SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Endovascular Graft
Device Trade Name:	Zenith Alpha™ Thoracic Endovascular Graft
Device Procode:	MIH
Applicant's Name and Address:	Cook Incorporated 750 Daniels Way P.O. Box 489 Bloomington, IN 47402-0489 USA
Date of Panel Recommendation:	None
Premarket Approval (PMA) Application Number:	P140016
Date of FDA's Notice of Approval:	September 15, 2015
Priority Review:	No

II. INDICATIONS FOR USE

The Zenith Alpha™ Thoracic Endovascular Graft is indicated for the endovascular treatment of patients with isolated lesions of the descending thoracic aorta (not including dissections) having vascular anatomy suitable for endovascular repair, including:

- Iliac/femoral anatomy that is suitable for access with the required introduction systems,
- Nonaneurysmal aortic segments (fixation sites) proximal and distal to the thoracic lesion:
    - with a length of at least 20 mm, and

- with a diameter measured outer wall to outer wall of no greater than 42 mm and no less than 15 mm.

III. CONTRAINDICATIONS

The Zenith Alpha™ Thoracic Endovascular Graft is contraindicated in:

- Patients who have a condition that threatens to infect the endovascular graft.
- Patients with known sensitivities or allergies to polyester, polypropylene, nitinol, or gold.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions are contained in the labeling (Instructions for Use).

V. DEVICE DESCRIPTION

The Zenith Alpha™ Thoracic Endovascular Graft System is comprised of four parts:

- Proximal Component
- Distal Component
- Introduction System
- Ancillary Component

The Zenith Alpha™ Thoracic Endovascular Graft is intended to be delivered endoluminally via access through the femoral or iliac artery to the site of the lesion using the Introduction System. The endovascular graft is inserted and constrained by the introduction system's outer sheath. The pre-loaded endovascular graft is advanced to the lesion location over a guidewire. Upon deployment, the endovascular graft self-expands due to the superelastic properties of the nitinol stents. The proximal and distal ends of the proximal and distal components of the endovascular 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. The Zenith Alpha™ Thoracic Endovascular Graft is a modular device that accommodates the use of additional components depending on the configuration of the anatomy, where single or multiple components may be required to achieve sufficient coverage of the lesion. To provide the added coverage often needed

during the treatment of thoracic aortic aneurysms (TAA), the distal component is overlapped with the proximal component. An ancillary component can also be used to extend graft coverage distally or extend the length of overlap between the proximal and distal components. To treat more focal aortic lesions, as are often found in blunt thoracic aortic injury (BTAI) patients and patients with ulcers, a proximal component can be used alone.

All endovascular graft components are constructed of self-expanding nitinol stents sewn to polyester graft material with braided polyester and monofilament polypropylene sutures.

A. Proximal Component

The proximal component uses an uncovered stent at the proximal end and an internal sealing stent with fixation barbs that protrude through the graft material. All other stents are external to the graft material, except for the distal stent, which is located internal to the graft material. The proximal components (Figure 1) are available in a number of diameters and lengths and can be either nontapered or tapered. If additional graft coverage is needed proximal to the first proximal component placed, a second proximal component can be used.

Gold radiopaque markers are sewn to the luminal side of the fabric (at the location of each seal stent apex) to facilitate visualization of the edge of the graft material. The markers are located at the proximal and distal edges of the graft material; each edge contains either 5 markers (18-30 mm diameter components), 6 markers (32-38 mm diameter components), 7 markers (40-42 mm diameter components), or 8 markers (44-46 mm diameter components), corresponding to the number of stent apices.

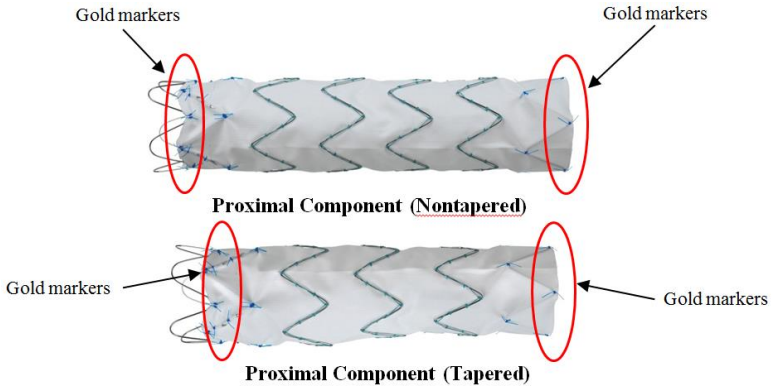

Figure 1. Zenith Alpha™ Thoracic Endovascular Graft proximal components

The available sizes of proximal components (nontapered and tapered) are listed in Table 1.

Table 1. Zenith Alpha™ Thoracic Endovascular Graft proximal component available sizes

Intended Aortic Vessel Diameter (mm)	Graft Diameter (mm)	Overall Length of Nontapered Proximal Component (mm)	Overall Length of Tapered Proximal Component (mm)[a]	Introducer Sheath (Fr)	Introducer Sheath Outer Diameter (OD) (mm)
15	18	105/127	N/A	16	6.0
16	18	105/127	N/A	16	6.0
17	20	105/127	N/A	16	6.0
18	22	105/127	105	16	6.0
19	22	105/127	105	16	6.0
20	24	105/127	N/A	16	6.0
21	24	105/127	N/A	16	6.0
22	26	105/149	105	16	6.0
23	26	105/149	105	16	6.0
24	28	109/132/155/201	N/A	16	6.0
25	28	109/132/155/201	N/A	16	6.0
26	30	109/132/155/201	108	16	6.0
27	30	109/132/155/201	108	16	6.0
28	32	109/132/155/201	178/201	18	7.1
29	32	109/132/155/201	178/201	18	7.1
30	34	113/137/161/209	161/209	18	7.1
31	36	113/137/161/209	161/209	18	7.1
32	36	113/137/161/209	161/209	18	7.1
33	38	117/142/167/217	167/217	18	7.1
34	38	117/142/167/217	167/217	18	7.1
35	40	117/142/167/217	167/217	20	7.7
36	40	117/142/167/217	167/217	20	7.7
37	42	121/147/173/225	173/225	20	7.7
38	42	121/147/173/225	173/225	20	7.7
39	44	125/152/179/233	179/233	20	7.7
40	46	125/152/179/233	179/233	20	7.7
41	46	125/152/179/233	179/233	20	7.7
42	46	125/152/179/233	179/233	20	7.7

[a]For tapered components, the proximal diameter is listed; the distal diameter is 4 mm smaller than the proximal diameter.

B. Distal Component

The distal component (Figure 2) is overlapped within the proximal component by at least three stents; therefore, the three most proximal stents of the distal component are located internal to the graft material to promote sealing between the proximal component and the distal component. The proximal edge of the graft is fashioned to the shape of the stent to further promote sealing. All other stents are located external to the graft material, except

for the second most distal stent, which is located internal to the graft material, and the distal stent, which is an uncovered stent with barbs for fixation.

Gold radiopaque markers are sewn to the luminal side of the fabric (at the location of each seal stent apex) to facilitate visualization of the edge of the graft material. The markers are located at the proximal and distal edges of the graft material; each edge contains either 5 markers (28-30 mm diameter components), 6 markers (32-38 mm diameter components), 7 markers (40-42 mm diameter components), or 8 markers (44-46 mm diameter components), corresponding to the number of stent apices.

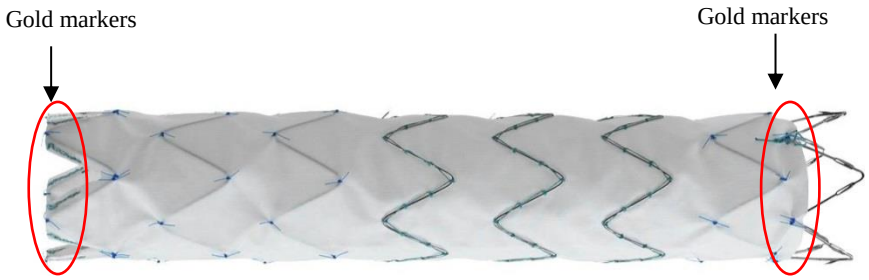

Figure 2. Zenith Alpha™ Thoracic Endovascular Graft distal component

The available sizes of distal components are listed in Table 2.

Table 2. Zenith Alpha™ Thoracic Endovascular Graft distal component available sizes

Intended Aortic Vessel Diameter (mm)	Graft Diameter (mm)	Overall Length of Distal Component (mm)	Introducer Sheath (Fr)	Introducer Sheath Outer Diameter (OD) (mm)
24	28	160/229	16	6.0
25	28	160/229	16	6.0
26	30	160/229	16	6.0
27	30	160/229	16	6.0
28	32	160/229	18	7.1
29	32	160/229	18	7.1
30	34	142/190	18	7.1
31	36	142/190	18	7.1
32	36	142/190	18	7.1
33	38	147/197	18	7.1
34	38	147/197	18	7.1
35	40	147/197	20	7.7
36	40	147/197	20	7.7
37	42	152/204	20	7.7
38	42	152/204	20	7.7
39	44	157/211	20	7.7

Intended Aortic Vessel Diameter (mm)	Graft Diameter (mm)	Overall Length of Distal Component (mm)	Introducer Sheath (Fr)	Introducer Sheath Outer Diameter (OD) (mm)
40	46	157/211	20	7.7
41	46	157/211	20	7.7
42	46	157/211	20	7.7

C. Introduction System

The Introduction System consists of a single use, disposable catheter with a rotational handle to provide the user with controlled deployment. Each Zenith Alpha™ Thoracic Endovascular Graft component is shipped preloaded onto a 16 Fr, 18 Fr, or 20 Fr Introduction System (Figure 3). All introduction systems use a rotation handle to retract the trigger-wires/release-wires and release the endovascular graft. The introduction system has a hemostatic valve and a sheath that is hydrophilically coated.

The proximal component introduction system is precurved and contains a single trigger-wire/release-wire mechanism, which attaches the proximal and distal ends of the endovascular graft to the introduction system following withdrawal of the sheath, until released by the operator. The distal component introduction system has a straight inner cannula that contains a dual trigger-wire/release-wire mechanism, which constrains the distal bare stent in a bottom cap and attaches the proximal end of the stent-graft to the introduction system, until released by the operator.

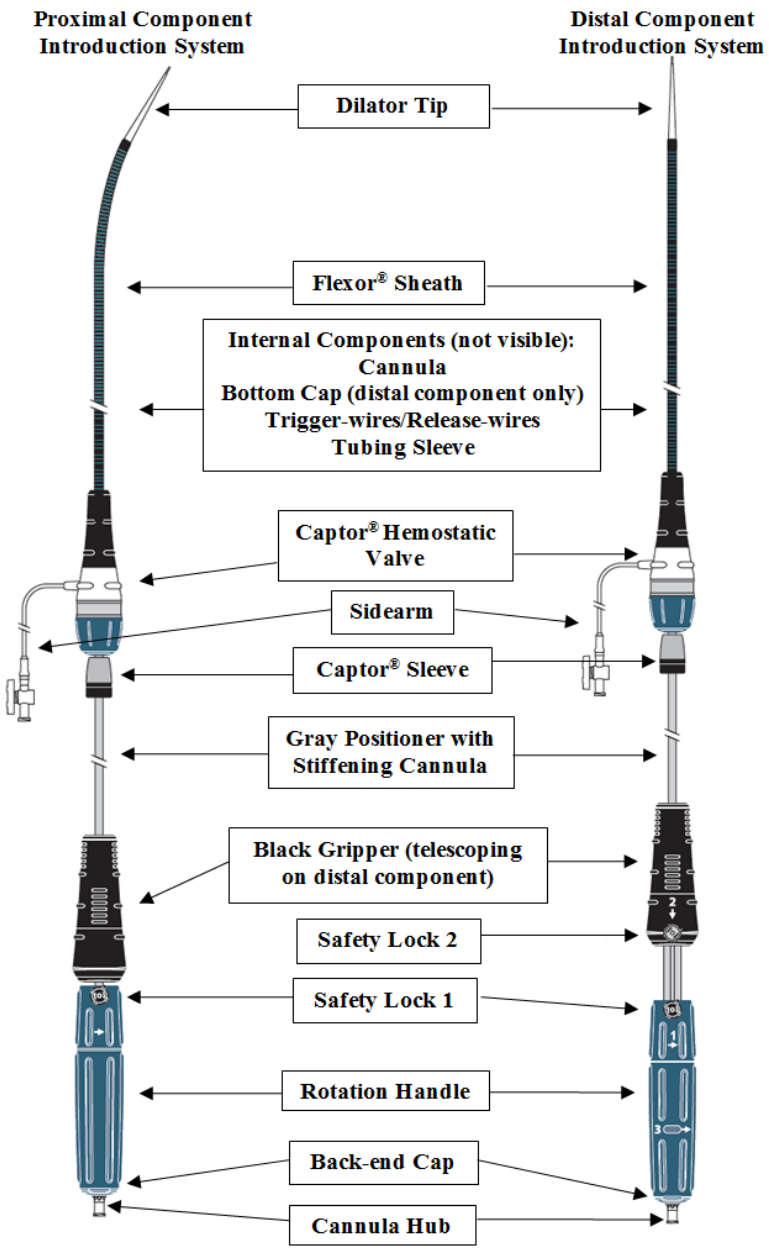

Figure 3. Zenith Alpha™ Thoracic Endovascular Graft Introduction Systems

D. Ancillary Component

The Zenith Alpha™ Thoracic Endovascular Graft product line includes an ancillary component that may be used to extend graft coverage distally or extend the length of overlap between components (such as between a proximal and distal component if the minimum recommended overlap length of 3 stents is not initially achieved). Note that the proximal component may be used to extend graft coverage proximally (see Section A

for details). The ancillary component (Figure 4) is constructed of the same materials as the proximal and distal components and is deployed from a 16 Fr, 18 Fr, or 20 Fr introduction system that has a single trigger-wire/release-wire mechanism (Figure 5).

Figure 4. Zenith Alpha™ Thoracic Endovascular Graft Ancillary component

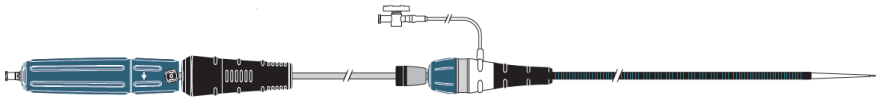

Figure 5. Zenith Alpha™ Thoracic Endovascular Graft Distal Extension Introduction System

The available sizes of distal extensions are listed in Table 3.

Table 3. Zenith Alpha™ Thoracic Endovascular Graft distal extension available sizes

Intended Aortic Vessel Diameter (mm)	Graft Diameter (mm)	Overall Lengths of Distal Extension (mm)	Introducer Sheath (Fr)	Introducer Sheath Outer Diameter (OD) (mm)
15	18	104/148	16	6.0
16	18	104/148	16	6.0
17	20	104/148	16	6.0
18	22	104/148	16	6.0
19	22	104/148	16	6.0
20	24	104/148	16	6.0
21	24	104/148	16	6.0
22	26	104/148	16	6.0
23	26	104/148	16	6.0
24	28	108/154	16	6.0
25	28	108/154	16	6.0
26	30	108/154	16	6.0
27	30	108/154	16	6.0
28	32	108/154	18	7.1
29	32	108/154	18	7.1
30	34	112/160	18	7.1
31	36	112/160	18	7.1
32	36	112/160	18	7.1
33	38	91/141	18	7.1

Intended Aortic Vessel Diameter (mm)	Graft Diameter (mm)	Overall Lengths of Distal Extension (mm)	Introducer Sheath (Fr)	Introducer Sheath Outer Diameter (OD) (mm)
34	38	91/141	18	7.1
35	40	91/141	20	7.7
36	40	91/141	20	7.7
37	42	94/146	20	7.7
38	42	94/146	20	7.7
39	44	97/151	20	7.7
40	46	97/151	20	7.7
41	46	97/151	20	7.7
42	46	97/151	20	7.7

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for treatment of isolated lesions of the descending thoracic aorta (not including dissections): endovascular repair with another endovascular graft system, open surgical repair involving implantation of a synthetic graft within the aneurysmal vessel, and medical management. Each alternative procedure has its own advantages and disadvantages. The physician should fully discuss these alternatives with the patient to select the method that best fits the patient's expectations and lifestyle.

VII. MARKETING HISTORY

The Zenith Alpha™ Thoracic Endovascular Graft has been available outside of the United States since August 2013, when it received CE Mark for the European Union; the device is also approved in Canada (2014), Colombia (2014), Argentina (2015), Thailand (2013), Hong Kong (2014), Israel (2014), and Serbia (2014). The Zenith Alpha™ Thoracic Endovascular Graft has not been withdrawn from any market due to reasons related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (i.e., complications) associated with the use of the device.

- Amputation
- Anesthetic complications and subsequent related problems (e.g., aspiration)
- Aneurysm enlargement
- Aneurysm rupture and death
- Aortic damage, including perforation, dissection (e.g., retrograde dissection), bleeding, rupture, and death
- Aortic valve damage
- Aortobronchial fistula
- Aortoesophageal fistula
- Arterial or venous thrombosis and/or pseudoaneurysm
- Arteriovenous fistula
- Bleeding, hematoma, or coagulopathy
- Bowel complications (e.g., ileus, transient ischemia, infarction, necrosis)
- Cardiac complications and subsequent related problems (e.g., arrhythmia, tamponade, myocardial infarction, congestive heart failure, hypotension, hypertension, angina)
- Claudication (e.g., buttock, lower limb)
- Death
- Edema
- Embolization (micro and macro) with transient or permanent ischemia or infarction
- Endoleak
- Endoprosthesis: improper component placement; incomplete and/or difficult component insertion, deployment (e.g., access failure), or removal; catheter breakage; component migration and/or separation; suture break; occlusion; infection; stent fracture; graft material wear; component twist/kink; dilatation; erosion; puncture; perigraft flow; barb separation; corrosion
- Excessive or inappropriate radiation exposure
- Femoral neuropathy
- Fever, localized inflammation, and/or post-implant syndrome
- Genitourinary complications and subsequent related problems (e.g., ischemia, erosion, fistula, incontinence, hematuria, infection)
- Hepatic failure
- Impotence
- Infection of the aneurysm, device, or access site, including abscess formation, transient fever, and pain
- Lymphatic complications and subsequent related problems (e.g., lymph fistula, lymphocele)
- Neurologic local or systemic complications and subsequent related problems (e.g., stroke, transient ischemic attack, paraplegia, paraparesis/spinal cord shock, paralysis, paresthesia, peripheral nerve injury, blindness, change in mental status)
- Occlusion of coronary arteries
- Pulmonary embolism
- Pulmonary/respiratory complications and subsequent attendant problems (e.g., pneumonia, respiratory failure, prolonged intubation, atelectasis)
- Renal complications and subsequent related problems (e.g., artery occlusion, contrast toxicity, insufficiency, failure)
- Surgical conversion to open repair
- Vascular access site complications (e.g., infection, pain, hematoma, pseudoaneurysm, arteriovenous fistula)
- Vascular spasm or vascular trauma (e.g., iliofemoral vessel dissection, intramural hematoma, bleeding, rupture, death)
- Vessel damage, (e.g., arterial stenosis)
- Wound complications and subsequent related problems (e.g., dehiscence, infection, tissue necrosis)

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

IX. SUMMARY OF PRECLINICAL STUDIES

The following preclinical studies were performed on the Zenith Alpha™ Thoracic Endovascular Graft and Introduction System:

A. Biocompatibility
B. Sterilization, Packaging, and Shelf Life
C. Nonclinical Bench Testing
D. Animal Studies

The introduction system (not the endovascular graft components) was modified following completion of enrollment in the pivotal clinical studies described in Section X. Specifically, the introduction system was modified to include the rotation handle and Captor® sleeve shown in Figure 3. Accordingly, additional preclinical studies were conducted to evaluate performance of the modified introduction system, as noted below. The modified introduction system was also assessed in a subset of patients treated during continued access (refer to Section XI, Part B) as well as during a European post-market survey (refer to Section XI, Part C).

