Summary of Safety and Effectiveness Data

I. GENERAL INFORMATION

Device Generic Name:	Fenestrated Endovascular Graft and Fenestration Stent
Device Trade Name:	Zenith® Fenestrated AAA Endovascular Graft and Zenith® Alignment Stent
Applicant's Name and Address:	Cook Incorporated 750 Daniels Way P.O. Box 489 Bloomington, IN 47402-0489 USA
Premarket Approval Application (PMA) Number:	P020018/S040
Date of Panel Recommendation:	None
Date of Notice of Approval to the Applicant:	April 4, 2012

Expedited: Granted expedited review status on November 22, 2011 because abdominal aortic aneurysms may be serious or life-threatening, or present a risk of serious morbidity. It is believed that the fenestrated endovascular graft configuration will provide an endovascular treatment option for some patients with abdominal aortic aneurysms who are not suitable for treatment with a currently-approved endovascular graft. This may offer a viable alternative to open surgical repair for these patients. Because no legally marketed endovascular device is available for the treatment of abdominal aortic aneurysms in these patients, the FDA decided to grant expedited review.

The original PMA (P020018) was for the Zenith AAA Endovascular Graft, which was approved on May 23, 2003 and is indicated for the endovascular treatment of patients with abdominal aortic or aorto-iliac aneurysms having morphology suitable for endovascular repair, including a non-aneurysmal infrarenal aortic

segment (neck) proximal to the aneurysm with a length of at least 15 mm. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the Zenith AAA Endovascular Graft product line to include the Zenith Fenestrated AAA Endovascular Graft (with the Zenith Alignment Stent), which is indicated for the endovascular treatment of patients with abdominal aortic or aorto-iliac aneurysms that have an infrarenal aortic neck at least 4 mm in length.

II. INDICATIONS FOR USE

A. Zenith Fenestrated AAA Endovascular Graft

The Zenith Fenestrated AAA Endovascular Graft is indicated for the endovascular treatment of patients with abdominal aortic or aortoiliac aneurysms having morphology suitable for endovascular repair, including:

- Adequate iliac/femoral access compatible with required introduction systems
- Nonaneurysmal infrarenal aortic segment (neck) proximal to the aneurysms with:
  - Length ≥4 mm and unsuitable for a non-fenestrated graft
  - Diameter ≤31 mm and ≥19 mm
  - Angle <45 degrees relative to long axis of aneurysm
  - Angle <45 degrees relative to axis of suprarenal aorta
- Ipsilateral iliac artery fixation site >30 mm in length and between 9 – 21 mm in diameter
- Contralateral iliac artery distal fixation site >30 mm in length and between 7 – 21 mm in diameter

B. Zenith Alignment Stent

The Zenith Alignment Stent is indicated for use as an adjunct to the Zenith Fenestrated AAA Endovascular Graft to secure positive alignment of fenestrations or scallops with the orifice of aortic branch vessels having diameters ranging from 3 to 8 mm.

III. CONTRAINDICATIONS

The Zenith® Fenestrated AAA Endovascular Graft and Zenith® Alignment Stent are contraindicated in:

- Patients with known sensitivities or allergies to stainless steel, polyester, nitinol, solder (tin, silver), polypropylene or gold
- Patients with systemic or local infection that may increase the risk of endovascular graft infection

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Zenith Fenestrated AAA Endovascular Graft and Zenith Alignment Stent labeling (Instructions for Use).

V. DEVICE DESCRIPTION

1. General Description – Fenestrated Endovascular Graft

The Zenith Fenestrated AAA Endovascular Graft is a modular system consisting of three components, a proximal body graft, a distal bifurcated body graft and one iliac leg (Figure 1). The graft modules are constructed of full-thickness woven polyester fabric sewn to self-expanding stainless steel Cook-Z® stents with braided polyester and monofilament polypropylene suture. These materials are identical to the materials used to construct the standard Zenith® AAA Endovascular Graft, with the Zenith Fenestrated AAA Endovascular Graft also having a nitinol wire ring around the graft fenestrations.

Ancillary devices that are currently available for the standard Zenith® AAA Endovascular Graft such as main body extensions, iliac leg extensions, converters, and iliac plugs may also be required.

