a number of clinical measures obtained before hospital discharge, including days in the ICU, days to discharge, days to oral fluids, days to normal diet, days to normal bowel function, days to ambulation, hours of intubation, and maximum core body temperature. These secondary endpoints are tabulated in Table 10.4.5-1.

Table 10.4.5-1. Secondary endpoints

Item	Zenith Standard Risk	Surgical Standard Risk	Zenith High Risk	Zenith Roll-in
Anesthesia time (min)	221.6 ± 67.3	304.5 ± 102.7	218.9 ± 69.6	213.9 ± 57.7
Procedure time (min)	153.2 ± 56.3	238.7 ± 92.2	153.5 ± 58.6	155.9 ± 43.2
Blood bank products received				
PRBC	4.5% (9/200)	61% (49/80)	10% (10/100)	3.8% (2/52)
FFP	0.0% (0/200)	8.8% (7/80)	1.0% (1/100)	0.0% (0/52)
Platelets	0.5% (1/200)	6.3% (5/80)	1.0% (1/100)	0.0% (0/52)
Cryoprecipitates	0.0% (0/200)	7.5% (6/80)	0.0% (0/100)	0.0% (0/52)
Blood loss (cc)	299 ± 324	1676 ± 1676	356 ± 514	265 ± 226
Days in ICU	0.4 ± 0.9	3.4 ± 4.6	0.5 ± 1.2	0.5 ± 0.9
Days to discharge	2.6 ± 1.7	8.8 ± 5.6	3.0 ± 2.8	2.7 ± 1.5
Days to oral fluids	0.5 ± 0.8	3.9 ± 2.5	0.5 ± 0.6	0.7 ± 0.5
Days to normal diet	1.3 ± 1.2	6.6 ± 4.9	1.3 ± 0.8	1.1 ± 0.7
Days to normal bowel function	2.6 ± 1.4	4.2 ± 2.1	2.6 ± 1.5	2.0 ± 1.2
Days to ambulation	1.2 ± 0.7	3.5 ± 3.4	1.2 ± 0.7	1.2 ± 0.6
Hours of intubation	1.9 ± 2.2	11.7 ± 13.6	1.2 ± 1.7	2.6 ± 4.6
Maximum temperature	101.1 ± 1.3	100.7 ± 1.2	100.8 ± 1.1	101.0 ± 1.2

10.4.6. Evaluation of Gender Bias

The occurrence of AAA disease is known to be higher in men than women and the ratio of men to women enrolled in this study reflects the general population. In order to more carefully evaluate possible gender based differences in outcomes of treatment with the Zenith® AAA Endovascular Graft, Cook requested and was granted approval to establish a registry for the treatment of AAA disease in women with standard medical risk.

Measures of survival, 30-day morbidity, conversion and death using these combined data sets are presented in Table 10.4.6-1 through Table 10.4.6-3.

Zenith⁷ AAA Endovascular Graft subjects exhibited no significant differences between males and females for survival and 30-day morbidity (31 measures). No gender based differences were identified in AAA-related mortality after treatment with the Zenith® AAA Endovascular Graft.

Table 10.4.6-1. Kaplan-Meier AAA-related survival rates by gender: All Zenith pivotal + female, and surgical

Item	All Zenith Pivotal + Female Registry			Surgical Standard Risk		
	Male	Female	P value	Male	Female	P Value
Survival rate at 30 days	98.8%	100%	.49	97.2%	100%	.61
Survival rate at 365 days	97.5%	100%	.35	97.0%	100%	.26

Table 10.4.6-2. 30-day morbidity (31 measures) by gender: All Zenith pivotal + female, and surgical

Item	All Zenith Pivotal + Female Registry			Surgical Standard Risk		
	Male (N=326)	Female (N=41)	P value	Male (N=71)	Female (N=9)	P value
30-day morbidity	0.34 ? 0.73	0.39 ? 0.63	.66	0.86 ? 1.46	1.44 ? 2.00	.28

Table 10.4.6-3. Conversion and death by gender: All Zenith pivotal + female, and surgical

Item	All Zenith Pivotal (including high risk patients) + Female Registry			Surgical Standard Risk		
	Male	Female	P value	Male	Female	P value
Conversion (0-365 days)	0.31% (1/324)	5.0% (2/40)	.03	n/a	n/a	n/a
All death (0-30 days)	1.2% (4/326)	0.0% (0/40) [†]	>.99	2.8% (2/71)	0.0% (0/9)	>.99
All death (0-365 days)	6.8% (22/323)	2.6% (1/38)	.49	3.0% (2/67)	11% (1/9)	.32
AAA-related	2.5% (8/323)	0.0% (0/38)	>.99	3.0% (2/67)	11% (1/9)	.32
Procedure-related	2.2% (7/323)	0.0% (0/38)	-	3.0% (2/67)	11% (1/9)	.32
Technique-related	0.62% (2/323)	0.0% (0/38)	-	3.0% (2/67)	11% (1/9)	.32
Device-related	0.0% (0/323) [‡]	0.0% (0/38)	-	0.0% (0/67)	0.0% (0/9)	-

[†]One patient did not receive a device (see text)

[‡]One high risk patient death was not device related but information was insufficient to rule out device involvement.

10.5. Device Failures and Replacements

There were no reports of devices malfunctioning causing a recall.

11. Conclusions Drawn from Studies

These studies have shown that the Zenith[?] AAA Endovascular Graft can be placed with a high level of technical success which is maintained over time, and is comparable to or better than a surgical control. Most aneurysms (68%) had decreased in size or remained stable (31%) at 12 months.

The additional clinical benefits associated with the Zenith[?] AAA Endovascular Graft compared to open surgical repair include reducing the risk of serious treatment-related complications, reducing the duration of intubation, reducing the number of days spent in the hospital, reducing the number of days spent in the ICU, reducing the number of days to the resumption of oral fluids, diet, and normal bowel functions, reducing the number of days to ambulation, reducing anesthesia time, reducing procedural time, reducing procedural blood loss and the need for blood products.

12. Panel Recommendation

To be inserted.

13. FDA Decision

To be inserted.