A. Biocompatibility

Biocompatibility of all materials (polyester graft material, nitinol stents, polyester sutures, polypropylene sutures, and gold radiopaque markers) used in the Zenith Alpha™ Thoracic Endovascular Graft implant was assessed by testing specified in ISO 10993-1, *Biological Evaluation of Medical Devices*, including cytotoxicity, sensitization, skin irritation or intracutaneous reactivity, acute systemic toxicity, pyrogenicity, genotoxicity and mutagenicity, hemocompatibility, subchronic toxicity, and reaction toward implantation, as summarized in Table 4. Testing for carcinogenicity was considered unnecessary due to the similarities of the materials used in the Zenith Alpha™ Thoracic Endovascular Graft to other implantable devices with a significant history of long-term biocompatibility.

Table 4. Summary of biocompatibility testing for the materials used in the Zenith Alpha™ Thoracic Endovascular Graft

Test Type	Purpose	Acceptance Criterion	Result
Cytotoxicity: ISO Elution Method (1X MEM Extract)	Determine whether extracts would cause cytotoxicity	The device/material shall not show more than 50% lysis (grade 2, mild cell lysis)	Pass
ISO Maximization Sensitization Study (Extract)	Evaluate the potential for delayed dermal contact for sensitization	The device/material shall show no evidence of causing delayed dermal contact sensitization	Pass
ISO Intracutaneous Study (Extract)	Determine whether extracts would cause local dermal irritant or toxic effects	The device/material shall not exhibit significant irritation	Pass
USP and ISO Acute Systemic Toxicity (Extracts)	Determine whether extracts would cause acute systemic toxicity	The device/material shall show no evidence of significant systemic toxicity	Pass
Subchronic Systemic Toxicity Study (in rats following subcutaneous implant)	Determine whether extracts would cause subchronic systemic toxicity	The device/material shall show no evidence of significant systemic toxicity	Pass
ISO Muscle Implantation Study	Evaluate the potential for irritation or toxicity in muscle tissue	The device/material shall not cause significant irritation	Pass
Genotoxicity: Bacterial Reverse Mutation Study (Extract)	Evaluate whether extracts cause mutagenic changes in bacteria	The device/material shall not cause mutagenic changes	Pass
Genotoxicity: *In Vitro* Chromosomal Aberration Study in Mammalian Cells (Extract)	Determine whether extracts would show genotoxicity in mammalian cells	The device/material shall show no evidence of genotoxicity in mammalian cells	Pass
Genotoxicity: Mouse Peripheral Blood Micronucleus Study (Extract)	Determine whether extracts would show genotoxicity in mouse peripheral blood cells	The device/material shall show no evidence of genotoxicity in mouse peripheral blood cells	Pass
Hemocompatibility: ASTM *In Vitro* Hemolysis (Extract)	Determine whether extracts would cause hemolysis *in vitro*	The device/material shall be considered nonhemolytic	Pass
Hemocompatibility: ASTM Partial Thromboplastin Time (Extract)	Evaluate whether extracts cause changes in the clotting time of human plasma	The device/material shall not significantly affect clotting time	Acceptable
Hemocompatibility: C3a Complement Activation Assay (Extract)	Evaluate the potential for activating the complement system	The device/material shall not exhibit significant complement activation	Pass
Hemocompatibility: SC5b-9 Complement Activation Assay (Extract)	Evaluate the potential for activating the complement system	The device/material shall not exhibit significant complement activation	Pass

The blood-contacting components of the Zenith Alpha™ Thoracic Endovascular Graft introduction system, with the exception of the gray positioner and bottom cap used in both the original and modified introduction systems, are the same as the components used in the introduction systems of the Zenith® TX2® TAA Endovascular Graft (TX2) (P070016) or the Zenith Flex® AAA Endovascular Graft (AAA) (P020018), which have established biocompatibility. Biocompatibility testing for the materials used with the TX2 and AAA devices was assessed by testing specified in ISO 10993-1, *Biological Evaluation of Medical Devices*, including cytotoxicity, sensitization, skin irritation or intracutaneous reactivity, acute systemic toxicity, and hemocompatibility.

The base materials for the gray positioner (polyvinyl chloride) and bottom cap (nylon) are the same as those used in the introduction systems of the Zenith® TX2® TAA Endovascular Graft or the Zenith Flex® AAA Endovascular Graft; however, the specific formulations have been slightly modified. Therefore, additional biocompatibility testing was considered necessary for these materials; results of testing are summarized in Tables 5 and 6.

Table 5. Results of biocompatibility testing of the gray positioner material

Test Type	Purpose	Acceptance Criterion	Result
Cytotoxicity: ISO Elution Method – 1X MEM Extract	Determine whether extracts would cause cytotoxicity	The device/material shall not show more than 50% lysis (grade 2, mild cell lysis)	Pass
Sensitization: ISO Maximization Sensitization Study – Extract (NaCl and sesame oil)	Evaluate the potential for delayed dermal contact for sensitization	The device/material shall show no evidence of causing delayed dermal contact sensitization	Pass
Intracutaneous reactivity: ISO Intracutaneous Study – Extract (NaCl and sesame oil)	Determine whether extracts would cause local dermal irritant or toxic effects	The device/material shall not exhibit significant irritation	Pass
Acute systemic toxicity: USP and ISO Systemic Toxicity Study – Extract (NaCl and sesame oil)	Determine whether extracts would cause acute systemic toxicity	The device/material shall show no evidence of significant systemic toxicity	Pass
Hemocompatibility: *In Vitro* Hemolysis – Modified ASTM-Extraction Method (NaCl)	Determine whether extracts would cause hemolysis *in vitro*	The device/material shall be considered nonhemolytic	Pass

Table 6. Results of biocompatibility testing of the bottom cap material

Test Type	Purpose	Acceptance Criterion	Result
Cytotoxicity: ISO Elution Method – 1X MEM Extract	Determine whether extracts would cause cytotoxicity	The device/material shall not show more than 50% lysis (grade 2, mild cell lysis)	Pass
Sensitization: Murine Local Lymph Node Assay – Extract (NaCl and DMSO)	Determine whether extracts would cause an increase in proliferation of lymphocytes within mouse lymph nodes	The device/material shall show no evidence of causing sensitization	Pass
Intracutaneous reactivity: ISO Intracutaneous Study – Extract (sesame oil)	Determine whether extracts would cause local dermal irritant or toxic effects	The device/material shall not exhibit significant irritation	Pass
Acute systemic toxicity: ISO Systemic Toxicity Study – Extract (NaCl and sesame oil)	Determine whether extracts would cause acute systemic toxicity	The device/material shall show no evidence of significant systemic toxicity	Pass
Hemocompatibility: ASTM Hemolysis – Direct Contact and Extract (CMS-PBS)	Determine whether test article or test article extract would cause hemolysis *in vitro*	The device/material shall be considered nonhemolytic	Pass

Results of these tests support the biocompatibility of the Zenith Alpha™ Thoracic Endovascular Graft. Based upon the previous history of the clinical use of the components and the results of the aforementioned tests, biocompatibility of the Zenith Alpha™ Thoracic Endovascular Graft was reasonably demonstrated.

B. Sterilization, Packaging, and Shelf Life

The Zenith Alpha™ Thoracic Endovascular Graft is sterilized using an ethylene oxide (EtO) sterilization process to achieve a minimum sterility assurance level (SAL) of 10^{-6}. Packaging, performance, and stability testing demonstrate that the packaging designs for the Zenith Alpha™ Thoracic Endovascular Graft including the modified introduction system are sufficient to adequately protect the device and maintain the integrity of the Zenith Alpha™ Thoracic Endovascular Graft package throughout its 3-year shelf life claim.

Shelf life testing results for 3-year time accelerated aged devices are presented with the *in vitro* bench testing results in Tables 7 through 9 (asterisk indicates test was also performed for shelf life testing). Accelerated shelf life product testing conducted on the Zenith Alpha™ Thoracic Endovascular Graft including the modified introduction system supports a 3-year shelf life claim.

C. Bench Testing

A testing plan for the Zenith Alpha™ Thoracic Endovascular Graft was developed to provide an assessment of device deployability, clinical/mechanical function, and integrity. The specific laboratory (*in vitro*) tests that were considered in assessing the Zenith Alpha™ Thoracic Endovascular Graft included tests listed in the testing standard ISO 25539-1, *Cardiovascular implants – Endovascular devices – Part 1: Endovascular prostheses*.

The following tables provide a summary of the laboratory (*in vitro*) testing results for the complete assembly (Table 7), introduction system (Table 8), and endovascular graft (Table 9). Except as noted in Table 8, all complete assembly testing and introduction system testing was performed on the modified introduction system. These test results verified that the Zenith Alpha™ Thoracic Endovascular Graft met product performance and design specifications.

Table 7. Complete assembly testing

Test Method	Purpose	Acceptance Criterion	Result
Force to Deploy*	Evaluate force necessary to deploy endovascular prosthesis	Sheath withdrawal < 100 N and trigger-wire/release-wire pull force < 45 N during alternate release sequence	Pass
Profile/ Diameter Test*	Determine maximum diameter of loaded introduction system	Because this test is for characterization only, there are no acceptance criteria	N/A
Visibility*	Evaluate visibility of endovascular system during simulated use	100% success for the following visibility parameters: • Visualization of the proximal tip • Visualization of the tip of the sheath • Visualize all stents and radiopaque markers • Visualization of the overlap zone	Pass

Test Method	Purpose	Acceptance Criterion	Result
Simulated Use*	Evaluate performance of endovascular system during simulated use	100% success for the following deployment parameters: • Successful flush through Captor® valve assembly and inner cannula with saline/heparin solution • Verification of placement of Captor® sleeve • Activation of hydrophilic coating • Advancement of device over wire guide and through anatomical model • Sheath pullback • Proximal bare stent remains attached to the delivery system during repositioning (proximal component only) • Distal bare stent remains attached to the delivery system during repositioning (distal component only) • Operation of rotating handle to release the distal trigger-wires • Operation of rotating handle to release the proximal trigger-wires • Successful retraction of telescoping handle (distal component only) • Successful deployment of distal bare stent (distal component only) • Graft expansion into model • Graft positioning • Subassembly removal from graft and sheath • Sheath removal from model • Operation of Captor® valve/Captor® sleeve • After withdrawal of grey positioner, the hemostatic valve remains in place	Pass

*Test also performed for shelf life testing on time-accelerated aged devices.

Table 8. Introduction system testing

Test Method	Purpose	Acceptance Criteria	Result
Bond Strength*	Evaluate tensile strength of introduction system bonds	Tensile strength • ≥ 4 N for UAT/wire[a] • ≥ 5 N for suture[a] • > 23 N for handle/positioner, cap/positioner, and tip/cannula • ≥ 26.88 N for captor body/VRTS • > 72 N for pin vise/cannula • ≥ 45 N for wire/bushing • > 77 N for sheath/valve	Pass
Torsional Bond Strength*	Evaluate torsional bond strength of introduction system bonds	Torsional strength > 0.068 Nm for pin vise/cannula, handle/cannula hub, handle/positioner, cap/positioner and tip/cannula	Pass

*Test also performed for shelf life testing on time-accelerated aged devices.

[a]Same for original and modified introduction systems; was not retested for modified system.

Table 9. Endovascular graft testing

Test Method	Purpose	Acceptance Criterion	Result
Circumferential Tensile Strength	Evaluate circumferential strength of graft material	Strength must be ≥ 2.1 N/mm	Pass
Corrosion	Evaluate susceptibility of metallic components of prosthesis to corrosion	Breakdown potential statistically greater than or equal to that of a currently approved endovascular graft	Pass
Dimensional Verification*	Evaluate diameters and lengths of deployed endovascular prosthesis	• Outside diameter ± 5% of nominal outside diameter • Length ± 5% of specified length	Pass
Seam Strength	Evaluate tensile strength of graft material seam	Strength must be ≥ 2.1 N/mm	Pass
Fatigue & Durability (pulsatile)	Evaluate pulsatile fatigue and durability of implant under intended conditions of use	*Aneurysm/ulcer indication* No stent fractures after the completion of 400 million pulsatile fatigue cycles *BTAI indication* No stent fractures that affect structural integrity after the completion of 400 million pulsatile fatigue cycles	Pass
Fatigue & Durability (longitudinal)	Evaluate longitudinal fatigue and durability of implant under intended conditions of use	*Proximal sealing stent* Following 400 million cycles: • No more than 3 (total) and 2 consecutive pairs of barb failures • No more than 4 consecutive stent-to-graft attachment site failures • No stent failures *Distal bare stent* Following 400 million cycles: • No more than 4 consecutive barb failures • No more than 2consecutive stent-to-graft attachment site failures • No stent failures	Pass
Flex/Kink	Evaluate minimum kink radius prosthesis can accommodate	Calculated maximum kink radius ≤ 20 mm	Pass
Integral Water Permeability	Evaluate rate of water leakage through endovascular prosthesis, including overlap	Rate of leakage < 362 ml/cm^2/min	Pass
Longitudinal Tensile Strength	Evaluate longitudinal strength of graft material	Strength > 100 N	Pass

Test Method	Purpose	Acceptance Criterion	Result
Migration Resistance	Evaluate force required to displace prosthesis	Minimum pull-out force > 8.14 N	Pass
MRI Testing	Evaluate magnetic field interactions between implant and MR system	•Deflection angle < 45 degrees •No torque •Heating < 5.7 ºC •Artifact assessed for characterization	Pass
Pull Test for Modular Components	Evaluate force required to separate modular components	Same as for the previously approved device (Zenith TX2 TAA Endovascular Graft), this test is for characterization only, as the forces acting to cause component separation in the thoracic aorta have not been definitively characterized, such that there are no established acceptance criteria.	N/A with respect to an established acceptance criterion; force was comparable to that for the previously approved device
Radial Force/Hoop Strength	Evaluate force exerted by self-expanding implant	Minimum and maximum forces: •$S_{min} \geq 2.3$ N and $S_{max} \leq 19.1$ N for internal sealing stents •$S_{min} > 0$ N and $S_{max} \leq 10.6$ N for external stents •$S_{min} > 0$ N and $S_{max} \leq 8.2$ N for bare stents	Pass
Stent-free Surface Area	Calculate the stent-free area percentages for the bare stent configurations	Because this test is for characterization only, there are no acceptance criteria	N/A
Strength of Stent-to-graft Attachment*	Evaluate strength of suture attachment between graft and stent	Attachment strength: • > 0 N for internal stents • > 0.81 N for proximal sealing stents • > 1.26 N for external stents • > 1.63 N for distal bare stents	Pass
Stress/Strain Analysis (FEA)	To evaluate maximum and minimum stresses and strains on the stents when subjected to *in vivo* pulsatile load conditions	Fatigue factor of safety > 1.0	Pass
	To evaluate maximum and minimum stresses and strains on the barbs when subjected to *in vivo* longitudinal loading conditions	Fatigue factor of safety > 1.0	Pass
Wall Thickness	Evaluate graft material thickness	Wall thickness must be within 0.127 mm ± 0.025 mm	Pass
Water Permeability	Evaluate rate of water leakage through graft material	Rate of leakage < 362 ml/cm^2/min	Pass

*Test also performed for shelf life testing on time-accelerated aged devices.

D. Animal Studies

The Zenith Alpha™ Thoracic Endovascular Graft is the same basic design as the Zenith® TX2® TAA Endovascular Graft, a cylindrical endovascular prosthesis with self-expanding stents sewn to graft material. Moreover, the Zenith® Alpha™ Thoracic Endovascular Graft is constructed of the same base raw nitinol, polyester, and polypropylene materials as are used in the Zilver® Vascular Stent (P050017), the Zenith Flex® AAA Endovascular Graft (P020018), and the Zenith® TX2® TAA Endovascular Graft (P070016). These devices have undergone animal testing and shown acceptable histopathological response. Additionally, these devices have shown acceptable biocompatible and have a history of safe clinical use in humans. Therefore, animal studies specific to the Zenith Alpha™ Thoracic Endovascular Graft were considered not necessary.

X. SUMMARY OF THE PIVOTAL CLINICAL STUDIES

The Zenith Alpha™ Thoracic Endovascular Graft is indicated for the endovascular treatment of patients with isolated lesions of the descending thoracic aorta (not including dissections) having vascular anatomy suitable for endovascular repair.

The Zenith Alpha™ Thoracic Endovascular Graft has been the subject of several documented clinical evaluations, including two pivotal studies (one international) that evaluated the safety and effectiveness of the Zenith Alpha™ Thoracic Endovascular Graft in patients with thoracic aneurysm/ulcer and blunt thoracic aortic injury (BTAI), as summarized in Table 10. Additional clinical evaluations (see Section XI) include a continued access study for the aneurysm/ulcer indication and a European post-market survey to further confirm performance of a user interface modification to the introduction system (rotation handle).

Table 10. Summary of primary pivotal studies

Pivotal Study	Study Design	Objective	Number of Sites with Enrollment	Number of Subjects
Aneurysm/ Ulcer	Prospective, nonrandomized, single-arm, multinational (US, Japan, Germany, England, Sweden) study	To evaluate safety and effectiveness of the Zenith Alpha™ Thoracic Endovascular Graft for the treatment of patients with aneurysms/ulcers of the descending thoracic aorta.	23	110

Pivotal Study	Study Design	Objective	Number of Sites with Enrollment	Number of Subjects
BTAI	Prospective, nonrandomized, noncomparative, single-arm, US multicenter study	To evaluate safety and effectiveness of the Zenith Alpha™ Thoracic Endovascular Graft for the treatment of blunt traumatic aortic injury.	17	50

ANEURYSM/ULCER PIVOTAL STUDY

A. Study Design

The Zenith Alpha™ Thoracic Endovascular Graft pivotal study was a prospective, nonrandomized, single-arm, multinational study that was conducted to evaluate the safety and effectiveness of the Zenith Alpha™ Thoracic Endovascular Graft for the treatment of patients with aneurysms/ulcers of the descending thoracic aorta. Patients were treated between March 17, 2010 (first US enrollment on October 1, 2010) and January 16, 2013. The database for this PMA reflected data collected on 110 subjects under G100079 through April 7, 2015. There were 23 investigational sites, including centers in the US (51 patients at 14 sites), Japan (43 patients at 3 sites), Germany (13 patients at 4 sites), Sweden (3 patients at 1 site), and England (1 patient at 1 site). The presenting anatomy, based on core laboratory analysis of pre-procedure imaging, was a thoracic aneurysm in 81.8% (90/110) of patients and a thoracic ulcer in 18.2% (20/110) of patients.