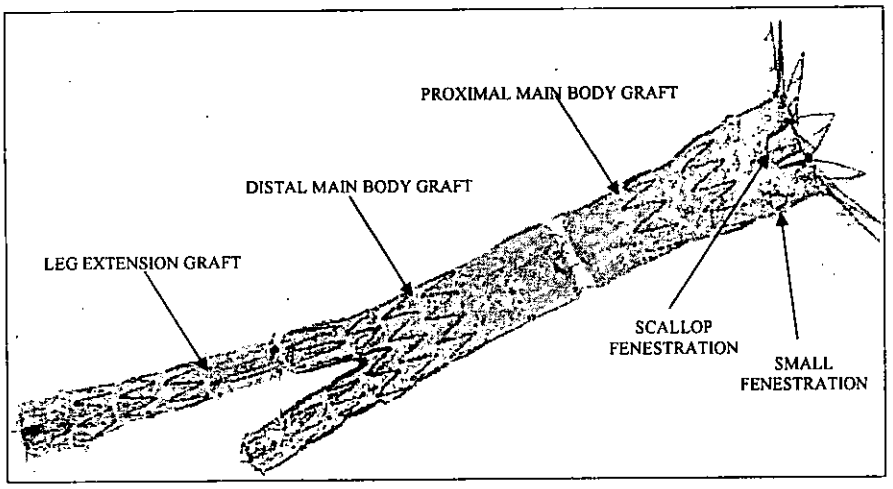

Figure 1. Zenith Fenestrated AAA Endovascular Graft main components.

Each component comes in a range of lengths and diameters which allows the physician to tailor the device to individual patient anatomies and select the best proximal and distal fixation sites.

Unlike the standard Zenith AAA Endovascular Graft, the Zenith Fenestrated AAA Endovascular Graft has fenestrations or scallops in the graft material, which allow the proximal edge of graft material to be placed above the renal arteries while still permitting blood flow to vessels accommodated by the fenestrations or scallops. In order to account for anatomical variation, each proximal body graft is made to order for a specific patient.

A. Proximal Body Graft

The proximal body graft is the first component of the Zenith Fenestrated AAA Endovascular Graft to be deployed during the procedure. The bare suprarenal stent at the proximal end of the proximal body graft contains barbs. This graft contains up to three precisely located holes (fenestration(s)), and cut-outs from the proximal margin (scallop(s)) of the graft material (Figure 1).

The fenestrations may be a combination of small fenestrations (Figure 2a), large fenestrations (Figure 2b), and scallop fenestrations (Figure 2c), and allow the proximal margin of the device to sit more cranially in the aorta than a standard

11

AAA endograft, including the Zenith Flex AAA Endovascular Graft, which are intended for placement of the proximal graft margin inferior to the lowest renal artery. This design permits uninterrupted blood flow to branch vessels of the aorta such as the renal and superior mesenteric arteries after device deployment. The choice and placement of the fenestrations and/or scallops is dependent on individual patient anatomy. Small fenestrations are generally used to accommodate renal arteries. Large fenestrations and scallops can be used to accommodate renal or superior mesenteric arteries. Also illustrated by Figure 2 are the gold markers used to identify the margins of each fenestration. The small and large fenestrations each contain 4 gold markers that are positioned around the perimeter at the graft material margin. The scallop fenestration is identified by 3 gold markers: 1 each at the left and right proximal most margins of the scallop, and 1 centered at the distal most margin of the scallop.

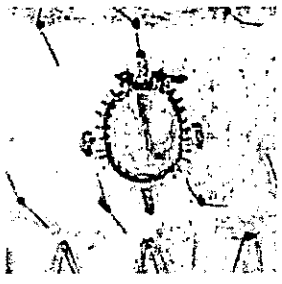

Figure 2a. Small fenestration

Figure 2b. Large fenestration

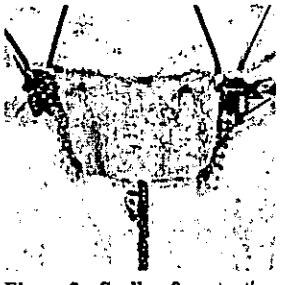

Figure 2c. Scallop fenestration

Additionally, gold radiopaque markers are positioned on the proximal component as follows to aid in fluoroscopic visualization; one at the distal end of the graft and four in a circumferential orientation at the proximal end of the graft (Figure 3).

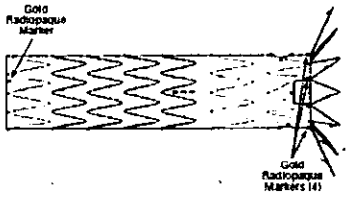

Figure 3. Gold markers at graft margin of proximal component

The proximal component also contains vertically-aligned gold markers located on the anterior aspect of the graft and horizontally-aligned gold markers located on the posterior aspect of the graft. These markers help with orientation of the proximal component by forming a cross (+) under fluoroscopy when the device is aligned as intended (Figure 4). Additional gold markers are positioned anteriorly in the shape of a tick or check marker.