The pivotal study endpoints were established based on performance goals derived from the pivotal study of the previous device, the Zenith® TX2® TAA Endovascular Graft. Similar inclusion/exclusion criteria were used between the two studies. A post hoc analysis was performed comparing demographic, comorbid, and baseline anatomical characteristics between the present study and the previous Zenith® TX2® TAA Endovascular Graft study used to derive the performance goals for hypothesis testing. Of the few variables that were found to be different between studies, none appeared to be relevant with respect to assessing the safety and effectiveness endpoints, thus confirming that comparing to performance goals derived from the previous study remained appropriate.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the pivotal study for the aneurysm/ulcer indication was limited to subjects who met the following inclusion criteria:

- Descending thoracic aneurysm with diameter ≥ 5.0 cm
- Descending thoracic aneurysm with a history of growth ≥ 5 mm per year
- Descending thoracic degenerative or atherosclerotic ulcer ≥ 10 mm in depth and 20 mm in diameter

Subjects were not permitted to enroll in the pivotal study if they met any of the following:

General Exclusion Criteria

- Less than 18 years of age (20 years in Japan)
- Life expectancy less than 2 years
- Pregnant or breastfeeding or planning on becoming pregnant within 60 months
- Unwilling to comply with the follow-up schedule
- Inability or refusal to give informed consent
- Less than 30 days beyond primary endpoint for other investigative drug or device study

Medical Exclusion Criteria

- Receiving home oxygen therapy
- FEV_1 < 1 liter
- Left ventricular ejection fraction < 20%
- New York Heart Association Classification 4
- Myocardial infarction within the last 3 months
- Stroke within the last 3 months
- Diagnosed or suspected congenital degenerative collagen disease (for example, Marfan's or Ehlers-Danlos syndrome)
- Systemic infection (e.g., sepsis)
- Bleeding diathesis, uncorrectable coagulopathy, or refuses blood transfusion
- Allergy to polyester, polypropylene, nitinol, or gold
- Untreatable reaction to contrast, which in the opinion of the investigator, cannot be adequately premedicated
- Symptomatic carotid disease warranting intervention, which will not be

performed prior to TAA repair

- Mycotic aneurysm, leaking/ruptured aneurysm, impending rupture, aortobronchial fistula, aortoesophageal fistula, or traumatic injury
- Surgical or endovascular AAA repair within 30 days before or after TAA repair
- Previous placement of a thoracic endovascular graft
- Aortic dissection
- Prior open repair involving the descending thoracic aorta including supra-renal aorta and/or arch (prior elephant trunk procedure is acceptable if > 30 days post-procedure)
- Interventional and/or open surgical procedures (unrelated to TAA repair) within 30 days before or after TAA repair

Anatomical Exclusion Criteria

- Treatment length (i.e., aneurysm/ulcer length including fixation sites) along greater curvature:
  - > 127 mm for 18 to 24 mm diameter grafts
  - > 149 mm for 26 mm diameter grafts
  - > 355 mm for 28 to 32 mm diameter grafts (nontapered and tapered)
  - > 324 mm for 34 and 36 mm diameter grafts (nontapered)
  - > 363 mm for 34 and 36 mm diameter grafts (tapered)
  - > 339 mm for 38 and 40 mm diameter grafts (nontapered)
  - > 332 mm for 38 and 40 mm diameter grafts (tapered)
  - > 354 mm for 42 mm diameter grafts (nontapered)
  - > 347 mm for 42 mm diameter grafts (tapered)
  - > 369 mm for 44 and 46 mm diameter grafts (nontapered)
  - > 355 mm for 44 mm diameter grafts (tapered)
  - > 362 mm for 46 mm diameter grafts (tapered)
- Proximal neck length measuring < 20 mm between the left common carotid artery and aneurysm (covering the subclavian artery is acceptable except in patients with LIMA bypass, anomalous vertebral artery off of the arch in the region of the subclavian artery, or dominant vertebral artery off of the subclavian artery)
- Distal neck length measuring < 20 mm between the celiac artery and the aneurysm
- Aortic arch radius < 20 mm (if device is deployed in arch)

- Proximal neck diameter, measured outer wall to outer wall on a sectional image or multiplanar reconstruction (CT), < 15 mm or > 42 mm
- Distal neck diameter, measured outer wall to outer wall on a sectional image or multiplanar reconstruction (CT), < 15 mm or > 42 mm (estimate from more proximal segment if diaphragm makes identification of the outer wall difficult)
- Tortuosity, calcification, occlusive disease, or arterial diameter, measured inner wall to inner wall on a sectional image, that is not conducive to placement of the introducer sheath (16 Fr for 18 to 30 mm diameter grafts, 18 Fr for 32 to 38 mm diameter grafts, or 20 Fr for 40 to 46 mm diameter grafts) – use of an access conduit is acceptable
- Prohibitive calcification, occlusive disease, or tortuosity of intended fixation sites
- Circumferential thrombus in region of intended fixation sites
- Inverted funnel-shaped proximal neck with > 10% increase in diameter over length of neck
- Funnel-shaped distal neck with > 10% increase in diameter over length of neck
- Inability to preserve the left common carotid artery and celiac artery
- Aneurysm or angulation in the distal thoracic aorta that would preclude advancement of the introduction system

2. Follow-up Schedule

The study follow-up schedule (Table 11) consisted of both clinical and imaging (CT and X-ray) assessments at post-procedure (pre-discharge), 30 days, 6 months, 12 months, and yearly thereafter through 5 years.

Table 11. Study follow-up schedule

Study Schedule							
	Pre-op	Intra-op	Post-procedure	30-Day	6-Month	12-Month	24-Month[d]
Clinical exam	X		X	X	X	X	X
Blood tests	X		X	X	X	X	X
CT scan	X[a]			X[c]	X[c]	X[c]	X[c]
Thoracic x-ray				X	X	X	X
Angiography	X[b]	X					

[a]It is recommended that imaging be performed within 6 months before the procedure.
[b]Required only to resolve any uncertainties in anatomical measurements necessary for graft sizing.
[c]MR imaging may be used for those patients experiencing renal failure or who are otherwise unable to undergo contrast-enhanced CT scan, with TEE being an additional option in the event of suboptimal MR imaging.

[d]Yearly thereafter through 5 years.

An independent core laboratory analyzed all patient imaging. An independent clinical events committee (CEC) adjudicated all major adverse events (MAEs), including all patient deaths; additionally the CEC also adjudicated core laboratory reports of migration and device integrity loss. An independent data safety monitoring board (DSMB) monitored the clinical trial according to an established safety monitoring plan.

3. Clinical Endpoints

The primary safety endpoint was 30-day freedom from major adverse events (MAEs), and the performance goal was 80.6%. MAEs were defined as the following: all-cause death; Q-wave myocardial infarction; cardiac event involving arrest, resuscitation, or balloon pump; ventilation > 72 hours or reintubation; pulmonary event requiring tracheostomy or chest tube; renal failure requiring permanent dialysis, hemofiltration, or kidney transplant in a patient with a normal pre-procedure serum creatinine level; bowel resection; stroke; paralysis; amputation involving more than the toes; aneurysm or vessel leak requiring reoperation; deep vein thrombosis requiring surgical or lytic therapy; pulmonary embolism involving hemodynamic instability or surgery; coagulopathy requiring surgery; or wound complication requiring return to the operating room.

The safety hypothesis of the study was that the freedom from MAEs at 30 days met the performance goal of 80.6%. The performance goal was said to have been met provided that the null hypothesis is rejected in favor of the alternative with a one-tailed exact binomial test at the 0.025 level. Given that πMAE (30) is the probability that a randomly selected patient experienced freedom from MAE at 30 days, the null and alternative hypotheses were as follows.

The primary effectiveness endpoint was 12-month device success, and the performance goal was 80.7%. Device success at 12 months was defined as: technical success, with none of the following at 12 months:

- Type I or type III endoleaks requiring re-intervention
- Aneurysm rupture or conversion to open surgical repair
- Aneurysm enlargement greater than 5 mm

When technical success was achieved, the physician accessed the aneurysm site and deployed the Zenith Alpha™ Thoracic Endovascular Graft at the intended location. The endovascular graft must be patent at the time of deployment completion as evidenced by intraoperative angiography.

The effectiveness hypothesis of the study was that device success at 12 months met the performance goal of 80.7%. The performance goal was said to have been met provided that the null hypothesis is rejected in favor of the alternative with a one-tailed exact binomial test at the 0.025 level. Given that $\pi DS(12)$ is the probability that a randomly selected patient experienced device success at 12 months, the null and alternative hypotheses were as follows.

Pre-specified Statistical Analysis Plan

Null Hypothesis: The 30-day freedom from MAE for patients treated with the Zenith Alpha™ Thoracic Endovascular Graft does not meet the performance goal (80.6%).

$$H0: \pi MAE(30) \leq 80.6\%$$

Alternate Hypothesis: The 30-day freedom from MAE for patients treated with the Zenith Alpha™ Thoracic Endovascular Graft meets the performance goal (80.6%).

$$HA: \pi MAE(30) > 80.6\%$$

Therefore, the null hypothesis will be rejected in favor of the alternative provided that no more than 13 of the 110 enrolled subjects experienced a major adverse event within 30 days.

Null Hypothesis: The 12-month device success for patients treated with the Zenith Alpha™ Thoracic Endovascular Graft does not meet the performance goal (80.7%).

$$H0: \pi DS(12) \leq 80.7\%$$

Alternate Hypothesis: The 12-month device success for patients treated with the Zenith Alpha™ Thoracic Endovascular Graft meets the performance goal (80.7%).

$$HA: \pi DS(12) > 80.7\%$$

Therefore, the null hypothesis will be rejected in favor of the alternative provided that no more than 12 of the 110 enrolled subjects experience a device failure within 12 months. This corresponds to 89.1% device success. The actual number of patients who can

experience an event may be less since the sample size of 110 was augmented to include subjects who may become lost to follow-up.

The statistical analysis plan used for the Zenith Alpha™ Thoracic Endovascular Graft clinical study was prospectively defined. Taking into account expected attrition, and a goal of achieving at least 80% statistical power at a one-sided significance level of 2.5%, a sample size of 110 enrolled subjects was considered to be sufficient using a margin of 10%. The safety and effectiveness endpoints were said to be met if the null hypothesis was rejected in favor of the alternate hypothesis using a one-tailed exact binomial test for each endpoint.

Success/Failure Criteria

The Zenith Alpha™ Thoracic Endovascular Graft clinical study was considered a success if both the primary safety and primary effectiveness endpoints were met. These endpoints were assessed by demonstrating accordance to a prespecified performance goal, sufficient to reject the null hypotheses in regards to freedom from MAE at 30 days and device success at 12 months. The analyses required that the performance goals, which were chosen based on the 30-day freedom from MAE rate and the 12-month device success for subjects treated with the currently approved Zenith® TX2® TAA Endovascular Graft, be met.

B. Accountability of PMA Cohort

At the time of the database lock, of 110 subjects enrolled in the PMA study, 90% (99/110) were eligible for follow-up at 12 months (Table 12). All subjects were evaluable for the primary safety endpoint (freedom from MAE at 30 days). All eligible subjects were also evaluable for the primary effectiveness endpoint (12-month device success) based on a component of the composite measure having been assessed at the time of the procedure, consistent with the performance goal development. Two patients, although enrolled in the study, did not receive the device due to an inability to advance/gain access to the target treatment site. Although the primary safety and effectiveness endpoints were evaluated at 30 days and 12 months, respectively, data presented herein include longer-term follow-up that was available at the time of the data lock (April 7, 2015). Table 12 reports the percent of follow-up data available through 4 years.

Table 12. Follow-up availability

Follow-up Visit	Patients Eligible for Follow-up	Percent of Data Available[a]				Adequate Imaging to Assess the Parameter[b]				Events Occurring Before Next Interval			
		Patients with Data for that Visit	CT[c]	X-ray	Patients with Follow-up Pending[d]	Size Increase	Endoleak	Migration	Fracture	Death	Conversion	LTF/ WTHD	Not Due for Next Visit
Operative	110	110/110 (100%)	NA	NA	0	NA	NA	NA	NA	0	0	0	0
30-day	110[e]	106/110 (96.4%)	105/108 (97.2%)	98/108 (90.7%)	0	105/108 (97.2%)	102/108 (94.4%)	NA	105/108 (97.2%)	3	0	0	2[e]
6-month	105	99/105 (94.3%)	97/105 (92.4%)	92/105 (87.6%)	0	96/105 (91.4%)	91/105 (86.7%)	94/105 (89.5%)	98/105 (93.3%)	2	0	4	0
12-month	99	91/99 (91.9%)	92/99 (92.9%)	84/99 (84.8%)	0	92/99 (92.9%)	83/99 (83.8%)	92/99 (92.9%)	92/99 (92.9%)	7	1	2	0
2-year	89	78/89 (87.6%)	79/89 (88.8%)	75/89 (84.3%)	8	77/89 (86.5%)	73/89 (82.0%)	77/89 (86.5%)	77/89 (86.5%)	3	0	7	45
3-year	34	23/34 (67.6%)	20/34 (58.8%)	18/34 (52.9%)	11	17/34 (50.0%)	15/34 (44.1%)	17/34 (50.0%)	17/34 (50.0%)	0	0	0	26
4-year	8	6/8 (75.0%)	6/8 (75.0%)	6/8 (75.0%)	2	6/8 (75.0%)	6/8 (75.0%)	6/8 (75.0%)	6/8 (75.0%)	0	0	0	8

NA – Not assessed.
LTF/WTHD – Lost-to-follow-up and withdrawn.
[a]Site-submitted data.
[b]Based on core laboratory analysis.
[c]Includes MRI or TEE imaging (which is allowed per protocol) when the patient is unable to receive contrast medium due to renal failure.
[d]Patients still within follow-up window, but data not yet available.
[e]Two patients did not receive the device at the time of the implant procedure and therefore only 30-day clinical follow-up was applicable before the patients exited the study, with no further follow-up due thereafter.

C. Study Population Demographics and Baseline Parameters

The tables below present the demographics, comorbidities, American Society of Anesthesiologists (ASA) Physical Status Classification, Society of Vascular Surgery/International Society of Cardiovascular Surgery (SVS-ISCVS) risk score classification, the type of lesion, and the baseline anatomic characteristics of the study population. The majority of subjects were male (58.2%) with a mean age of 72.2 years. The most common medical conditions noted at the pre-procedure visit were hypertension, hypercholesterolemia, smoking, history of aneurysm, chronic obstructive pulmonary disease (COPD), and peripheral vascular disease. Subjects were most commonly classified as ASA II (55.5%), followed by ASA III (26.4%) and ASA IV 10%. The SVS-ISCVS classification was used to further characterize vascular morbidity. These comorbidities mirror the population with aneurysms and ulcers of the descending thoracic aorta (DTA). The demographics and characteristics are presented in Table 13.

Table 13. Demographics and patient characteristics

Demographic	Mean ± SD (n, range) or Percent Patients (number/total number)
Age (years)	
All patients	72.2 ± 9.8 (n=110, 42 – 92)
Male	70.7 ± 9.9 (n=64, 42 – 85)
Female	74.3 ± 9.4 (n=46, 44 – 92)
Gender	
Male	58.2% (64/110)
Female	41.8% (46/110)
Ethnicity	
White	53.6% (59/110)
Hispanic or Latino	0
Black or African American	8.2% (9/110)
American Indian or Alaska Native	0
Asian	38.2% (42/110)
Native Hawaiian or other Pacific Islander	0
Other	0
Height (in)	65.3 ± 4.5 (n=110, 55.1 – 75.2)
Weight (lbs)	161.7 ± 44.3 (n=110, 79.2 – 330.0)
Body mass index	26.5 ± 6.0 (n=110, 16.4 – 50.0)

The medical history and comorbid medical conditions for the patient cohort are presented in Table 14.

Table 14. Pre-existing comorbid medical conditions

Medical History	Percent Patients (number/total number)
Cardiovascular	
Myocardial infarction (MI)	12.7% (14/110)
Angioplasty/stent	10.0% (11/110)
Cardiac or thoracic surgery	16.4% (18/110)
Prior diagnosis of symptomatic congestive heart failure (CHF)	10.0% (11/110)
Angina	16.4% (18/110)
Prior diagnosis of arrhythmia	23.6% (26/110)
Hypertension	88.2% (97/110)
Coronary artery bypass graft	11.8% (13/110)
Vascular	
Thromboembolic event	0.9% (1/110)
Peripheral vascular disease	21.8% (24/110)
Symptomatic carotid disease warranting intervention	1.8% (2/110)
Any aneurysm (other than the study lesion)	45.5% (50/110)
Thoracic aortic aneurysm	2.7% (3/110)
Abdominal aortic aneurysm	26.4% (29/110)
Other aneurysm[a]	16.4% (18/110)
Degenerative or atherosclerotic ulcer (other than the study lesion)	0.9% (1/110)
Any dissection	9.1% (10/110)[b]
Thoracic aortic dissection	6.4% (7/110)[c]
Abdominal aortic dissection	0
Other dissection[d]	2.7% (3/110)
Thoracic trauma	3.6% (4/110)[e]
Aortobronchial fistula	0.9% (1/110)
Aortoesophageal fistula	0
Bleeding diathesis or uncorrectable coagulopathy	0
Endarterectomy	1.8% (2/110)
Diagnosed or suspected congenital degenerative collagen disease	0
Pulmonary	
Chronic obstructive pulmonary disease (COPD)	25.5% (28/110)
Home oxygen	1.8% (2/110)
Renal	
Chronic renal failure	10.0% (11/110)
Hemodialysis	1.8% (2/110)
Chronic peritoneal dialysis	0
Endocrine	
Diabetes	19.1% (21/110)
Hypercholesterolemia	73.6% (81/110)
Infectious disease	
Systemic infection	0
Gastrointestinal	
Gastrointestinal disease	34.5% (38/110)
Hepatobiliary	
Liver disease	12.7% (14/110)
Neoplasms	
Cancer	24.5% (27/110)
Neurologic	
Stroke	10.9% (12/110)
Substance use	
Past or current smoker	71.8% (79/110)
Allergies	
Allergies	41.8% (46/110)

[a]The "other" aneurysm category includes patients with aneurysms in different locations (i.e., not descending thoracic or abdominal aorta) and patients with aneurysms in multiple locations.
[b]All patients had a history of aortic dissection but at the time of enrollment had no radiographic evidence of aortic dissection.
[c]The treated aneurysm/ulcer was located in the same aortic segment as the previously diagnosed dissection in four patients.
[d]The "other" dissection category includes patients with dissection in different locations (i.e., not descending thoracic or abdominal aorta) and patients with dissections in multiple locations.
[e]All patients had a history (> 1 year) of traumatic thoracic injury.

Table 15 reports the ASA classification.

Table 15. ASA physical status classification

ASA Classification	Percent Patients (number/total number)
Healthy patient (1)	8.2% (9/110)
Mild systemic disease (2)	55.5% (61/110)
Severe systemic disease (3)	26.4% (29/110)
Incapacitating systemic disease (4)	10.0% (11/110)
Moribund patient (5)	0

Table 16 reports the SVS-ISCVS risk score.

Table 16. SVS-ISCVS risk score classification

SVS-ISCVS Category	Percent Patients (number/total number)
Diabetes risk score	
0	83.6% (92/110)
1	5.5% (6/110)
2	9.1% (10/110)
3	1.8% (2/110)
4	0
Smoking risk score	
0	47.3% (52/110)
1	30.0% (33/110)
2	13.6% (15/110)
3	9.1% (10/110)
Hypertension risk score	
0	11.8% (13/110)
1	29.1% (32/110)
2	31.8% (35/110)
3	27.3% (30/110)
Hyperlipidemia risk score	
0	26.4% (29/110)
1	17.3% (19/110)
2	1.8% (2/110)
3	54.5% (60/110)

SVS-ISCVS Category	Percent Patients (number/total number)
Cardiac status risk score	
0	70.0% (77/110)
1	18.2% (20/110)
2	11.8% (13/110)
3	0
Carotid disease risk score	
0	84.5% (93/110)
1	13.6% (15/110)
2	0.9% (1/110)
3	0.9% (1/110)
Renal status risk score	
0	87.3% (96/110)
1	10.9% (12/110)
2	0
3	1.8% (2/110)
Pulmonary status risk score	
0	66.4% (73/110)
1	26.4% (29/110)
2	6.4% (7/110)
3	0.9% (1/110)
Total SVS/ISCVS risk score	5.9 ± 2.6 (n=110, 1 – 14)

The majority of subjects (81.8%) had fusiform aneurysms and the remaining 18.2% had penetrating atherosclerotic ulcers. Table 17 reports the presenting morphology.

Table 17. Presenting morphology type per the core laboratory

Morphology	Percent Patients (number/total number)
Aneurysm	81.8% (90/110)
Ulcer	18.2% (20/110)

The main baseline anatomical measurements were as follows: mean proximal neck diameter at the left common carotid artery (LCCA) was 34.0 ± 3.0 mm, mean proximal neck length was 94.7 ± 57.8 mm, mean maximum aneurysm diameter was 60.9 ± 11.4 mm, mean distal neck diameter was 31.0 ± 5.1 mm, and mean aneurysm length was 113.5 ± 63.0 mm. The mean ulcer depth was 14.1 ± 3.7 mm and the mean ulcer length was 34.8 ± 20.3 mm. Table 18 reports presenting anatomical dimensions of the aneurysm/ulcer, the proximal and distal aortic necks, and the right and left iliac arteries.