Figure 4. Vertically-aligned gold markers on the anterior aspect and horizontally-aligned gold markers on the posterior aspect of the proximal component

The proximal body graft is available in a number of diameters and lengths, as provided in Table 1. Table 1 also lists the corresponding delivery system sheath sizes.

Table 1. Proximal body graft sizes and corresponding delivery system sizes

	Diameter (mm)	Body Length (mm)	Introducer Sheath (Fr)	Introducer Sheath Length (cm)
Proximal Body Graft	24	76 / 91 / 94 / 106 / 109 / 121 / 124	20	50
	26	76 / 91 / 94 / 106 / 109 / 121 / 124	20	50
	28	76 / 91 / 94 / 106 / 109 / 121 / 124	20	50
	30	76 / 91 / 94 / 106 / 109 / 121 / 124	20	50
	32	76 / 91 / 94 / 106 / 109 / 121 / 124	20	50
	34	84 / 99 / 114 / 129 / 107 / 122 / 137	20	50
	36	84 / 99 / 114 / 129 / 107 / 122 / 137	20	50

B. Proximal Body Graft Delivery System

The Zenith® Fenestrated AAA Endovascular Graft proximal graft is shipped preloaded onto the H&L-B One-Shot™ Introduction System (Figure 5). The H&L-B One-Shot™ Introduction System is constructed from identical materials and is similar in design and deployment characteristics to the H&L-B One-Shot™ Introduction System that the standard Zenith Flex AAA Endovascular Graft is loaded on. It has a sequential deployment method to provide control of the endovascular graft throughout the deployment procedure. During manufacture, the graft is reduced in diameter by an independent wire tied to removable diameter reducing ties (Figure 6). This is unique to the Fenestrated device and allows the partially constrained graft to be manipulated within the aorta to allow positioning of the graft so that the fenestrations can line up with the desired arteries before complete device deployment. Same as with the standard device, the bare suprarenal stent is constrained within a top cap and held there by a trigger wire. The distal end of the graft is also attached to the delivery system and held by an independent wire. The H&L-B One-Shot™ Introduction System allows readjustment of the final graft position before deployment of the bare barbed suprarenal stent. The delivery system uses a 20 French H&L-B One-Shot™ Introduction System. All systems are compatible with a 0.035 inch wire guide.

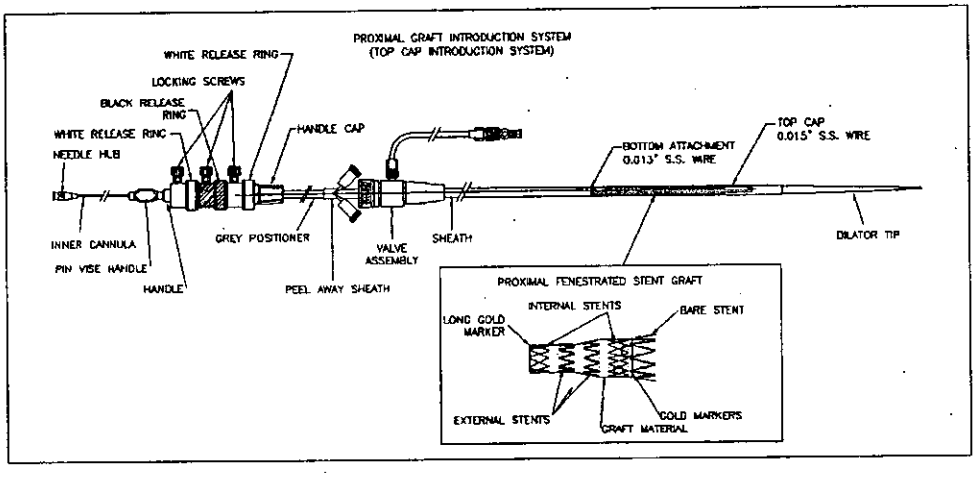

Figure 5. Proximal introduction system

Figure 6. Diameter reducing ties on the proximal main body component

C. Distal Bifurcated Body Graft

The Zenith Fenestrated AAA Endovascular Distal Bifurcated Body Graft has one long ipsilateral iliac limb and one short contralateral limb. There is a radiopaque marker at the proximal end of the graft as well as at the graft bifurcation and at the distal end of the contralateral limb (Figure 7).

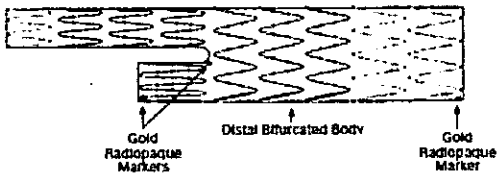

Figure 7. Gold markers on distal bifurcated body

The distal main body graft is available in a number of diameters and lengths, as listed in Table 2. Table 2 also lists the corresponding delivery system sheath sizes.

Table 2. Distal body graft sizes and corresponding delivery system sizes

	Diameter (mm)	Body Length (mm)	Leg Length (mm)	Introducer Sheath (Fr)	Introducer Sheath Length (cm)
Distal Bifurcated Body Graft	12	76 / 91 / 106 / 121	28 / 45 / 62	20	40
	16	76 / 91 / 106 / 121	28 / 45 / 62	20	40
	20	76 / 91 / 106 / 121	28 / 45 / 62	20	40
	24	76 / 91 / 106 / 121	28 / 45 / 62	20	40

D. Distal Bifurcated Body Graft Delivery System

The Zenith® Fenestrated AAA Endovascular Graft distal body graft is shipped preloaded onto the H&L-B One-Shot™ Introduction System (Figure 8). Both the proximal and distal ends of the graft are attached to the delivery system and held by independent wires. The H&L-B One-Shot™ Introduction System allows readjustment of the final graft position before deployment of the stent-graft. The delivery system uses a 20 French H&L-B One-Shot™ Introduction System. All systems are compatible with a 0.035 inch wire guide.

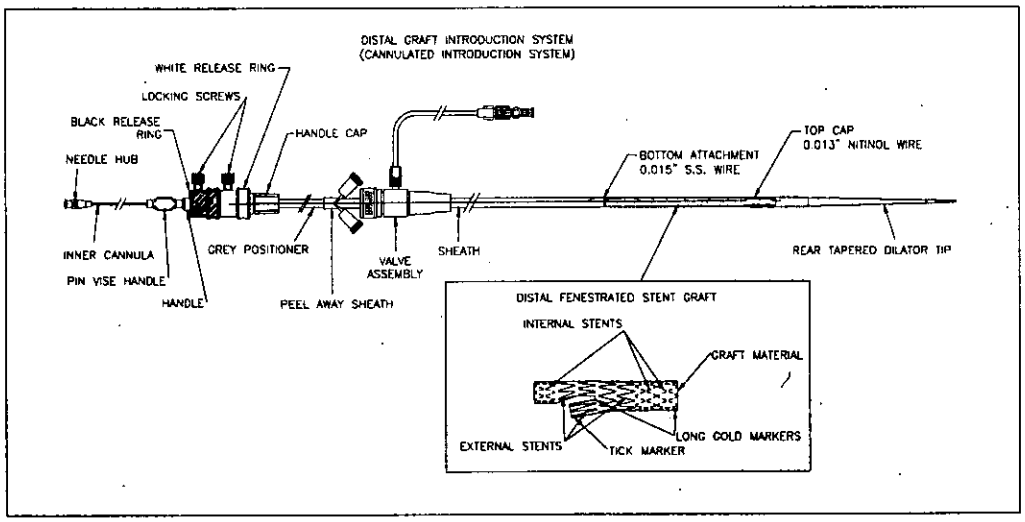

Figure 8. Distal introduction system

E. Iliac Leg Graft and Delivery System

The fenestrated Zenith graft uses the same iliac legs as the standard Zenith graft. The iliac legs are tubular grafts which are used to extend the fenestrated graft into the iliac arteries. An iliac leg must be placed into the short limb from the contralateral side.

F. Ancillary Components and Delivery System

The fenestrated Zenith graft is compatible with the same ancillary components as the standard Zenith graft. The following ancillary endovascular components are available:

- Main body extensions
- Leg extensions
- Converters
- Iliac occluders

G. Zenith Alignment Stent

Zenith Alignment Stents may be placed in branch vessels targeted by fenestrations or scallops to secure positive alignment. The Zenith Alignment Stent is a balloon-expandable stent that can be deployed through scallops or small fenestrations in a Zenith Fenestrated AAA Endovascular Graft into branch vessels of the aorta. The stent is constructed of 316L stainless steel. The distal segment of the stent is designed to be expanded into the target vessel. The flarable proximal segment of the stent is designed to extend into the lumen of a Zenith Fenestrated AAA Endovascular Graft already deployed in the aorta and can be flared using a standard non-compliant balloon, to allow for ease in reintervention. The margin between the flarable proximal segment and non-flarable distal segment of the Zenith Alignment Stent is denoted by circumferentially arranged gold markers on the stent that are to be aligned with the graft fenestrations. As depicted in Figure 9, the region/zone of the stent likely to be in contact with the fenestration is reinforced. The Zenith Alignment Stent is available in lengths of 18 and 26 mm, and nominal expanded diameters of 3, 4, 5, 6, 7, and 8 mm (Table 3). Figure 7 depicts the Zenith Alignment Stent before and after flaring.

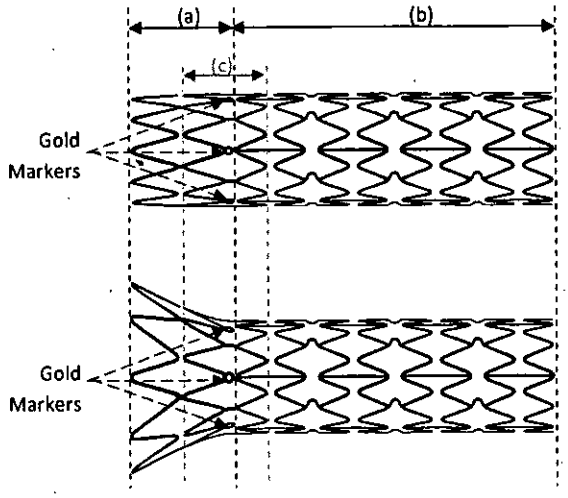

Figure 9. Zenith Alignment Stent (a) flarable proximal segment, (b) non-flarable distal segment, and (c) reinforced zone

Table 3. Available diameters and lengths of the Zenith Alignment Stent and corresponding sheath compatibility

Nominal Stent Size (Diameter x Length)	Crimped Stent	Expanded Stent		Introducer Sheath Compatibility
	Total Length (mm)	Total Length (mm)	Non-flarable Segment Length (mm)	
3 x 18 mm	18.4	18.3	13.3	6 Fr
3 x 26 mm	25.3	25.3	20.2	6 Fr
4 x 18 mm	18.3	18.1	13.2	6 Fr
4 x 26 mm	25.3	25.2	20.3	6 Fr
5 x 18 mm	17.7	17.7	12.2	6 Fr
5 x 26 mm	26.3	26.7	20.8	6 Fr
6 x 18 mm	17.8	17.8	12.3	6 Fr
6 x 26 mm	26.4	26.6	20.9	6 Fr
7 x 18 mm	18.3	18.2	12.2	6 Fr
7 x 26 mm	26.9	27.0	20.8	6 Fr
8 x 18 mm	18.3	17.9	12.2	7 Fr
8 x 26 mm	26.9	27.1	20.8	7 Fr

H. Zenith Alignment Stent Balloon Delivery System

The Zenith Alignment Stent is pre-mounted and positioned between two radiopaque (platinum) marker bands on the balloon catheter, which serves as the delivery system. The delivery system is advanced through an introducer sheath into a target artery. The sheath is withdrawn and the gold markers on the stent are aligned with the gold markers designating a fenestration or scallop. The stent is then deployed by inflating the balloon to the recommended expansion pressure as indicated in the stent IFU. After removal of the Zenith Alignment Stent balloon catheter, a 10 mm non-compliant balloon catheter is inserted within the flarable proximal segment of the stent and inflated to the recommended expansion pressure indicated in the balloon IFU.

The delivery system is 80 cm in length and its profile permits vascular access via 6.0 or 7.0 French introducer sheaths (dependent on the selected Zenith Alignment Stent size). A depiction of the delivery system is presented in Figure 10.