Table 18. Presenting anatomical dimensions reported per the core laboratory

Measure	Mean ± SD (n, range)
Aneurysm dimensions	
Major diameter (mm)	60.9 ± 11.4 (n=90, 41 – 99)
Minor diameter (mm)	51.7 ± 11.1 (n=90, 30 – 92)
Length (mm)	113.5 ± 63.0 (n=90, 25.4 – 324.0)
Ulcer dimensions	
Ulcer depth (mm)	14.1 ± 3.7 (n=20, 8 – 25)
Length (mm)	34.8 ± 20.3 (n=20, 11.0 – 85.7)
Proximal neck diameter	
Left common carotid artery	
Major (mm)	34.0 ± 3.0 (n=110, 24 – 42)
Minor (mm)	31.1 ± 3.5 (n=110, 18 – 39)
20 mm distal to left common carotid artery	
Major (mm)	33.3 ± 4.3 (n=110, 22 – 54)
Minor (mm)	30.6 ± 4.3 (n=110, 20 – 49)
Distal neck diameter	
20 mm proximal to celiac artery	
Major (mm)	31.0 ± 5.1 (n=110, 20 – 48)
Minor (mm)	28.9 ± 4.7 (n=110, 19 – 42)
Celiac artery	
Major (mm)	29.5 ± 4.4 (n=110, 20 – 44)
Minor (mm)	27.3 ± 3.8 (n=110, 19 – 38)
Proximal neck length	
Left common carotid artery to distal part of neck (mm)	94.7 ± 57.8 (n=110, 14.4 – 276.7)
Distal neck length	
Celiac artery to proximal part of neck (mm)	105.2 ± 63.2 (n=110, 5.6 – 268.5)
Right iliac artery diameter	
Narrowest segment (mm)	6.7 ± 1.6 (n=105, 3 – 10)[a]
Left iliac artery diameter	
Narrowest segment (mm)	6.9 ± 1.8 (n=104, 0 – 11)[a]

[a]CT imaging was not always adequate for measurement of the iliac arteries.

Table 19 reports the distribution in aneurysm diameter/ulcer depth.

Table 19. Distribution in range of maximum aneurysm diameter or ulcer depth per the core laboratory

Type	Size Range[a]	Percent Patients (number/total number)
Aneurysm	40 mm – < 50 mm	8.9% (8/90)
	50 mm – < 60 mm	40.0% (36/90)
	60 mm – < 70 mm	36.7% (33/90)
	70 mm – < 80 mm	6.7% (6/90)
	80 mm – < 90 mm	4.4% (4/90)
	90 mm – < 100 mm	3.3% (3/90)

Type	Size Range[a]	Percent Patients (number/total number)
Ulcer	< 20 mm	95.0% (19/20)
	20 mm – < 30 mm	5.0% (1/20)
	30 mm – < 40 mm	0
	40 mm – < 50 mm	0
	50 mm – < 60 mm	0
	60 mm – < 70 mm	0
	70 mm – < 80 mm	0

[a]Diameter for aneurysms and depth for ulcers.

Table 20 provides the distribution in location of the aneurysm/ulcer.

Table 20. Location of the primary aneurysm/ulcer as determined by the core laboratory

Location	Percent Patients (number/total number)		
	Aneurysm Patients	Ulcer Patients	All Patients
Location in the descending thoracic aorta			
Proximal	26.7% (24/90)	50.0% (10/20)	30.9% (34/110)
Middle	53.3% (48/90)	30.0% (6/20)	49.1% (54/110)
Distal	20.0% (18/90)	20.0% (4/20)	20.0% (22/110)

D. Procedural Information

The majority (71.8%) of procedures were performed under general anesthesia, followed by local anesthesia in 21.8% of procedures. Vascular access was gained via femoral artery cutdown in 62.7% of subjects, percutaneously in 36.4% of subjects, and by using a conduit in 0.9% of subjects. The mean procedure time was 99.4 ± 53.6 minutes (range 31-362 minutes) and the mean procedural blood loss was 121.8 ± 137.7 ml. The mean anesthesia time was 162.7 ± 61.4 minutes and the mean fluoroscopy time was 20.0 ± 20.1 minutes.

Adjunctive techniques for spinal cord protection to prevent paraplegia were performed in 40.0% of subjects (72.7% were cerebral spinal fluid (CSF) drainage), and induced hypotension to ease deployment was performed in 7.3% of subjects. The left subclavian artery (LSA) was covered completely in 13% of subjects. No LCCA to LSA bypass or LSA transposition were performed.

The access method used to insert the Zenith Alpha™ Thoracic Endovascular Graft is presented in Table 21. Three types of methods were used: percutaneous (direct needle puncture of the access vessel), cutdown (surgical exposure of the access vessel), and conduit (surgical technique used to bypass prohibitive access vessels). For the

percutaneous access method, the procedure time was 88.8 ± 44.7 minutes, blood loss was 128.5 ± 136.4 cc, and incidence of access site complications was 7.3%. For the cutdown/conduit access method, the procedure time was 105.4 ± 57.6 minutes, blood loss was 118.0 ± 139.3 cc, and incidence of access site complications was 5.7%. These data support the use of either method of access for the device.

Table 21. Access method used to insert the endovascular graft

Type	Percent Patients (number/total number)		
	Aneurysm Patients	**Ulcer Patients**	**All Patients**
Percutaneous	31.1% (28/90)	60.0% (12/20)	36.4% (40/110)
Cutdown	67.8% (61/90)	40.0% (8/20)	62.7% (69/110)
Conduit	1.1% (1/90)	0	0.9% (1/110)

The location of the graft components relative to an identified site is provided as percent of subjects in Table 22.

Table 22. Graft location per core laboratory

Location	Percent Patients (number/total number)		
	Aneurysm Patients	**Ulcer Patients**	**All Patients**
Proximal aspect of graft			
Above LCCA	0	0	0
Below LCCA, above LSA	9.1% (8/88)	30.0% (6/20)	13.0% (14/108)
Below LSA	83.0% (73/88)	60.0% (12/20)	78.7% (85/108)
Unable to assess[a]	8.0% (7/88)	10.0% (2/20)	8.3% (9/108)
Distal aspect of graft			
Above celiac artery	95.5% (84/88)	90.0% (18/20)	94.4% (102/108)
Below celiac artery	0	0	0
Unable to assess[a]	4.5% (4/88)	10.0% (2/20)	5.6% (6/108)

LCCA = left common carotid artery; LSA = left subclavian artery.
[a]All patients had post-procedure angiography but not all imaging was adequate for core laboratory review.

Two patients required axillary-axillary bypasses prior to the index procedure (both from a Japanese site). Additional procedures performed after graft deployment included use of a vessel closure device in 26 patients, LCCA stent placement in one patient, LSA stent placement in one patient, LSA coil embolization in five patients, femoral endarterectomy in two patients, thromboendarterectomy and patch right femoral in one patient, iliac artery stent placement in three patients, and chimney stent to maintain blood flow to the

LCCA and LSA coil embolization in one patient. Table 23 reports additional procedures performed either before or after graft implantation.

Table 23. Additional procedures

Procedure	Percent Patients (number/total number)	
	Before Graft Deployment	After Graft Deployment
Left carotid artery stent	0	0.9% (1/110)
Left subclavian artery stent	0	0.9% (1/110)
Iliac artery angioplasty	0.9% (1/110)	0
Iliac artery stent	0	2.7% (3/110)
Vessel closure device	0	23.6% (26/110)
Other	1.8% (2/110)[a]	8.2% (9/110)[b]

[a]Two patients from Japan (1040051 and 1040069) underwent axillary-axillary bypass prior to the index procedure.

[b]Two patients (1030005 and 1030044) underwent right femoral endarterectomy after the index procedure. One patient (0465997) underwent thromboendarterectomy and patch right femoral after the index procedure. Five patients (1040023, 1040033, 1040039, 1040051, and 1040069) underwent coil embolization of the left subclavian artery after the index procedure. One patient (1040080) had a chimney stent placed to maintain blood flow to the left common carotid artery and coil embolization of the left subclavian artery after the index procedure.

The device was successfully implanted in 98.2% of subjects (two patients did not receive the device due to the inability to insert/advance the introduction system) and all subjects (100%) survived the endovascular procedure. Overall, the procedural results were as expected for the treatment of patients with aneurysms or ulcers of the DTA.

Clinical Utility Measures

The mean hospital stay after endovascular treatment was 7 days (range 1-185 days). One patient remained in the hospital 185 days due to a stroke the day of the procedure and was discharged to a long-term care facility. The mean stay in the intensive care unit (ICU) was 2.3 ± 8.9 days, and the mean days to ambulation was 1.6 ± 1.5 days. The clinical utility results are presented in Table 24.

Table 24. Clinical utility measures

Clinical Utility Measure	Mean ± SD (n, range)[a]		
	Aneurysm	Ulcer	All patients
Duration of ICU stay (days)	2.6 ± 9.9 (n=88, 0 – 91)	0.8 ± 0.6 (n=20, 0 – 2)	2.3 ± 8.9 (n=108, 0 – 91)
Days to resumption of oral fluid intake	0.4 ± 0.6 (n=89, 0 – 3)	0.5 ± 0.8 (n=20, 0 – 3)	0.4 ± 0.6 (n=109, 0 – 3)

Clinical Utility Measure	Mean ± SD (n, range)[a]		
	Aneurysm	Ulcer	All patients
Days to resumption of regular diet	1.3 ± 1.1 (n=89, 0 – 6)	1.5 ± 3.1 (n=19, 0 – 14)	1.3 ± 1.6 (n=108, 0 – 14)
Days to resumption of bowel function	2.3 ± 1.5 (n=70, 0 – 8)	2.0 ± 2.1 (n=15, 0 – 8)	2.3 ± 1.6 (n=85, 0 – 8)
Days to ambulation	1.6 ± 1.3 (n=88, 0 – 9)	1.8 ± 2.2 (n=20, 0 – 10)	1.6 ± 1.5 (n=108, 0 – 10)
Days to hospital discharge	7.4 ± 19.6 (n=90, 1 – 185)	5.0 ± 5.3 (n=20, 1 – 19)	7.0 ± 17.8 (n=110, 1 – 185)

[a]Not all clinical utility measures were assessed for all 110 patients.

Devices Implanted

Table 25 shows the percent of patients who received each type of Zenith Alpha™ Thoracic Endovascular Graft component (proximal, distal, or distal extension) during the initial implant procedure. Also included is the graft diameter range implanted for each component type. Although available for use in the aneurysm/ulcer study, graft diameters ranging from 18 mm to 26 mm were used only in the BTAI study.

Table 25. Stent-graft component type deployed

Type	Percent Patients (number/total number)[a]			Graft Diameter Range (All Patients)
	Aneurysm Patients	Ulcer Patients	All patients	
Proximal component (nontapered or tapered)	100% (88/88)	100% (20/20)	100% (108/108)	28 to 46 mm
Distal component	37.5% (33/88)	0	30.6% (33/108)	32 to 46 mm
Ancillary component	27.3% (24/88)[b]	5.0% (1/20)	23.1% (25/108)	28 to 46 mm
Additional proximal component	13.6% (12/88)	5.0% (1/20)	12.0% (13/108)	
Distal extension	14.8% (13/88)[c]	0	12.0% (13/108)	

[a]Two aneurysm patients did not receive a device as the introduction system could not be successfully advanced; therefore, the denominator is 108, not 110.
[b]One patient received both an additional proximal component and a distal extension.
[c]Includes 12 patients who received 1 distal extension, and 1 patient who received 2 distal extensions.

Table 26 further summarizes the total number of components placed during the initial implant procedure.

Table 26. Total number of components placed during the initial implant procedure

Main Body Design	Percent Patients (number/total number)[a]		Percent Patients (number/total number)		
			1	2	3
One-piece (proximal only)	Aneurysm Patients	62.5% (55/88)	69.1% (38/55)	29.1% (16/55)	1.8% (1/55)
	Ulcer Patients	100% (20/20)	95.0% (19/20)	5.0% (1/20)	0
	All Patients	69.4% (75/108)	76.0% (57/75)	22.7% (17/75)	1.3% (1/75)
Two-piece (proximal and distal)	Aneurysm Patients	37.5% (33/88)	N/A	78.8% (26/33)	21.2% (7/33)
	Ulcer Patients	N/A	N/A	N/A	N/A
	All Patients	30.6% (33/108)	N/A	78.8% (26/33)	21.2% (7/33)

[a]Two aneurysm patients did not receive a device as the introduction system could not be successfully advanced; therefore, the denominator is 108, not 110.

Table 27 reports the sizes (diameters and lengths) of the nontapered proximal components used during the initial implant procedure.

Table 27. Diameters and lengths of nontapered proximal component (ZTLP-P) sizes used

Diameter (mm)	Length (mm)	n
28	132	2
	155	2
30	132	8
	155	2
32	132	7
	155	4
	201	5
34	137	3
	161	6
	209	2
36	137	10
	161	6
	209	1
38	142	7
	167	3
	217	6
40	142	2
	167	3
	217	1
42	121	3
	173	4
44	125	2
	233	1
46	179	4

Table 28 reports the sizes (diameters and lengths) of the tapered proximal components used during the initial implant procedure.

Table 28. Diameters and lengths of tapered proximal component (ZTLP-PT) sizes used

Diameter (mm)	Length (mm)	n
34	161	4
	209	1
36	161	7
	209	4
38	167	1
	217	3
42	173	5
44	179	1
46	179	1

Table 29 reports the sizes (diameters and lengths) of the distal components used during the initial implant procedure.

Table 29. Diameters and lengths of distal component (ZTLP-D) sizes used

Diameter (mm)	Length (mm)	n
32	160	4
	229	1
34	142	2
	190	1
36	142	3
	190	1
38	147	4
	197	5
40	147	1
42	152	6
44	157	3
46	157	2

Table 30 reports the size (diameters and lengths) of the ancillary components used during the initial implant procedure.

Table 30. Diameters and lengths of ancillary component sizes used

Diameter (mm)	Length (mm)	n
28	108	1
32	108	2
34	112	2
36	112	1

Diameter (mm)	Length (mm)	n
38	91	4
42	94	3
46	97	1

E. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the 110 patients enrolled in the Zenith Alpha™ Thoracic Endovascular Graft pivotal study for the treatment of aneurysms/ulcers of the descending thoracic aorta. Table 31 presents the results of hypothesis testing for the primary safety endpoint (30-day freedom from MAEs). MAEs were defined as the following: all-cause death; Q-wave myocardial infarction; cardiac event involving arrest, resuscitation, or balloon pump; ventilation > 72 hours or reintubation; pulmonary event requiring tracheostomy or chest tube; renal failure requiring permanent dialysis, hemofiltration, or kidney transplant in a patient with a normal pre-procedure serum creatinine level; bowel resection; stroke; paralysis; amputation involving more than the toes; aneurysm or vessel leak requiring reoperation; deep vein thrombosis requiring surgical or lytic therapy; pulmonary embolism involving hemodynamic instability or surgery; coagulopathy requiring surgery; or wound complication requiring return to the operating room.

Table 31. Results from primary safety hypothesis testing (MAE endpoint)

Performance Goal	30-day Freedom from MAE Rate	*P*-value	95% Confidence Interval	Performance Goal Met
80.6%	96.4% (106/110)	< 0.001	(91%, 99%)	Yes

The 30-day freedom from MAE rate was 96.4% for the present study, which met the performance goal of 80.6% ($p < 0.001$). Four patients experienced MAEs: 1 patient had a stroke (1040045), 2 patients required ventilation > 72 hours/reintubation (1030062, 1030041), and 1 patient had a stroke and required ventilation > 72 hours/reintubation (1040069).

Death, Rupture, Conversion, and MAE

Table 32 provides the results from Kaplan-Meier analysis for freedom from death (all-cause and TAA-related), rupture, conversion, and MAEs through 2 years. Aneurysm-

related mortality was defined as death occurring within 30 days of the initial implant procedure or a secondary intervention, or any death adjudicated to be aneurysm-related by the CEC. There has been one TAA-related death (1040069)that occurred at 253 days post-procedure due to aspiration pneumonia, which the CEC had indicated was likely related to the severely debilitating stroke that the patient had suffered on the same day as the procedure. There has been one conversion to open surgical repair (1040073), which occurred at 330 days post-procedure due to aortoesophageal fistula.

Table 32. Kaplan-Meier estimates for freedom from death (all-cause and TAA-related), rupture, conversion, and MAEs

Event	Parameter	30 Days			180 Days			365 Days			730 Days		
		Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All
All-cause mortality	Number at risk[a]	89	20	109	86	19	105	80	18	98	69	18	87
	Cumulative events[b]	0	0	0	2	1	3	4	1	5	11	1	12
	Cumulative censored[c]	1	0	1	2	0	2	6	1	7	10	1	11
	KM estimate[d]	1.000	1.000	1.000	0.977	0.950	0.972	0.954	0.950	0.953	0.869	0.950	0.884
	Standard error	0.000	0.000	0.000	0.016	0.049	0.016	0.023	0.049	0.020	0.037	0.049	0.032
TAA-related mortality	Number at risk[a]	89	20	109	86	19	105	80	18	98	69	18	87
	Cumulative events[b]	0	0	0	0	0	0	1[e]	0	1	1	0	1
	Cumulative censored[c]	1	0	1	4	1	5	9	2	11	20	2	22
	KM estimate[d]	1.000	1.000	1.000	1.000	1.000	1.000	0.988	1.000	0.990	0.988	1.000	0.990
	Standard error	0.000	0.000	0.000	0.000	0.000	0.000	0.012	0.000	0.010	0.012	0.000	0.010
Rupture	Number at risk[a]	89	20	109	86	19	105	80	18	98	69	18	87
	Cumulative events[b]	0	0	0	0	0	0	0	0	0	0	0	0
	Cumulative censored[c]	1	0	1	4	1	5	10	2	12	21	2	23
	KM estimate[d]	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Standard error	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Conversion	Number at risk[a]	89	20	109	86	19	105	80	18	98	69	18	87
	Cumulative events[b]	0	0	0	0	0	0	1[f]	0	1	1	0	1
	Cumulative censored[c]	1	0	1	4	1	5	9	2	11	20	2	22
	KM estimate[d]	1.000	1.000	1.000	1.000	1.000	1.000	0.988	1.000	0.990	0.988	1.000	0.990
	Standard error	0.000	0.000	0.000	0.000	0.000	0.000	0.012	0.000	0.010	0.012	0.000	0.010
MAE[g]	Number at risk[a]	85	20	105	81	19	100	74	18	92	60	18	78
	Cumulative events[b]	4	0	4	7	1	8	12	1	13	24	1	25
	Cumulative censored[c]	1	0	1	2	0	2	4	1	5	6	1	7
	KM estimate[d]	0.956	1.000	0.964	0.922	0.950	0.927	0.864	0.950	0.879	0.722	0.950	0.763
	Standard error	0.022	0.000	0.018	0.029	0.049	0.025	0.037	0.049	0.032	0.049	0.049	0.042

[a]Number of patients at risk at the beginning of the interval.

[b]Total events up to and including the specific interval represents all patients who have had the event. Note, only the first event is represented in the Kaplan-Meier estimate. A patient may have multiple events in each category.

[c]Total censored patients up to and including the specific interval represents all patients who have met a study exit criteria or for whom data are not available at the specific interval.

[d]At end of interval.

[e]Death due to aspiration pneumonia (1040069).

[f]Conversion due to aortoesophageal fistula, adjudicated by the CEC as procedure-related (1040073).

[g]MAEs were defined as the following: all-cause death; Q-wave myocardial infarction; cardiac event involving arrest, resuscitation, or balloon pump; ventilation > 72 hours or reintubation; pulmonary event requiring tracheostomy or chest tube; renal failure requiring permanent dialysis, hemofiltration, or kidney transplant in a patient with a normal pre-procedure serum creatinine level; bowel resection; stroke; paralysis; amputation involving more than the toes;

aneurysm or vessel leak requiring reoperation; deep vein thrombosis requiring surgical or lytic therapy; pulmonary embolism involving hemodynamic instability or surgery; coagulopathy requiring surgery; or wound complication requiring return to the operating room.

All Adverse Events

Table 33 presents the number of patients experiencing events according to organ system category at 0-30 days, 31-180 days, 181-365 days and 366-730 days. Of note with respect to cerebrovascular/neurological morbidity, there were no cases of paraplegia/paralysis and one (1) case of paraparesis, which resolved with medication and cerebral spinal fluid drainage. Five (5) patients experienced stroke; two (2) occurred within 30 days, while the other three (3) occurred beyond 30 days (none of the three beyond 30 days were adjudicated by the CEC as TAA-related). One of the strokes within 30 days was a non-disabling stroke rated as "0" on the Modified Rankin Scale, which is indicative of "no symptoms at all". The other stroke within 30 days was a disabling stroke rated as "5" on the Modified Rankin Scale, which is indicative of "severe disability: bedridden, incontinent and requiring constant nursing care and attention"; as noted previously, this same patient (1040069) died from aspiration pneumonia 253 days post-procedure, which the CEC had indicated was likely related to the severely debilitating stroke that the patient had suffered on the same day as the procedure.

Table 33. Percent of patients experiencing events by category

	Percent of Patients Experiencing Event (n/N)											
Category	**0-30 Days**			**31-180 Days**			**181-365 Days**			**366-730 Days**		
	Aneur	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**
Access site/incision[a]	5.6% (5/90)	5.0% (1/20)	5.5% (6/110)	3.4% (3/89)	0	2.8% (3/109)	0	0	0	0	0	0
Cardiovascular[b]	5.6% (5/90)	0	4.5% (5/110)	0	0	0	2.3% (2/86)	0	1.9% (2/105)	1.3% (1/80)	0	1.0% (1/98)
Cerebrovascular/ neurological[c]	3.3% (3/90)	0	2.7% (3/110)	1.1% (1/89)	0	0.9% (1/109)	2.3% (2/86)	0	1.9% (2/105)	0	0	0
Gastrointestinal[d]	1.1% (1/90)	5.0% (1/20)	1.8% (2/110)	4.5% (4/89)	5.0% (1/20)	4.6% (5/109)	1.2% (1/86)	0	1.0% (1/105)	2.5% (2/80)	5.6% (1/18)	3.1% (3/98)
Pulmonary[e]	4.4% (4/90)	0	3.6% (4/110)	1.1% (1/89)	0	0.9% (1/109)	1.2% (1/86)	0	1.0% (1/105)	3.8% (3/80)	0	3.1% (3/98)
Renal[f]	3.3% (3/90)	0	2.7% (3/110)	4.5% (4/89)	0	3.7% (4/109)	3.5% (3/86)	0	2.9% (3/105)	2.5% (2/80)	0	2.0% (2/98)

Category	Percent of Patients Experiencing Event (n/N)											
	0-30 Days			31-180 Days			181-365 Days			366-730 Days		
	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All
Vascular[g]	4.4% (4/90)	0	3.6% (4/110)	2.2% (2/89)	5.0% (1/20)	2.8% (3/109)	4.7% (4/86)	0	3.8% (4/105)	10.0% (8/80)	5.6% (1/18)	9.2% (9/98)
Miscellaneous/ other[h]	31.1% (28/90)	35.0% (7/20)	31.8% (35/110)	29.2% (26/89)	20.0% (4/20)	27.5% (30/109)	25.6% (22/86)	15.8% (3/19)	23.8% (25/105)	31.3% (25/80)	22.2% (4/18)	29.6% (29/98)

Note: Denominators represent the number of patients available at the start of each interval.
[a]Access site/incision events included: hematoma (n=5), hernia (n=1), infection (n=2), lymph fistula (n=0), pseudoaneurysm (n=0), seroma (n=1), and wound complication requiring return to operating room (n=0).
[b]Cardiovascular events included: cardiac arrhythmia (n=4), cardiac arrest (n=0), cardiac ischemia (n=1), congestive heart failure (n=1), myocardial infarction (n=3), and refractory hypertension (n=0).
[c]Cerebrovascular/neurological events included: paralysis (n=0), paraplegia (n=0), paraparesis > 30 days (n=1), spinal cord shock (n=0), transient ischemic attack (n=0), and stroke (n=5).
[d]Gastrointestinal events included: bleeding (n=4), bowel ischemia (n=2), infection (n=4), mesenteric ischemia (n=1), and paralytic ileus > 4 days (n=0).
[e]Pulmonary events included: COPD (n=1), hemothorax (n=0), pleural effusion (n=1), pneumonia (n=6), pneumothorax (n=0), pulmonary edema (n=0), pulmonary embolism (n=1), and pulmonary embolism involving hemodynamic instability or surgery (n=0).
[f]Renal events included: renal failure (n=4), UTI (n=6), serum creatinine rise > 30% above baseline resulting in a persistent value > 2.0 mg/dl (n=2).
[g]Vascular events included: aneurysm (n=11), aortobronchial fistula (n=1), aortoesophageal fistula (n=1), aortoenteric fistula (n=0), coagulopathy (n=1), deep vein thrombosis (n=0), dissection (n=3), embolism (n=2), hematoma (n=1), pseudoaneurysm (n=1), thrombosis (n=1), and vascular injury (n=5).
[h]Miscellaneous/other events included: hypersensitivity/allergic reaction (n=1), multi-organ failure (n=2), sepsis (n=2), and other (n=70).

2. Effectiveness Results

The analysis of effectiveness was based on the 110 patients enrolled in the Zenith Alpha™ Thoracic Endovascular Graft pivotal study for the treatment of aneurysms/ulcers of the descending thoracic aorta. Table 34 presents the results of hypothesis testing for the primary effectiveness endpoint (12-month device success).

Table 34. Results from primary effectiveness hypothesis testing (device success endpoint)

Performance Goal	12-month Device Success Rate	*P*-value	95% Confidence Interval	Performance Goal Met
80.7%	92.7% (102/110)[a]	< 0.001	(86.2%, 96.8%)	Yes

[a]The performance goal was originally calculated with a 365-day cutoff for inclusion of events (e.g., secondary interventions) and the results in the present study were analyzed in the same fashion for consistency such that the 12-month device success rate was 95.5% (105/110) with a 95% confidence interval of 89.7%, 98.5%. However, there were 3 additional patients in the present study who had an endoleak detected at the 12-month follow-up and subsequently underwent secondary intervention > 365 days after the index procedure; therefore, a conservative analysis was performed that included these 3 additional patients as failures (as shown in the table).

The 12-month device success rate was 92.7% for the present study (using the conservative analysis shown in Table 34), which met the performance goal of 80.7% ($p < 0.001$). There were 5 patients who did not meet the effectiveness endpoint of 12-month device success (using the original 365-day cutoff for events), as follows. Two patients (1030014, 1030098) did not receive the device due to an inability to insert/advance the introduction system and were therefore technical failures. In patient 1030014 (87-year-old white female), the introduction system became lodged at the aortic bifurcation in the right common iliac artery despite attempts to increase the diameter of the iliac artery. In patient 1030098 (73-year-old white female), the index procedure was aborted due to difficulty inserting a dilator in the left limb of a previous aneurysm repair; the previous endovascular abdominal aortic aneurysm repair made the patient a poor candidate for a conduit. Three patients (1030017, 1030046, 1040073) experienced aneurysm growth greater than 5 mm at the 12-month follow-up, one of whom (1040073) also underwent conversion to open surgical repair 330 days post-procedure due to an aortoesophageal fistula. There were 3 additional patients who had endoleak detected at 12-month follow-up and subsequently underwent secondary intervention > 365 days after the index procedure (1030047, 1030072, 1030095). Sensitivity to missing data, including a worst-case analysis, was performed, and met the performance goal.

Device Performance

Table 35 presents changes in aneurysm size, as observed from the 30-day (baseline) measurement to each follow-up exam through 2 years (based on core laboratory evaluation). A total of 11 patients experienced aneurysm growth (> 5 mm) at one or more follow-up time points based on core laboratory analysis through 2 years. Aneurysm growth was associated with detectable endoleak in six patients, four of whom underwent secondary intervention. There was no detectable endoleak in the remaining five patients with aneurysm growth, two of whom had no change in aneurysm size (≤ 5 mm change compared to baseline) as of the last available follow-up without the need for secondary intervention. Among the three other patients with growth and no detectable endoleak, two required secondary intervention and one had growth at the last available follow-up; each growth was associated with an inadequate seal zone length (i.e., length < 20 mm) as well as graft undersizing. Each patient who had growth that did not resolve spontaneously or was not associated with a Type II endoleak was initially treated for an aneurysm using only a proximal component, underscoring the importance of adhering to the sizing guidelines in the Instructions for Use (IFU), both in terms of component diameter as well as component type and length, which includes the use of a two-component repair (proximal and distal components) when treating aneurysms.

Table 35. Change in aneurysm diameter/ulcer depth based on results from core laboratory analysis

Item	Percent Patients (number/total number)								
	Aneurysm			Ulcer			All		
	6-month	12-month	2-year	6-month	12-month	2-year	6-month	12-month	2-year
Increase (> 5 mm)	4.2% (3/72) [a,b,c]	4.2% (3/71) [a,c,d]	14.8% (9/61)[a,d,e-k]	0	0	0	3.3% (3/90)	3.4% (3/88)	12.0% (9/75)
Decrease (> 5 mm)	19.4% (14/72)	31.0% (22/71)	24.6% (15/61)	33.3% (6/18)	52.9% (9/17)	64.3% (9/14)	22.2% (20/90)	35.2% (31/88)	32.0% (24/75)
No change (≤ 5 mm)	76.4% (55/72)	64.8% (46/71)	60.7% (37/61)	66.7% (12/18)	47.1% (8/17)	35.7% (5/14)	74.4% (67/90)	61.4% (54/88)	56.0% (42/75)

Note: the number of patients with adequate imaging to assess for size increase reflects the number of exams in which aneurysm diameter/ulcer depth was able to be assessed at each specified time point, whereas the denominators in this table also take into account the availability of a baseline exam to which to compare.

[a]Patient 1030046 – The patient was treated at the time of the index procedure with a single proximal component. The patient underwent a secondary intervention prior to the 2-year follow-up (Table 40) to treat the unexplained aneurysm growth (i.e., no detectable endoleaks). Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing and a proximal seal length < 20 mm.

[b]Patient 1040060 – The patient has not required a secondary intervention. Per core laboratory evaluation, no endoleaks have been identified in this patient. Aneurysm size was stable at 12 months (< 5 mm increase).

[c]Patient 1040073 – The patient had a Type IIb endoleak, which was treated prior to the 12-month follow-up (Table 40).

[d]Patient 1030017 – The patient was treated at the time of the index procedure with a single proximal component. The patient had no evidence of detectable endoleak. The patient underwent a secondary intervention beyond 2 years (placement of a distal component 922 days post-procedure for aneurysm growth). Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing and a distal seal length < 20 mm.

[e]Patient 1040034 – The patient has not had a secondary intervention and core laboratory results indicate no growth at 3 years.

[f]Patient 1030047 – The patient was treated at the time of the index procedure with a single proximal component. The patient also had distal Type I endoleak (Table 36) and CEC-confirmed migration (Table 37). A secondary intervention was performed (ancillary component placement) on post-operative day 727 (Table 40) and no growth was noted at 3 years. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing as well as a distal seal length < 20 mm.

[g]Patient 1030051 – The patient was treated at the time of the index procedure with a single proximal component. A distal Type I endoleak was also noted at the 2-year follow-up (Table 36). The patient underwent a secondary intervention beyond 2 years (ancillary component placement 753 days post-procedure for the site-reported reasons of distal Type I endoleak and device migration). Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests a distal seal length < 20 mm as well as graft undersizing.

[h]Patient 1030100 – The patient was treated at the time of the index procedure with a single proximal component. Per core laboratory evaluation, a Type II endoleak was identified at the 1-month and 6-month follow-ups. A distal Type I endoleak (Table 36) has been identified in the patient at 2 years (previous endoleaks identified were Type II). Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing.

[i]Patient 1040041 – The patient was treated at the time of the index procedure with a single proximal component. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing as well as a distal seal length < 20 mm. The patient withdrew from the study 906 days post-procedure.

[j]Patient 1040044 – The patient was treated at the time of the index procedure with a single proximal component. The patient also had a distal Type I endoleak (Table 36) and CEC-confirmed migration (Table 37). The patient underwent a secondary intervention beyond 2 years (ancillary component placement 798 days post-procedure for the site-reported reasons of distal Type I endoleak and device migration). Review of core laboratory measurements at first follow-up (relative to the location of the actual graft placement) suggests graft undersizing.

[k]Patient 1040045 – The patient was treated at the time of the index procedure with a single proximal component. A distal Type I endoleak was noted at the 1-month, 6-month, 12-month and 2-year follow-ups (Table 36). A Type IIb endoleak was also identified at the 6-month and 12-month follow-ups. No secondary interventions have been performed to date. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests a distal seal length < 20 mm.

Endoleaks classified by type, as assessed by the core laboratory at each exam period through 2 years, are reported in Table 36. In total, there were seven patients found to have a Type I (distal) endoleak and two patients found to have a Type III (nonjunctional) endoleak at one or more time points, two of which (one with Type I and one with Type III) had no evidence of the same endoleak at last available follow-up and without the patients having undergone secondary intervention. Endoleak in the other seven patients (five of which required secondary intervention) was associated with an inadequate seal zone length (i.e., length < 20 mm) and/or graft undersizing, which occurred following aneurysm treatment with only a proximal component in six of the patients, underscoring the importance of adhering to the sizing guidelines in the IFU, both in terms of component diameter as well as component type and length, including the use of a two-component repair (proximal and distal components) when treating aneurysms.

Table 36. Endoleak based on results from core laboratory analysis

Type	Percent Patients (number/total number)											
	1-month			6-month			12-month			2-year		
	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All
Any (new only)	8.5% (7/82)	10.0% (2/20)	8.8% (9/102)	4.1% (3/73)	5.6% (1/18)	4.4% (4/91)	4.5% (3/66)	0	3.6% (3/83)	8.5% (5/59)	0	6.8% (5/73)
Any (new and persistent)	8.5% (7/82)	10.0% (2/20)	8.8% (9/102)	11.0% (8/73)	11.1% (2/18)	11.0% (10/91)	10.6% (7/66)	0	8.4% (7/83)	16.9% (10/59)	0	13.7% (10/73)
Multiple	2.4% (2/82)[a]	0	2.0% (2/102)	2.7% (2/73)[a]	0	2.2% (2/91)	1.5% (1/66)	0	1.2% (1/83)	0	0	0
Proximal Type I	0	0	0	0	0	0	0	0	0	0	0	0

Type	Percent Patients (number/total number)											
	1-month			6-month			12-month			2-year		
	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All
Distal Type I	2.4% (2/82)[a,b]	0	2.0% (2/102)	4.1% (3/73)[a,b,d]	0	3.3% (3/91)	4.5% (3/66)[b,d,e]	0	3.6% (3/83)	8.5% (5/59)[b,e,g-i]	0	6.8% (5/73)
Type II	7.3% (6/82)[a]	0	5.9% (6/102)	9.6% (7/73)[a,b]	5.6% (1/18)	8.8% (8/91)	6.1% (4/66)[b]	0	4.8% (4/83)	6.8% (4/59)	0	5.5% (4/73)
Type III	0	5.0% (1/20)[c]	1.0% (1/102)	0	5.6% (1/18)[c]	1.1% (1/91)	1.5% (1/66)[f]	0	1.2% (1/83)	0	0	0
Type IV	0	0	0	0	0	0	0	0	0	0	0	0
Unknown	1.2% (1/82)	5.0% (1/20)	2.0% (2/102)	0	0	0	0	0	0	1.7% (1/59)	0	1.4% (1/73)

[a]Patient 0463776 – Distal Type I and Type IIb endoleaks were noted at the 1- and 6-month follow-ups. The endoleak type was noted as unknown at last follow-up (unscheduled follow-up at day 300); a decrease in aneurysm size was also noted at last follow-up. No secondary interventions have been performed to date and the patient has since withdrawn from the study.

[b]Patient 1040045 – The patient was treated at the time of the index procedure with a single proximal component. A distal Type I endoleak was noted at the 1-month, 6-month, 12-month and 2-year follow-ups. A Type IIb endoleak was also identified at the 6-month and 12-month follow-ups. The patient also had aneurysm growth (Table 35). No secondary interventions have been performed to date. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests a distal seal length < 20 mm.

[c]Patient 1040051 – The Type III (nonjunctional) endoleak noted at the 1-month and 6-month follow-ups was no longer present at the 12-month follow-up. The location of the endoleak coincided with an area of prominent calcification in the aorta. No secondary interventions have been performed to date and the patient has not demonstrated an increase in aneurysm size.

[d]Patient 1030072 – A distal Type I endoleak was noted at the 6-month and 12-month follow-ups. A secondary intervention has occurred (for the site-reported reason of distal Type I endoleak after 12-month follow-up). The patient has not experienced an increase in aneurysm size. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing and a distal seal length < 20 mm. The patient underwent a secondary intervention on post-operative day 420 (Table 40) and there was no endoleak detected at the 2-year follow-up.

[e]Patient 1030047 – The patient was treated at the time of the index procedure with a single proximal component. A distal Type I endoleak was first noted at the 12-month follow-up (and again at an unscheduled CT (596 days post procedure)) and the 2-year follow-up, at which time the patient underwent secondary intervention. The patient also had aneurysm growth (Table 35) and CEC-confirmed migration (Table 37). The patient underwent a secondary intervention (ancillary component placement) 727 days post-procedure (Table 40). Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing and a distal seal length < 20 mm. There was no endoleak detected at the 3-year follow-up.

[f]Patient 1030095 – The patient was treated at the time of the index procedure with a single proximal component. A Type III (nonjunctional) endoleak was noted at the 12-month follow-up (a secondary intervention involving distal component placement was performed after the 12-month follow-up for the site-reported reason of distal Type I endoleak; Table 40). The patient has not experienced an increase in aneurysm size. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) in combination with the site-reported reason for secondary intervention (distal Type I, not Type III, endoleak) suggest graft undersizing. Patient has subsequently withdrawn from the study on post-operative day 695.

[g]Patient 1030051 – The patient was treated at the time of the index procedure with a single proximal component. A distal Type I endoleak was noted at the 2-year follow-up. The patient also had aneurysm growth (Table 35) and underwent a secondary intervention beyond 2 years (ancillary component placement 753 days post-procedure for the site-reported reasons of distal Type I endoleak and device migration). Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests a distal seal length < 20 mm as well as graft undersizing.
[h]Patient 1030100 – The patient was treated at the time of the index procedure with a single proximal component. Per core laboratory evaluation, a Type II endoleak was identified at the 1-month and 6-month follow-ups. A distal Type I endoleak has been identified in the patient at 2 years (previous endoleaks identified were Type II). The patient also had aneurysm growth (Table 35). Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing.
[i]Patient 1040044 – The patient was treated at the time of the index procedure with a single proximal component. The patient also had aneurysm growth (Table 35) and CEC-confirmed migration (Table 37) and underwent a secondary intervention beyond 2 years (ancillary component placement 798 days post-procedure for the site-reported reasons of distal Type I endoleak and device migration). Review of core laboratory measurements at first follow-up (relative to the location of the actual graft placement) suggests graft undersizing.

The results for migration through 2 years, as confirmed by the CEC, are provided in Table 37. There were three cases of CEC-confirmed migration (two also with aneurysm growth, distal Type I endoleak, and the need for secondary intervention), each of which was associated with an inadequate seal zone length (i.e., length < 20 mm) and/or graft undersizing and occurred following aneurysm treatment with only a proximal component, underscoring the importance of adhering to the sizing guidelines in the IFU, both in terms of component diameter as well as component type and length, including the use of a two-component repair (proximal and distal components) when treating aneurysms.

Table 37. Percent of patients (aneurysm and ulcer) with CEC-confirmed migration (date of first occurrence)

Item	Percent Patients (number/total number)		
	6-month	12-month	2-year
Migration (> 10 mm)	0% (0/94)	0% (0/92)	3.9% (3/77)[a,b,c]

[a]Patient 1030012 – The patient was treated at the time of the index procedure with a single proximal component. The patient had cranial migration of the distal end of the proximal component first confirmed by the CEC at 2 years. There was no evidence of endoleak, and the aneurysm size has continuously decreased from 61 mm at 1 month to 40 mm at 2 years and 38 mm at 3 years. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing.

[b]Patient 1030047 – The patient was treated at the time of the index procedure with a single proximal component. The patient had cranial migration of the distal end of the proximal component first confirmed by the CEC at 2 years. The patient also had aneurysm growth (Table 35), distal Type I endoleak (Table 36), and underwent a secondary intervention (Table 40). Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing and a distal seal length < 20 mm.

[c]Patient 1040044 – The patient was treated at the time of the index procedure with a single proximal component. The patient had cranial migration of the distal end of the proximal component first confirmed by the CEC at 2 years. The patient also had aneurysm growth (Table 35), a distal Type I endoleak (Table 36), and underwent a secondary intervention beyond 2 years (ancillary component placement 798 days post-procedure for the site-reported reasons of distal Type I endoleak and device migration). Review of core laboratory measurements at first follow-up (relative to the location of the actual graft placement) suggests graft undersizing.

The results from core laboratory analysis for graft kink/compression through 2 years are summarized in Table 38.

Table 38. Core laboratory reports of graft kink/compression

Item	30-day	6-month	12-month	2-year
Kink/compression	0	0	0	1.3% (1/77)[a]

[a]Patient 0468761 – The patient had a kink in the proximal and distal components identified by the core laboratory on the 2-year CT scan. There were no clinical sequelae associated with the kink; at the 2-year follow-up, the aneurysm had decreased in size and the device was patent. The patient died prior to the next follow-up visit.

CEC-confirmed device integrity observations at each exam period through 2 years are summarized in Table 39.

Table 39. CEC-confirmed loss of device integrity

Finding	Percent Patients (number/total number)											
	30-day			6-month			12-month			2-year		
	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All
Barb separation	0	0	0	0	0	0	0	0	0	0	0	0
Stent fracture	1.2% (1/85)[a]	0	1.0% (1/105)	1.3% (1/80)[a]	0	1.0% (1/98)	1.3% (1/75)[a]	0	1.1% (1/92)	1.6% (1/63)[a]	0	1.3% (1/77)
Component separation	0	0	0	0	0	0	0	0	0	0	0	0

[a]Patient 1030069 – Patient had a report of a single stent fracture (of the second covered stent in the proximal device) seen on the 30-day, 6-month, 12-month and 2-year x-rays. Nothing uncharacteristic regarding the anatomy or deployment of the graft was observed. This patient has had no clinical sequelae from the stent fracture.

Tables 40 and 41 summarize the site-reported reasons for secondary intervention and types of secondary intervention within 2 years (all patients), respectively.

Table 40. Site-reported reasons for secondary intervention

Reason	0-30 Days	31-180 Days	181-365 Days	366-730 Days
Device migration	0	0	0	1[g]
Endoleak				
Type I distal	0	0	0	3[d,g,h]
Type II	0	0	1[b]	0
Type IV (through graft body)	0	0	0	1[i]
Other	1[a]	0	1[c]	2[e,f]

[a]Patient 1040058 (ulcer) – Patient had pre-planned left subclavian artery embolization and right-to-left subclavian artery bypass 7 days after the index procedure.
[b]Patient 1040073 (aneurysm) – Patient had two separate secondary interventions for Type II endoleak: unsuccessful attempt at placing embolization coils in the intercostal artery, followed by successful direct puncture of the aneurysm with delivery of N-butyl cyanoacrylate.
[c]Patient 1040037 (aneurysm) – Patient had additional component placed for aortic dissection proximal to the study device 324 days after the index procedure.
[d]Patient 1030072 (aneurysm) – Patient had a persistent Type I distal endoleak treated with additional distal components and balloon angioplasty 420 days after the index procedure.
[e]Patient 0467042 (aneurysm) – Patient had a dissection distal to the most distal stent. Ancillary components were placed 433 days after the index procedure.
[f]Patient 1030046 (aneurysm) – Patient had observed progression of disease treated with additional proximal and distal components 594 days after the index procedure.
[g]Patient 1030047 (aneurysm) – Patient had observed device migration and Type I distal endoleak treated with ancillary components 727 days after the index procedure.
[h]Patient 1030095 (aneurysm) – Patient had a persistent Type I distal endoleak treated with additional distal components 534 days after the index procedure.
[i]Patient 1040054 (aneurysm) – Patient had persistent Type IV endoleak per site analysis (unknown type endoleak per core laboratory analysis) treated with ancillary components 599 days after the index procedure.

Table 41. Types of secondary interventions

Type*	0-30 Days	31-180 Days	181-365 Days	366-730 Days
Percutaneous				
Ancillary component placed	0	0	1[b]	6[d-i]
Balloon angioplasty	0	0	0	1[d]
Other	0	0	1[b]	0
Surgical				
Conversion to open repair	0	0	0	0
Surgical bypass procedure	0	0	0	0
Other	1[a]	0	0	0
Other	0	0	1[c]	0

*A patient may have had more than one treatment type,
[a-i]Refer to footnotes in Table 40 for additional details.

3. Gender Subset Analysis

There was nearly an equal proportion of males (n = 64, 58.2%) and females (n = 46, 41.8%) enrolled in this study, allowing for further analysis of outcomes

by gender. There was no significant difference in age between male (70.7 ± 9.9 years; 42-85 years) and female (74.3 ± 9.4 years; 44-92 years) patients. Furthermore, the access method used (cutdown vs. percutaneous vs. conduit) was not significantly different between male (56.3% cutdown, 43.8% percutaneous, 0% conduit) and female (71.7% cutdown, 26.1% percutaneous, 2.2% conduit) patients.

No significant differences between males and females with respect to primary safety and effectiveness endpoints were found. For the primary safety endpoint, the 30-day freedom from MAE rate was 96.9% (62/64) for males and 95.7% (44/46) for females. For the primary effectiveness endpoint, the 12-month device success rate was 96.9% (62/64) for males and 93.5% (43/46) for females. Overall, males and females treated with the Zenith Alpha™ Thoracic Endovascular Graft had similar outcomes, indicating the device is likely to be equally safe and effective for both males and females.

F. Summary and Conclusions

All but two patients received at least one proximal component, and approximately one-third of patients also received a distal component (i.e., a two-piece system), as compared to approximately two-thirds of patients in the previous study who were treated with a two-piece system. Therefore, a two-component repair was less often used in this study compared to the previous study, despite similar percentages of patients from both studies having been treated for aneurysms. The IFU for the Zenith Alpha™ Thoracic Endovascular Graft was therefore updated to emphasize the importance of a two-component repair when treating aneurysms given that the reports of growth, migration, and distal Type I endoleak tended to occur in only aneurysm patients who were treated using a single proximal component.

Two patients did not receive a device in this study due to an inability to advance/gain access to the target treatment site; two patients also did not receive a device in the previous study for similar reasons. In patients where access was gained (n = 108), all devices were deployed successfully in the intended location and all vessels were patent at the time of deployment. An access conduit was

necessary for graft delivery in 0.9% of patients, and percutaneous access was used in 36% of patients.

There were no deaths within 30 days of endovascular repair. There was one TAA-related death within 365 days due to aspiration pneumonia, resulting in a 99% freedom from TAA-related mortality at 1 year. There were no ruptures reported at any follow-up time period. One patient underwent conversion to open repair 330 days post-procedure due to an aortoesophageal fistula; the CEC adjudicated the event as related to the procedure. The patient survived the surgical repair and investigational device explant and has since exited the study. Patients experienced adverse events in each of the organ system categories.

A total of 11 patients experienced aneurysm growth (> 5 mm) at one or more follow-up time points based on core laboratory analysis through 2 years. Aneurysm growth was associated with detectable endoleak in six patients, four of whom underwent secondary intervention. There was no detectable endoleak in the remaining five patients with aneurysm growth, two of whom had no change in aneurysm size (≤ 5 mm change compared to baseline) as of the last available follow-up without the need for secondary intervention. Among the three other patients with growth and no detectable endoleak, two required secondary intervention and one had growth at the last available follow-up; each growth was associated with an inadequate seal zone length (i.e., length < 20 mm) as well as graft undersizing.

The majority of endoleaks detected were Type II, and there were no proximal Type I or Type IV endoleaks at 24 months. In total, there were seven patients found to have a Type I (distal) endoleak and two patients found to have a Type III (nonjunctional) endoleak at one or more time points, two of which (one with Type I and one with Type III) had no evidence of the same endoleak at last available follow-up and without the patients having undergone secondary intervention. Endoleak in the other seven patients (five of which required secondary intervention) was associated with an inadequate seal zone length (i.e., length < 20 mm) and/or graft undersizing. Note that these observations have led to the inclusion of strengthened warnings and precautions in the IFU to mitigate future problems.

There were three cases of CEC-confirmed migration (two also with aneurysm growth, distal Type I endoleak, and the need for secondary intervention), each of

which was associated with an inadequate seal zone length (i.e., length < 20 mm) and/or graft undersizing. There was one report of loss of device integrity (a single stent fracture) within 24 months, but with no adverse clinical sequelae.

In total, nine patients required a secondary intervention within 24 months for the site reported reasons of left subclavian artery embolization with bypass (n=1), Type II endoleak (n=1), distal Type I endoleak (n=2), distal Type I endoleak and migration (n=1), Type IV endoleak (n=1), disease progression (n=1), and aortic dissection (n=2).

Both the safety (30-day freedom from MAEs) and effectiveness (12-month device success) hypotheses were met. Overall, the results provide a reasonable assurance of the safety and effectiveness of the Zenith Alpha™ Thoracic Endovascular Graft.

BLUNT TRAUMATIC AROTIC INJURY (BTAI) PIVOTAL STUDY

A. Study Design

The Zenith Alpha™ Thoracic Endovascular Graft clinical study is a prospective, nonrandomized, noncomparative, single-arm, multicenter study that was conducted to evaluate the safety and effectiveness of the Zenith Alpha™ Thoracic Endovascular Graft for the treatment of patients with BTAI. Enrollment in the clinical trial began on January 23, 2013 and was completed May 7, 2014. Seventeen US institutions enrolled a total of 50 patients in the study for the BTAI indication under IDE G120085. The database for this PMA reflected data collected through April 1, 2015

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the pivotal study for the BTAI indication was limited to patients who met the following inclusion criteria:

- Blunt thoracic aortic injury of the descending thoracic aorta
- Suitable for treatment with the Zenith Alpha™ Thoracic Endovascular Graft and 16 Fr, 18 Fr, or 20 Fr Z-Trak Plus® Introduction System
- Treatment with the Zenith Alpha™ Thoracic Endovascular Graft can be performed within 14 days of the blunt thoracic aortic injury

- Age ≥ 16 years
- Proximal fixation site length measuring ≥ 20 mm between the left common carotid artery and most proximal extent of the injury site (covering left subclavian artery is acceptable)
- Distal fixation site length measuring ≥ 20 mm between the distal-most aspect of aortic injury and most distal extent of graft
- No previous placement of a thoracic endovascular graft
- No prior open surgical repair involving the descending thoracic aorta including suprarenal aorta and/or arch
- Proximal neck diameter, measured outer wall to outer wall on a sectional image or multiplanar reconstruction (CT), ≥ 15 mm and ≤ 42 mm
- Distal neck diameter, measured outer wall to outer wall on a sectional image or multiplanar reconstruction (CT), ≥ 15 mm and ≤ 42 mm
- Ability to preserve the left common carotid artery and celiac artery
- Willing and able to comply with the follow-up schedule
- Informed consent given by the patient or a legally authorized representative [Note: For pediatric patients, in addition to obtaining permission from their parents or guardians, assent from the patients may need to be obtained based on IRB requirements.]

Patients were excluded from the study if any of the following conditions were true:

General Exclusion Criteria

- Injury severity score at the time of initial hospital admission is 75
- Aortic injuries classified as grade 1

Medical Exclusion Criteria

- Pregnancy
- Known allergy to polyester, polypropylene, nitinol, or gold
- Allergic reaction to contrast, which in the opinion of the investigator, cannot be adequately premedicated
- Aortic dissection
- Systemic infection (e.g., sepsis)

- Degenerative connective tissue disorder (e.g., Marfan's disease)
- Bleeding diathesis, uncorrectable coagulopathy, or refusal of blood transfusion
- Simultaneously participating in another investigative device or drug study (The patient must have completed the primary endpoint of any previous study at least 30 days prior to enrollment in this study and not enroll in another study until 30 days after blunt thoracic aortic injury repair in this study)

Anatomical Exclusion Criteria

- Treatment length (i.e., length of aortic injury including proximal and distal fixation sites) along greater curvature:
  > 105 mm for 18 mm to 26 mm diameter grafts
  > 109 mm for 28 mm to 32 mm diameter grafts
  > 113 mm for 34 mm to 36 mm diameter grafts
  > 117 mm for 38 mm to 40 mm diameter grafts
  > 121 mm for 42 mm diameter grafts
  > 125 mm for 44 mm to 46 mm diameter grafts
- Aortic arch radius of curvature < 20 mm (only if the device is intended to be deployed in the aortic arch)
- Tortuosity, calcification, occlusive disease, or arterial diameter of the intended access vessels (e.g., iliac and/or femoral arteries), measured inner wall to inner wall on a sectional image, that are not conducive to placement of the introducer sheath (16 Fr for 18 mm to 30 mm diameter grafts, 18 Fr for 32 mm to 38 mm diameter grafts, 20 Fr for 40 mm to 46 mm diameter grafts) – use of an access conduit is acceptable
- Prohibitive calcification, occlusive disease, or tortuosity of intended fixation sites
- Circumferential thrombus in region of intended fixation sites
- Aneurysm or angulation in the distal thoracic aorta that would preclude advancement of the introduction system

2. Follow-up Schedule

The study follow-up schedule (Table 42) consisted of imaging (CT) and clinical assessments at post-procedure (clinical assessment only at pre-discharge), 30 days, 6 months, 12 months, and yearly thereafter through 5 years.

Table 42. Study follow-up schedule

	Pre-op	Intra-op	Post-procedure	30-day	6-month	12-month[c]
Clinical exam	X		X	X	X	X
Blood tests	X		X			
CTA	X[a]			X[b]	X[b]	X[b]
Angiography		X				

[a]The CTA must be obtained as close as possible to the study procedure.
[b]MR or noncontrast CT imaging may be used for those patients experiencing renal failure or who are otherwise unable to undergo contrast-enhanced CT scan, with TEE being an additional option in the event of suboptimal MR imaging.
[c]Performed yearly for 5 years.

An independent core laboratory analyzed all patient imaging. An independent CEC adjudicated relevant adverse events, including all patient deaths. An independent DSMB monitored the clinical trial according to an established safety monitoring plan.

3. Clinical Endpoints

The Zenith Alpha™ Thoracic Endovascular Graft for BTAI study had two endpoints. The primary safety endpoint was all-cause and aortic-injury-related mortality at 30 days, the latter of which was defined as any death determined by the independent CEC to be causally related to the initial implant procedure, secondary intervention, or rupture of the transected aorta. The primary effectiveness endpoint was device success, which was defined as successful access of the injury site and deployment of the Zenith Alpha™ Thoracic Endovascular Graft in the intended location with patency at the time of deployment completion (technical success) plus none of the following at 30 days: device collapse, Type I or III endoleak requiring reintervention, or conversion to open surgical repair.

Success/Failure Criteria

The primary endpoints of this study were analyzed using only descriptive statistics, and will not be analyzed for the purpose of statistical inference, as these patients typically have extensive concomitant injuries that would confound the interpretation of statistical comparisons to alternative treatments.

Pre-specified Statistical Analysis Plan

All data were analyzed using descriptive statistics. Confidence intervals (95%) were calculated for both the safety and effectiveness endpoints.

B. Accountability of PMA Cohort

Although the primary safety and effectiveness endpoints were evaluated at 30 days, patient data presented herein include longer-term follow-up that was available at the time of the data lock (April 1, 2015). Table 43 reports the percent of follow-up data available through 24 months. The low follow-up compliance at 12 months is due to the eleven subjects who were eligible for follow-up but had not completed their follow-up visit.

Table 43. Follow-up availability

Follow-up Visit	Patients Eligible for Follow-up	Percent of Data Available[a]			Adequate Imaging to Assess the Parameter[b]			Events Occurring Before Next Interval			
		Clinical	CT[c]	ND	Endoleak	Migration	Aortic Injury Healing	Death	Conversion to Open Repair	Lost to Follow-up/ Withdrawal	Not Due for Next Visit
Operative	50	50/50 (100%)	NA	0	NA	NA	NA	0[d]	0	0	0
30-day	50[d]	46/50 (92.0%)	43/50 (86.0%)	0	42/50 (84.0%)	10/50 (20.0%)[e]	42/50 (84.0%)	5[d]	0	4	0
6-month	41	32/41 (78.0%)	34/41 (82.9%)	0	34/41 (82.9%)	33/41 (80.5%)	34/41 (82.9%)	0	1	1	0
12-month	39	26/39 (66.7%)	26/39 (66.7%)	11	25/39 (64.1%)	20/39 (51.3%)	25/39 (64.1%)	0	0	2	32
24-month	5	0.0% (0/5)	0.0% (0/5)	5	0.0% (0/5)	0.0% (0/5)	0.0% (0/5)	0	0	0	5

ND – Visit not done, but patient still eligible for follow-up.
NA – Not assessed.
[a]Site-submitted data.
[b]Based on core laboratory analysis – Does not include imaging exams received by the core laboratory for analysis, but that have not yet been analyzed.
[c]Includes MRI or TEE imaging (which is allowed per protocol) when a patient is unable to receive contrast medium due to renal failure.
[d]Patient 1200054 – The patient underwent 30-day follow-up (CT scan and clinical exam) 22 days post-procedure before exiting the study due to death 24 days post-procedure.
[e]As the 30-day time point represented the baseline CT for migration assessments, the core laboratory only assessed 30-day migration for 10 patients, who had an unscheduled post-procedure CT scan that was used as the baseline scan.

C. Study Population Demographics and Baseline Parameters

The tables below present the demographics, comorbidities, American Society of Anesthesiologists (ASA) Physical Status Classification, Injury Severity Score (ISS), concomitant injuries, and etiology of the BTAI. Most subjects were male (88%), and the mean age was 42.7 years (range 18-89). The most common comorbidities at the pre-procedure visit were history of smoking (46%) and hypertension (26%). Most (68%) subjects were classified as ASA IV or V, indicating the injuries were a threat to life (ASA IV) or the subjects were not expected to live 24 hours without operation (ASA V). The mean ISS was 31, which represents polytrauma (ISS > 17). The demographics and patient characteristics are presented in Table 44. Height and weight measurements were not assessed.

Table 44. Demographics and patient characteristics

Demographic	Mean ± SD (n, range) or Percent Patients (number/total number)
Age (years)	
All patients	42.7 ± 18.7 (n=50, 18 – 89)
Male	42.3 ± 19.6 (n=44, 18 – 89)
Female	45.5 ± 11.0 (n=6, 28 – 59)
Gender	
Male	88.0% (44/50)
Female	12.0% (6/50)
Ethnicity	
White	76.0% (38/50)
Hispanic or Latino	10.0% (5/50)
Black or African American	8.0% (4/50)
American Indian or Alaska Native	0
Asian	6.0% (3/50)
First Nations	0

The medical history and comorbid medical conditions for the patient cohort are presented in Table 45.

Table 45. Pre-existing comorbid medical conditions

Medical History	Percent Patients (number/total number)[a]
Cardiovascular	
Cardiac arrhythmia	2.0% (1/50)
Congestive heart failure (CHF)	0
Coronary artery disease	6.0% (3/50)
Myocardial infarction (MI)	4.0% (2/50)
Surgical or percutaneous treatment	6.0% (3/50)

Medical History	Percent Patients (number/total number)[a]
Vascular	
Thromboembolic event	0
Peripheral vascular disease	0
Aneurysm (patient history)	0
Dissection	0
Bleeding diathesis or uncorrectable coagulopathy	0
Carotid endarterectomy	0
Hypertension	26.0% (13/50)
Pulmonary	
Chronic obstructive pulmonary disease (COPD)	2.0% (1/50)
Renal	
Chronic renal insufficiency	0
Dialysis	0
Endocrine	
Diabetes	10.0% (5/50)
Infectious disease	
Sepsis	0
Hepatobiliary	
Liver disease	4.0% (2/50)
Neoplasms	
Cancer	6.0% (3/50)
Neurologic	
Paralysis	0
Paraparesis	0
Stroke	0
Transient ischemic attack/reversible ischemic neurologic deficit	0
Connective tissue	
Marfan Syndrome	0
Ehlers Danlos	0
Substance use	
Past or current smoker	46.0% (23/50)

Assessments of pre-procedure risk (ASA classification, Glasgow coma scale, and injury severity score) are presented in Table 46.

Table 46. Pre-procedure risk

Measure	Percent Patients (number/total number) or Mean ± SD or Median (n, range)
ASA classification	
1	0
2	8.0% (4/50)
3	26.0% (13/50)
4	50.0% (25/50)
5	16.0% (8/50)
Glasgow coma scale (GCS)	
Mild ≥ 13	48.0% (24/50)
Moderate 9 – 12	18.0% (9/50)
Severe ≤ 8	34.0% (17/50)

Measure	Percent Patients (number/total number) or Mean ± SD or Median (n, range)
Injury severity score (ISS)	
Mean	31.0 ± 14.0 (n=50, 3 – 66)
Median	29.0 (n=50, 3 – 66)

Concomitant injuries are presented in Table 47.

Table 47. Concomitant injuries

Injury	Percent Patients (number/total number)
Abdominal injuries (solid organ, bowel, bladder)	62.0% (31/50)
Head injury	40.0% (20/50)
Long bone fracture	58.0% (29/50)
Lung injury	60.0% (30/50)
Neurological deficits	18.0% (9/50)
Pelvis fracture	30.0% (15/50)
Rib fractures	72.0% (36/50)
Scapula fracture	12.0% (6/50)
Unstable fractures (cervical/thoracic/lumbar spine)	14.0% (7/50)
Other[a]	34.0% (17/50)

[a]Other concomitant injuries as reported by the sites include: open fracture right tibia and fibula, left knee traumatic arthrotomy, right radial and ulnar fractures, C6-C7 abnormality (widening of space), grade 11B left ICA dissection at C2 level, open dislocation of ankle, closed fracture of distal phalanx or phalanges (thumb), open scalp wound, open pubis fracture, closed fracture of the nasal bones, closed fracture of pubis, closed fracture of shaft of the tibia, fracture of navicular (scaphoid) bone of foot, respiratory distress syndrome, pneumonia, clavicle fracture, right external ventricular drain placement, small hemorrhagic left pleural effusion, small left pneumothorax, right first metatarsal fracture, right orbital floor fracture, right maxillary sinus fractures, facial fractures, severed left lower extremity, bruising on the abdomen, left hip contusion, right and left knee abrasions, history of seizure disorder, and bilateral nasal bone fracture.

Motor vehicle accident was the most common etiology of BTAI and was observed in 72% of subjects, followed by motorcycle accident, which was observed in 14% subjects. The etiology of thoracic aortic injury for the patients enrolled in the study is presented in Table 48.

Table 48. Etiology of the thoracic injury

Etiology of Thoracic Injury	Percent Patients (number/total number)
Fall	4.0% (2/50)
Motor vehicle accident	72.0% (36/50)
Motorcycle accident	14.0% (7/50)
Pedestrian hit by a motor vehicle	6.0% (3/50)
Other[a]	4.0% (2/50)[a]

[a]One patient (1200070) was riding a moped and was hit by a motor vehicle. One patient (1200046) was riding a bicycle and was hit by a motor vehicle.

All subjects underwent pre-procedure imaging to assess aortic morphology. Most lesions were pseudoaneurysms (86%). The main baseline anatomical measurements were as follows: the mean proximal landing zone diameter was 27.9 ± 6.0 mm, the mean proximal landing zone length was 27.8 ± 13.3 mm, the mean maximum lesion diameter was 31.5 ± 6.4 mm, the mean distal landing zone diameter was 186.0 ± 28.8 mm, and the mean lesion length was 31.5 ± 18.0 mm. The results from core laboratory analysis of pre-procedure aortic injury grade are provided in Table 49.

Table 49. Pre-procedure aortic injury grade based on core laboratory analysis

Characteristic	Percent Patients (number/total number)[a]
Traumatic aortic injury grade	
1 (intimal tear)	0
2 (intramural hematoma/large intimal flap)	8.0% (4/50)
3 (pseudoaneurysm)	86.0% (43/50)
4 (rupture)	6.0% (3/50)

Table 50 reports presenting anatomical dimensions.

Table 50. Presenting anatomical dimensions reported per the core laboratory

Measure	Mean ± SD (n, range)
Aortic injury	
Maximum diameter (mm)	31.5 ± 6.4 (n=47, 21.3 – 48.4)
Length (mm)	31.5 ± 18.0 (n=49, 9.8 – 118.6)
Length from left common carotid artery to most proximal extent of aortic injury (mm)	27.8 ± 13.3 (n=48, 0.1 – 73.1)
Length from celiac artery to most distal extent of aortic injury	186.0 ± 28.8 (n=41, 103.9 – 252.7)
Maximum aortic diameter in intended proximal seal zone (mm)	27.9 ± 6.0 (n=45, 19.7 – 48.2)
Maximum aortic diameter in intended distal seal zone (mm)	25.2 ± 5.9 (n=38, 16.8 – 41.3)
Right common iliac artery	
Narrowest segment (mm)	6.7 ± 1.6 (n=38, 3.5 – 10.3)
Left common iliac artery	
Narrowest segment (mm)	6.9 ± 1.5 (n=38, 3.9 – 9.7)

D. Procedural Information

The majority (98.0%) of procedures were performed under general anesthesia. Vascular access was gained via femoral artery cutdown in 56.0% of patients and percutaneously in 44.0% of patients. Adjunctive procedures to prevent paraplegia, specifically CSF drainage, were performed in 4.0% of subjects, and induced hypotension for accurate deployment was used in 10.0% of subjects. The LSA was covered partially or completely in 47.8% of subjects. No supra-aortic vessel bypass was performed. The most common location of the aortic injury was at the isthmus in 56.0% of subjects, followed by the distal descending thoracic aorta in 34.0% of subjects. The mean procedure time was 85.3 ± 44.3 minutes (range 34-278 minutes) and the mean procedural blood loss was 102.5 ± 144.6 ml. The mean anesthesia time was 182.9 minutes and the mean fluoroscopy time was 8.6 ± 8.3 minutes. The access techniques used are presented in Table 51.

Table 51. Access technique used to insert the endovascular graft

Type	Percent Patients (number/total number)
Percutaneous	44.0% (22/50)[a]
Cutdown	56.0% (28/50)
Conduit	0

[a]For 2 patients, device delivery was preformed percutaneously; however, subsequent cutdown was required to close the access site due to a percutaneous closure device failure (1200075) and to treat femoral artery stenosis (1200042).

The location of the graft components relative to an identified site is provided in Table 52.

Table 52. Graft location based on core laboratory analysis

Location	Percent Patients (number/total number)
Proximal edge of graft material	
Above left common carotid artery	0
Below left common carotid artery, above left subclavian artery	47.8% (22/46)[a]
Below left subclavian artery	52.1% (24/46)
Distal aspect of graft	
Above celiac artery	100% (46/46)
Below celiac artery	0

[a]The left subclavian artery was completely covered in 7 patients and partially covered in 15 patients.

All subjects survived the endovascular procedure. Technical success was achieved in all subjects (100%). Overall, the procedural results were as expected for the treatment of patients with BTAI.

Clinical Utility Measures

The median hospital stay after endovascular treatment was 25 days (range 2-125 days). All subjects had an ICU stay, with a mean ICU stay of 17.8 ± 20.1 days. The hospital survival was 98%. The clinical utility results are presented in Table 53.

Table 53. Clinical utility measures

Clinical Utility	Mean ± SD (n, range)
Duration of ICU stay (days)	17.8 ± 20.1 (n=50, 1 – 126)[a]
Duration of mechanical ventilation (days)	13.4 ± 20.9 (n=50, 0 – 127)[a]
Days to resumption of oral fluid intake	10.4 ± 14.9 (n=45, 0 – 78)[b-d]
Days to resumption of regular diet	14.3 ± 18.8 (n=44, 0 – 99)[a-d]
Days to resumption of bowel function	5.8 ± 4.9 (n=46, 0 – 24)[e]
Days to hospital discharge	25.0 ± 24.3 (n=50, 2 – 125)[a]

[a]Patient 1200079 required ICU stabilization 1 day prior to the procedure (126 days total) and required mechanical ventilation for 2 days prior to the procedure (127 days total). The BTAI treatment was postposed as the patient required further resuscitation and stabilization of a left lower extremity injury. This patient has not resumed regular diet intake and is currently receiving nutrition from a percutaneous endoscopic gastrostomy (PEG) tube.
[b]Days to resumption of oral fluid intake and regular diet were not reported for patient 1200041. The patient was placed on a feeding tube until death occurred on post-operative day 36.
[c]Three patients (1200024, 1200051, and 1200057) were discharged from the hospital before resumption of oral fluid intake and regular diet occurred.
[d]Days to resumption of oral fluid intake and regular diet were unknown for 1 patient (1200074).
[e]Days to resumption of bowel function was unknown for 4 patients (1200015, 1200023, 1200041, and 1200067).

Devices Implanted

Table 54 presents the percent of subjects who received one or more Zenith Alpha™ Thoracic Endovascular Graft proximal components during the implant procedure. Also reported is the range of graft diameters that were implanted. One patient (1200012) received two study components (the second component was placed to extend graft coverage distally). While all other patients received a single study component, it should be noted that one patient (1200040) received two commercial components in combination with a single study component. The first study component and first commercial component placed were the same diameter and had been undersized, as measurements were taken from a pre-procedure CT scan performed while the patient was not fully resuscitated; the final component placed (second commercial component) was larger in

diameter than the two previously placed components. The IFU therefore underscores that graft sizing for BTAI should be based on measurements in a fully resuscitated patient.

Table 54. Number of study components deployed and graft diameter range

Number of Components Deployed	Percent Patients (number/total number)	Graft Diameter Range
1	98.0% (49/50)[a]	18 to 38 mm
2	2.0% (1/50)[b]	

[a]Patient 1200040 received one study component and two commercial components. The first study component and first commercial component placed were the same diameter and had been undersized, as measurements were taken from a pre-procedure CT scan performed while the patient was not fully resuscitated; the final component placed (second commercial component) was larger in diameter than the two previously placed components.
[b]Patient 1200012 received two study components; the additional study component was placed to extend graft coverage distally.

Table 55 reports the specific sizes (diameters and lengths) of the nontapered proximal components used during the initial implant procedure.

Table 55. Diameters and lengths of nontapered proximal component (ZTLP-P) sizes used

Diameter (mm)	Length (mm)	n
18	105	2
20	105	1
22	105	1
24	105	11
26	105	6
28	109	4
30	109	6
32	109	3[a]
34	113	3
36	113	1
38	117	3

[a]Patient 1200012 received two 32 x 109 mm proximal components.

Table 56 reports the specific sizes (diameters and lengths) of the tapered proximal components used during the initial implant procedure.

Table 56. Diameters and lengths of tapered proximal component (ZTLP-PT) sizes used

Diameter (mm)	Length (mm)	n
26	105	9
30	108	1

E. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the 50 subjects enrolled in the Zenith Alpha™ Thoracic Endovascular Graft pivotal study for the treatment of BTAI. The primary safety endpoint for the study was all-cause and aortic-injury-related mortality at 30 days. Aortic-injury-related mortality was defined as any death determined by the independent CEC to be causally related to the initial implant procedure, secondary intervention, or rupture of the transected aorta. Table 57 presents the primary safety endpoint results from the study of the Zenith Alpha™ Thoracic Endovascular Graft for BTAI.

Table 57. Results for the primary safety endpoint (30-day mortality)

Endpoint	Measure	Percent Patients (number/total number)
Safety	30-day all-cause mortality	2.0% (1/50)
	30-day aortic-injury-related mortality	0.0% (0/50)

There were no aortic-injury-related deaths within 30 days of the index procedure. The one patient death (1200054) was adjudicated as unrelated to BTAI repair by the CEC (death due to respiratory failure), resulting in an all-cause mortality rate of 2.0%.

Four deaths were reported beyond 30 days (1 related to BTAI repair; 3 unrelated to BTAI repair). The one patient death adjudicated as related to BTAI repair occurred on day 116 due to exsanguination from aortoesophageal fistula (1200024). This same patient previously underwent reintervention on day 74 to treat a pseudoaneurysm (see Table 63), which may have resulted from an infectious process.

Adverse Events

Table 58 reports the frequency of patients with adverse events in each organ system within 0 to 30 days, 31 to 365 days, 366 to 730 days, or 731 to 1095 days following BTAI repair.

Table 58. Number of patients experiencing adverse events by category

Category	0-30 Days	31-365 Days	366-730 Days
Access site/incision[a]	4	0	0
Cardiovascular[b]	7	1	0
Cerebrovascular/neurological[c]	2	0	0

Gastrointestinal[d]	5	1	0
Pulmonary[e]	20	2	1
Renal/urologic[f]	5	4	0
Vascular[g]	7	5	0
Miscellaneous[h]	22	19	2

Note: The same patient may have experienced events in multiple categories.
[a]Access site/incision events included: hematoma (n=2), infection (n=0), dehiscence (n=0), seroma (n=0), pseudoaneurysm (n=1), hernia (n=0), and wound complication requiring return to the operating room (n=1).
[b]Cardiovascular events included: cardiac arrhythmia requiring intervention (n=7), cardiac arrest (n=1), congestive heart failure (n=0), myocardial infarction (n=0), and refractory hypertension (n=0).
[c]Cerebrovascular/neurological events included: paraplegia (n=0), paraparesis > 30 days (n=0), spinal cord shock (n=0), transient ischemic attack (n=0), and stroke (n=2).
[d]Gastrointestinal events included: bowel obstruction (n=2), infection (n=1), paralytic ileus > 4 days (n=1), mesenteric ischemia (n=0), and bleeding (n=2).
[e]Pulmonary events included: respiratory distress syndrome (n=3), COPD (n=0), pneumonia (n=16), hemothorax (n=2), pneumothorax (n=2), pulmonary edema (n=1), pleural effusion requiring intervention (n=3), and pulmonary embolism (n=2).
[f]Renal/urologic events included: renal failure (n=1), UTI requiring antibiotics (n=7), and serum creatinine rise > 30% above baseline resulting in a persistent value > 2 mg/dl (n=1).
[g]Vascular events included: aortic aneurysm (n=0), aortoesophageal fistula (n=1), aortobronchial fistula (n=0), aortoenteric fistula (n=0), hematoma (n=1), arterial thrombosis (n=1), pseudoaneurysm requiring intervention (n=2), coagulopathy (n=0), deep vein thrombosis (n=6), aortic dissection (n=1), aortic rupture (n=0), and distal embolization with tissue loss (n=0).
[h]Miscellaneous events included: device infection (n=0), hypersensitivity/allergic reaction (n=0), multi-organ failure (n=3), sepsis (n=2), and other (n=30).

There were no ruptures or conversions to open repair within 30 days.

2. Effectiveness Results

The analysis of effectiveness was based on the 50 subjects enrolled in the Zenith Alpha™ Thoracic Endovascular Graft pivotal study for the treatment of BTAI. The primary effectiveness endpoint was device success at 30 days. Device success at 30 days was defined as successful access of the injury site and deployment of the Zenith Alpha™ Thoracic Endovascular Graft in the intended location with patency at the time of deployment completion (technical success), plus none of the following at 30 days: device collapse, Type I or Type III endoleak requiring reintervention, or conversion to open surgical repair. Table 59 presents the primary effectiveness endpoint results from the study of the Zenith Alpha™ Thoracic Endovascular Graft for BTAI.

Table 59. Results for the primary effectiveness endpoint (30-day device success)

Endpoint	Measure	Percent Patients (number/total number)
Effectiveness	30-day device success	96.0% (48/50)

Device success was achieved in 96.0% of subjects. There were two patients (1200012, 1200033) who did not meet the effectiveness endpoint of 30-day device success for the following reasons: one patient (1200012) had device compression and one patient (1200033) had a site-reported Type I endoleak requiring secondary intervention – note that the compression observed in patient 1200012 was not consistent with collapse of the proximal end of the device (refer to Table 62 for additional details); nonetheless, the patient was counted as a failure for conservatism.

Beyond 30 days, there was one patient (1200006) who required placement of an additional stent-graft (described in Table 63) to treat an area of residual injury or possible endoleak (counted as a Miscellaneous/Other event between 31-365 days in Table 58).

Device Performance

The extent of injury healing, as determined by maximum transverse diameter (including the aorta) at the site of injury, observed from the pre-procedure measurement to the 30-day, 6-month, and 12-month follow-up exams (based on core laboratory evaluation), is presented in Table 60. Two patients (both at 6 months) had an increase in diameter > 5 mm at the site of injury when compared to the pre-procedure measurement, which was associated with endoleak in one patient that required secondary intervention followed by conversion to open surgical repair in the setting of graft undersizing. There were no reports of endoleak or secondary intervention in the other patient, nor was there any change in size (< 5 mm change) when compared to the measurement at first follow-up.

Table 60. Aortic injury size and status based on results from core laboratory analysis

Follow-up	Result
30-day	
Injury no longer visible (%, n/N)	76.7% (33/43)
Max diameter change at site of injury (mm) (Mean ± SD, n, range)*	1.0 ± 2.3 (n=8, -2.4 – 4.6)
6-month	
Injury no longer visible (%, n/N)	88.2% (30/34)
Max diameter change at site of injury (mm) (Mean ± SD, n, range)*	3.1 ± 3.4 (n=4, -0.3 – 6.3)[a,b]
12-month	
Injury no longer visible (%, n/N)	96.0% (24/25)
Max diameter change at site of injury (mm) (Mean ± SD, n, range)*	-0.1 (n=1, -0.1)

*Max diameter change at the site of injury as compared to the pre-procedure measurement applied only if the injury was still visible at follow-up.

[a]Patient 1200058 – The max diameter increased > 5 mm at the site of injury when compared to the pre-procedure measurement; there was no change (≤ 5 mm change) when compared to the measurement at first follow-up. There were no reports of endoleak by the core lab and the patient has not undergone a secondary intervention.

[b]Patient 1200033 – The max diameter increased > 5 mm at the site of injury when compared to the pre-procedure measurement; the patient was reported to have an unknown endoleak type by the core laboratory

(proximal Type I endoleak by the site), which required secondary intervention followed by conversion to open surgical repair in the setting of graft undersizing.

Endoleaks classified by type, as assessed by the core laboratory at each exam period, are reported in Table 61.

Table 61. Endoleak based on results from core laboratory analysis

Type	Percent Patients(number/total number)		
	30-day[a]	6-month	12-month
Any (new only)	7.1% (3/42)	0	0
Any (new and persistent)	7.1% (3/42)	2.9% (1/34)	0
Multiple	0	0	0
Proximal Type I	0	0	0
Distal Type I	0	0	0
Type II	2.4% (1/42)[b]	0	0
Type III	0	0	0
Type IV	0	0	0
Unknown	4.8% (2/42)[c,d]	2.9% (1/34)[d]	0

[a]Endoleak was not assessed for 1 patient (1200012) due to a suboptimal exam submission (noncontrast exam).
[b]Patient 1200061.
[c]Patient 1200035.
[d]Patient 1200033 – Patient underwent secondary intervention as described further in Table 63.

No loss of patency was observed out to 12 months, as assessed by the core laboratory at 30 days. While not a loss in graft patency, one patient (1200060) required placement of an additional stent-graft at 435 days post-procedure (described in Table 63) to treat thrombus in the distal stent-graft and native aorta (counted as a Miscellaneous/Other event between 366-730 days in Table 58).

Table 62 reports device integrity findings based on the results from core laboratory analysis of follow-up imaging.

Table 62. Device integrity based on results from core laboratory analysis

Finding	Percent Patients (number/total number)		
	30-day	6-month	12-month
Kink	0	0	0
Device compression	2.3% (1/43)[a]	0	0
Device infolding	0	0	0
Stent fracture	0	0	0

[a] Patient 1200012 – Symmetrical compression occurred to the proximal section of the second component that was placed in this patient, due possibly to the component having been deployed through the distal suture loop of the proximal (first) component, which then restricted the second component from fully opening. This finding of compression is considered different from the compression/infolding due to hemodynamic forces commonly associated with the most proximal aspect of a stent-graft. The patient had

not experienced any adverse sequelae, but underwent a secondary intervention 335 days post-procedure. Balloon angioplasty was performed and the secondary intervention was deemed successful. Core laboratory analysis of the secondary intervention angiogram revealed no device compression.

Tables 63 and 64 summarize the site-reported reasons for secondary intervention and types of secondary intervention, respectively. One patient underwent placement of screws for Type I endoleak. One patient underwent balloon angioplasty for device compression. Four patients underwent secondary interventions involving additional stent-graft placement (one to treat dissection, one to treat a pseudoaneurysm, one to treat an area of residual injury or possible endoleak, and one to treat an area of thrombus).

Table 63. Site-reported reasons for secondary intervention

Reason	0-30 Days	31-365 Days	366-730 Days
Device compression	0	1[b]	0
Endoleak			
Type I proximal	1[a]	0	0
Type I distal	0	0	0
Type II	0	0	0
Type III (graft component overlap)	0	0	0
Type III (hole/tear in graft)	0	0	0
Type IV (through graft body)	0	0	0
Unknown	0	0	0
Clinical signs/symptoms	0	1[e]	0
Other	0	2[c,d]	1[f]

[a]Patient 1200033 – The patient was treated for a proximal Type I endoleak (per site assessment; core laboratory reported an unknown type of endoleak) 30 days post-procedure; the graft appeared undersized based on core laboratory-assessed aortic diameter measurements. Six Heli-FX™ screws were placed but the endoleak persisted and the secondary intervention was deemed unsuccessful. The patient later underwent conversion to open surgical repair 181 days after the index procedure. The patient survived the surgery and has not experienced any adverse events subsequent to the conversion as of 212 days post-procedure.

[b]Patient 1200012 underwent balloon angioplasty 335 days post-procedure to correct device compression of the proximal section of the second component (with no associated adverse sequelae) noted on the 1-month CT scan (refer to additional details in Table 62). The secondary intervention was deemed successful.

[c]Patient 1200024 underwent two secondary interventions following the index procedure. An unsuccessful secondary intervention (stent-graft placement) was attempted to treat a pseudoaneurysm proximal to the previously placed stent-graft (counted as a Vascular event in Table 58) on post-procedure day 74. On post-procedure day 79, the patient underwent a mini-sternotomy, aortic arch debranching, aortic bypass to the innominate and left carotid arteries with Hemashield™ graft, placement of a commercially available endograft, and bilateral chest tube placement to successfully treat the pseudoaneurysm. As described previously, the patient subsequently died on post-operative day 116. The death was adjudicated as procedure-related by the CEC (cause of death was exsanguination due to aortoesophageal fistula).

[d]Patient 1200006 underwent placement of a commercially available stent-graft 219 days post-procedure to treat an area of residual injury or possible endoleak (counted as a Miscellaneous/Other event in Table 58). The injury was incompletely treated during the index procedure due to the device having been placed too far distally (noted on the 6-month CT scan). The patient also required a left subclavian artery bypass. The secondary intervention was deemed successful.

[e]Patient 1200036 was diagnosed with an aortic dissection distal to the previously placed stent-graft (counted as a Vascular event in Table 58) on post-operative day 286 after returning to the hospital for chest pain. The site noted that the patient was hypertensive and had stopped taking his blood pressure

medication. An additional stent-graft was placed the following day, which resolved the patient's symptoms. The patient was discharged 2 days after the reintervention.
[f]Patient 1200060 required placement of an additional stent-graft (overlapped with the existing graft) 435 days post-procedure to treat thrombus in the distal stent-graft and native aorta that was noted on the 12-month CT scan (counted as a Miscellaneous/Other event in Table 58). The site reported that the intervention was successful.

Table 64. Types of secondary interventions

Type*	0-30 Days	31-365 Days	366-730 Days
Percutaneous			
Additional proximal component	0	1[d]	1[f]
Balloon angioplasty	0	1[b]	0
Stent	0	2[c,e]	0
Other	0	0	0
Surgical			
Conversion to open repair	0	0	0
Other	1[a]	2[c,d]	0
Other	0	0	0

*A patient may have had more than one treatment type.
[a-f]Refer to footnotes in Table 63 for additional details.

F. Summary and Conclusions

This study enrolled 50 subjects and they were treated with the Zenith Alpha™ Thoracic Endovascular Graft for BTAI. All but one patient received a single study component at the index procedure (one patient received two study components). One patient who received a single study component also received two commercially available components; the first study component and first commercial component placed were the same diameter and had been undersized, as measurements were from a pre-procedure CT scan performed while the patient was not fully resuscitated, prompting additional labelling instruction that graft sizing for BTAI should be based on measurements in a fully resuscitated patient. All grafts were deployed successfully in the intended location, and all graft components were patent upon completion of deployment, yielding a technical success rate of 100%.

There was one death within 30 days of endovascular repair, which was adjudicated by an independent CEC as not related to the BTAI repair. There were no ruptures reported at any follow-up time point. There were no conversions to open repair within the first 30 days following the index procedure. Patients experienced adverse events in each of the organ system categories.

There were no core laboratory-identified Type I or Type III endoleaks, device migrations, device infolding, or stent fractures. One occurrence of device compression was noted without any adverse clinical sequelae, and resolved after a secondary intervention. One

patient underwent successful conversion to open surgical repair 181 days post-procedure (due to a site-reported Type I endoleak that was the result of graft undersizing) and remained alive beyond 30 days following the conversion procedure. There was one aortic-injury-related death, which occurred greater than 30 days after the index procedure (in a patient with aortoesophageal fistula).

The results for the primary safety and effectiveness endpoints were within the expected ranges for treatment of patients with BTAI. Overall, the results provide a reasonable assurance of safety and effectiveness of the Zenith Alpha™ Thoracic Endovascular Graft for the treatment of BTAI.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. Longer-term Follow-up (> 2 years) – Aneurysm/Ulcer Pivotal Study

As of April 7, 2015 there were 34 subjects eligible for follow-up beyond 2 years (as shown in Table 12). Three patient deaths have been reported > 730 days following endovascular repair (2 of which were CEC-adjudicated as not related to TAA-repair and 1 which the CEC was unable to adjudicate). There are no reports of rupture or conversion to open surgical repair > 730 days. One additional patient experienced aneurysm growth (> 5 mm) after 2 years, which was associated with an inadequate landing zone length. There were no new reports of migration or Type I or III endoleak beyond 2 years. One new stent fracture was identified at 3 years, without adverse clinical sequelae. Three patients have undergone reintervention beyond 2 years, each of which was described previously due to having exhibited aneurysm growth within 2 years (one patient also had distal Type I endoleak and migration within 2 years, while another also had distal Type I endoleak within 2 years).

B. Continued Access – Aneurysm/Ulcer Indication

The results from eighteen (18) subjects treated during the continued access investigation of the aneurysm/ulcer indication were consistent with the results described for the pivotal study cohort, including one patient with aneurysm growth and Type I endoleak (at 6 months) that was associated with graft undersizing following initial treatment of the aneurysm with only a proximal component. Additionally, a portion of the subjects enrolled in the continued access investigation (n = 11) were treated with the rotation

handle version of the introduction system, which successfully deployed the stent-graft in all cases, consistent with the deployment results based on bench testing.

C. Longer-term Follow-up (> 30 days) – BTAI Study

The information obtained > 30 days following endovascular repair appears consistent with results through 30 days with respect to morbidity, mortality, and device performance. The only event types observed during longer-term follow-up that were not previously observed within 30 days were aortic-injury-related death in 1 patient who developed an aortoesophageal fistula, aortic dissection distal to the endovascular graft in one patient who had stopped taking their blood pressure medications and was treated with placement of an additional endovascular graft component, and one patient who underwent conversion to open surgical repair due to the site-reported reason of proximal Type I endoleak in the setting of an undersized graft.

D. European Post-market Survey – Delivery System with Rotational Handle

A post-market survey was implemented in Europe to gather additional supportive information regarding clinical performance of the rotation handle introduction system. Physician users in Europe were surveyed on the procedural performance of the rotation handle system beginning March 31, 2014. A total of 38 surveys were completed as of June 30, 2014. Table 65 summarizes the survey results.

Table 65. Results of European post-market survey

Survey Question	Response Percent (number/total number)	
Did the introduction system with the rotation handle successfully retract the release-wires without the use of the alternate sequence?	Yes	100% (38/38)
	No	0
Was the alternate sequence successful in retracting the release-wires?	Yes	Not applicable
	No	Not applicable
	Not applicable	100% (38/38)
Was the graft successfully deployed in the intended location?	Yes	97.4% (37/38)
	No	2.6% (1/38)[a]
Was the graft patent at the completion of the procedure?	Yes	100% (38/38)
	No	0

[a]Slight distal migration of a tapered proximal component was reported.

All grafts were successfully deployed in the intended location using the primary release sequence, as described in the IFU, with the exception of one report of a slight distal migration during deployment. The alternate release sequence, which is also described in the IFU and is intended to be used in situations in which deployment difficulties involving the handle are encountered, was not used in any case. Furthermore, all grafts were patent at the completion of the procedure and no unique findings were observed as compared to the results from the pivotal clinical studies. These results in combination with the results from the preclinical studies and uses of the introduction system with rotation handle during continued access provide a reasonable assurance of safety and effectiveness of the modifications that were made to the user interface since the time of enrollment completion in the pivotal clinical studies.

XII. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR Part 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 59 investigators, of whom 0 investigators were full-time or part-time employees of the sponsor and 11 investigators had disclosable financial interests/arrangements as defined in 21 CFR Part 54.2(a), (b), (c), and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none.
- Significant payment of other sorts: 11 investigators.
- Proprietary interest in the product tested held by the investigator: none.
- Significant equity interest held by investigator in sponsor of covered study: none.

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XIII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

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

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint for the aneurysm/ulcer pivotal study was device success at 12 month, where device success was defined as technical success, with none of the following at 12 months:

- Type I or type III endoleaks requiring re-intervention
- Aneurysm rupture or conversion to open surgical repair
- Aneurysm enlargement greater than 5 mm

Technical success was defined as successful access of the aneurysm site and deployment of the Zenith Alpha™ Thoracic Endovascular Graft at the intended location. The endovascular graft must be patent at the time of deployment completion as evidenced by intraoperative angiography.

The effectiveness hypothesis was that the device should meet the 80.7% performance goal. The 12-month device success rate was 92.7%. Therefore the performance goal was met ($p < 0.001$). 108 devices were successfully delivered and deployed in 110 subjects; two (2) patients did not receive the device due to an inability to insert/advance the introduction system. Three (3) patients experienced aneurysm growth greater than 5 mm at the 12-month follow-up; three (3) patients with reported endoleak at 12-month follow-up required a secondary intervention; one (1) stent fracture was observed at the 30-day follow-up; and one (1) patient underwent a successful conversion to open repair at 12-month follow-up due to an aortoesophageal fistula. No aneurysm ruptures, device migrations, kinks, barb or component separations were observed at the 12-month follow-up.

With regards to device success during longer-term follow-up beyond the 12-month primary endpoint for the aneurysm/ulcer pivotal study, there were no reports of rupture or conversion to open surgical repair. There were eight (8) additional patients who experienced aneurysm growth, one (1) of which had no associated endoleak and resolved spontaneously at subsequent follow-up without reintervention. Among the seven (7) remaining cases with growth (all aneurysm patients treated with a single proximal component), there were five (5) who also had distal Type I endoleak, three (3) of which required secondary intervention (all three for the site-reported reasons of distal Type I endoleak and migration; the CEC confirmed migration in two). There was one (1) additional report of CEC-confirmed migration (without associated growth, endoleak, or secondary intervention) and no additional core laboratory reports of Type I or III endoleak.

The primary effectiveness endpoint for the BTAI pivotal study was device success at 30 days. Device success was defined as successful access of the injury site and deployment of the device; it was 96% at 30 days. No formal hypothesis were analyzed for this pivotal study; descriptive statistics were used to assess the data. All devices were successfully delivered and deployed in the 50 subjects. One (1) patient had a device compression (requiring secondary intervention) and one (1) patient had a site-reported Type I endoleak requiring secondary intervention (the same patient with endoleak

requiring secondary intervention subsequently underwent successful conversion to open surgery between 31-365 days; no other conversions to open surgery were reported). Beyond 30 days, there was one (1) patient who required placement of an additional stent-graft to treat an area of residual injury or possible endoleak. There were no Type III endoleaks reported. Two (2) Type II endoleaks were reported at the 30-day follow-up and were resolved without treatment by the 6-month visit. There were no reports of misaligned deployment, aortic perforation, retrograde Type A dissection, or migration. No kinks, infoldings or stent fractures were observed, and all devices remained patent as reported by the core lab.

Additionally, the change to a rotational handle on the Introduction system was introduced in G100079/S015 and G120085/S005, and was evaluated in eleven (11) patients in the continued access arm of the aneurysm/ulcer indication. All devices were successfully delivered and deployed. Successful delivery and deployment using the rotational handle was also assessed as part of a post-market survey in Europe, during which the only notable finding among 38 cases was one report of slight distal migration of a graft during deployment.

The clinical data derived from the two pivotal studies and the additional supportive clinical information provide reasonable assurance of effectiveness for the Zenith Alpha™ Thoracic Endovascular Graft when indicated for the endovascular treatment of patients with isolated lesions of the descending thoracic aorta, not including dissections, having vascular anatomy suitable for endovascular repair.

B. Safety Conclusions

The primary safety endpoint for the aneurysm/ulcer pivotal study was freedom from Major Adverse Events (MAE) within 30 days as described above. The safety hypothesis was that the device should meet the 80.6% performance goal. The 30-day freedom from MAE rate was 96.4%. Therefore the performance goal was met ($p < 0.001$). Four (4) patients experienced MAEs: one (1) patient had a stroke, two (2) patients required ventilation > 72 hours/re-intubation, and one (1) patient had a stroke and required ventilation > 72 hours/re-intubation.

No lesion ruptures were observed, and the freedom from TAA-related mortality and all-cause mortality at 365 days was 99% and was 95.3%, respectively.

The observed rates for freedom of harmful serious adverse events (SAE) were as follows at 365 days:

- 91.7% freedom from wound events,
- 93.5% freedom from cardiovascular events,
- 94.3% freedom neurological events,
- 92.6% freedom from gastrointestinal events,
- 94.4% freedom from pulmonary events,
- 90.5% freedom from renal events,
- 89.6% freedom from vascular events,
- 40.2% freedom from other events

Events of special attention for thoracic endovascular grafts are those related to the cerebrovascular/neurological morbidity. With respect to the spinal cord, no cases of paraplegia were reported and one case of paraparesis was reported but the patient recovered with cerebral spinal fluid drain and medication. Five (5) patients experienced strokes within 365 days of the procedure; two (2) occurred within 30 days. One stroke was non-disabling stroke "0" on the Modified Rankin Scale which is indicative of "no symptoms at all", and the other was a disabling stroke that was rated as "5" on the Modified Rankin Scale which is indicative of "severe disability: bedridden, incontinent and requiring constant nursing care and attention."

These overall incidences of SAEs are consistent with those from the previous Cook Zenith TX2 thoracic aortic aneurysm/ulcer clinical study (P070016).

The primary safety endpoint for the BTAI pivotal study was all cause and aortic-injury-related mortality through 30 days post-treatment. No formal hypotheses were analyzed; descriptive statistics were used to assess the data. One (1) patient died within 30 days post-procedure (2.0%). Most SAEs were related to the initial trauma (mean Injury Severity Score was 31, which represents polytrauma (ISS >17)) rather than to the device or procedure. This result shows a low 30 day mortality rate for this group of patients who had BTAI and were treated with the Zenith Alpha™ Thoracic Endovascular Graft.

The clinical data derived from these two pivotal provides reasonable assurance of safety for the Zenith Alpha™ Thoracic Endovascular Graft when indicated for the endovascular treatment of patients with isolated lesions of the descending thoracic aorta, not including dissections, having vascular anatomy suitable for endovascular repair.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in clinical studies conducted to support PMA approval as described above. The probable benefit of the Zenith Alpha™ Thoracic Endovascular Graft is improving outcomes in patients with isolated lesions of the descending thoracic aorta (not including dissections).

Alternative treatments, including the use of other endovascular grafts, open surgical repair, and medical management, were carefully considered. Endovascular repair is often highly valued by patients because it is less invasive than open surgical repair. The risks and benefits of the Zenith Alpha™ Thoracic Endovascular Graft were found to be similar to the risks and benefits of other approved endovascular grafts. Patient risk is minimized by limiting use of the device in patients suitable for endovascular repair and to operators who have the necessary training to use the device safely and effectively, and adherence with the Instructions for Use.

An additional consideration for determining the probable risks and benefits for the Zenith Alpha™ Thoracic Endovascular Graft is the known risk of aneurysm growth. Aneurysm growth was observed in patients whose graft was undersized and/or the aneurysm had a short seal zone. This underscores the importance of using the device in accordance with the labelling. The concerns have been addressed in the Instructions for Use.

Additionally, Zenith Alpha™ Thoracic Endovascular Graft provides a lower profile introduction system as compared to currently approved thoracic endovascular grafts with similar indications. Additionally, the device has smaller diameter endovascular grafts with can be used to treat smaller diameter aortas. These features enable physicians to treat patients with both smaller access vessels and smaller aortic anatomy.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for the endovascular treatment with the Zenith Alpha™ Thoracic Endovascular Graft of patients with isolated lesions of the descending thoracic aorta (not including dissections) having vascular anatomy suitable for endovascular repair.

D. Overall Conclusions

The nonclinical and clinical data provided in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Moreover, the enrollment for the pivotal trial for the aneurysm/ulcer indication was balanced between males (58%) and females (42%), and thus allowed for a more robust evaluation of the results between men and women. Finally, the clinical data

collected from the studies of aneurysms, ulcers and BTAI can be assumed relevant for the treatment of all other types of isolated lesions, including intramural hematomas and pseudoaneurysms, but not including dissections. Treatment of isolated lesions in the descending thoracic aortic (not including dissections) do not present any unique device placement or other effectiveness challenges and treatment of these isolated lesions would not be expected to be associated with a different safety profile.

XV. CDRH DECISION

CDRH issued an approval order on September 15, 2015. The final conditions of approval cited in the approval order are described below.

1. The applicant will provide a clinical update to physician users at least annually with current information regarding the Zenith Alpha™ Thoracic Endovascular Graft device. All clinical updates are to include information from the two pivotal studies for the aneurysm/ulcer and blunt traumatic aortic injury indications, and continued access clinical studies for the aneurysm/ulcer indication. At a minimum, the information to be included regarding the clinical studies will include a summary of the number of patients for whom data are available, with the rates of death, aneurysm-related mortality, secondary endovascular procedures, conversion to open surgical repair, major device events, endoleak, aneurysm enlargement, prosthesis migration, losses of device integrity, aortic rupture and patency. Reports of losses of device integrity, reasons for secondary interventions and conversions to open surgical repair, and causes of death that may be associated with the lesion treated (e.g., death within 30 days of a secondary procedure to treat the index lesion and death from bleeding through the index lesion) 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 U.S. is also to be included. The clinical updates for physician users and the information supporting the updates must be provided in the Annual Report.

2. In addition to the Annual Report requirements outlined above, the applicant agrees to report Post-Approval Study data that consists of extended follow-up data out to 5 years for subjects enrolled in the aneurysm/ulcer clinical study initiated prior to device approval. This includes data from the pivotal study and continued access cohorts in accordance with the previously approved Investigational Device Exemption protocol. The data should include a summary of the number of patients

for whom data are available and the rates of adverse events, such as death, aneurysm-related mortality, secondary endovascular procedures, conversion to open surgical repair, major device events, endoleak, aneurysm enlargement, prosthesis migration, losses of device integrity, aortic rupture and patency.

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

XVI. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.