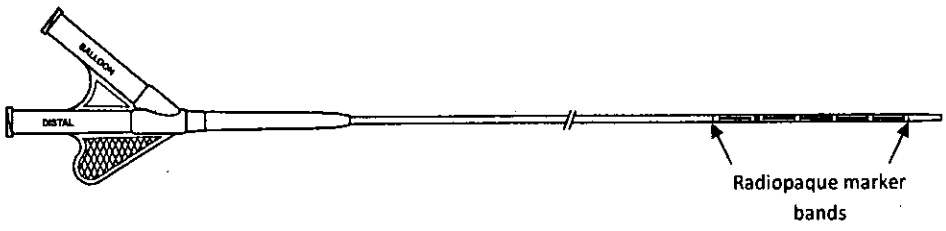

Figure 10. Zenith Alignment Stent delivery system.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are no approved endovascular graft options for the treatment of patients with a short infrarenal aortic neck. The available treatment options for patients with an abdominal aortic aneurysm and a short infrarenal aortic neck are conventional surgical repair and medical management. Each alternative has advantages and disadvantages. The physician should fully discuss these alternatives with the patient to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Zenith Fenestrated AAA Endovascular Graft has been commercially available outside the US since November 2002. The Zenith Fenestrated AAA Endovascular Graft is available in Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Costa Rica, Dominican Republic, European Union, Hong Kong, India, Malaysia, New Zealand, Serbia, Singapore, Taiwan, Thailand, Turkey, and Uruguay. The Zenith Fenestrated AAA Endovascular Graft has not been withdrawn from any market for reasons related to safety and effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events that may occur and/or require intervention include, but are not limited to:

- Amputation
- Anesthetic complications and subsequent attendant problems (e.g., aspiration)
- Aneurysm enlargement
- Aneurysm rupture and death
- Aortic damage, including perforation, dissection, bleeding, rupture, and death
- Arterial or venous thrombus and/or pseudoaneurysm
- Bleeding, hematoma or coagulopathy
- Bowel complications (e.g., ileus, transient ischemia, infarction, necrosis)
- Cardiac complications and subsequent attendant problems (e.g., arrhythmia, myocardial infarction, congestive heart failure, hypotension, hypertension)
- 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 component deployment; component migration; suture break; occlusion; infection; stent fracture; graft material wear; dilation; erosion; puncture; perigraft flow; barb separation and corrosion
- Fever and localized inflammation
- Fistula (e.g., aortoenteric, arteriovenous)

- Genitourinary complications and subsequent attendant 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 attendant problems (e.g., lymph fistula)
- Neurologic local or systemic complications and subsequent attendant problems (e.g., confusion, stroke, transient ischemic attack, paraplegia, paraparesis, paralysis)
- Occlusion of device or native vessel
- Organ impairment/loss due to side-branch vessel occlusion (in particular, renal and/or gastrointestinal impairment/loss)
- Pulmonary/respiratory complications and subsequent attendant problems (e.g., pneumonia, respiratory failure, prolonged intubation)
- Renal complications and subsequent attendant problems (e.g., artery stenosis or occlusion, contrast toxicity, insufficiency, failure)
- Surgical conversion to open repair
- Vascular access site complications, including infection, pain, hematoma, pseudoaneurysm, arteriovenous fistula
- Vascular spasm or vascular trauma (e.g., iliofemoral vessel dissection, bleeding, rupture, death)
- Vessel damage
- Wound complications and subsequent attendant problems (e.g., dehiscence, infection, hematoma, seroma, cellulitis)

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

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Biocompatibility

1. Zenith Fenestrated AAA Endovascular Graft

The Zenith Fenestrated AAA Endovascular Graft System is a product line extension of the Zenith Flex AAA Endovascular Graft System and utilizes the same materials as with the currently-approved system. Therefore, additional biocompatibility testing was not necessary for the Zenith Fenestrated AAA Endovascular Graft.

2. Zenith Alignment Stent

A panel of biocompatibility testing was performed on the Zenith Alignment Stent and delivery system in accordance with FDA's biocompatibility testing guidance, ISO 10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing, and 21 CFR 58 Good Laboratory Practice (GLP) requirements. The stent was assessed by tests considered appropriate for a permanent (>30 days) blood-contacting implant, and the delivery systems were assessed by tests considered appropriate for a limited time, circulating-blood contacting, externally-communicating device.

Biocompatibility testing performed on the Zenith Alignment Stent and the delivery system are summarized in Table 4. The test articles in each of the following biocompatibility tests consisted of the Zenith Alignment Stent and delivery system. The stents included in this testing did not have gold markers; however, gold radiopaque markers have been included on every Zenith device to date, with no adverse clinical sequelae related to the presence of gold markers. Therefore, additional testing of the Zenith Alignment Stent with gold markers was not considered necessary. Longer-term biocompatibility testing for the Zenith Alignment Stent was leveraged from the Formula™ Balloon-Expandable Stent (approved for renal use under P100028) and has been reviewed by FDA previously. Test results for the Formula™ Balloon-Expandable Stent are considered applicable as the stent is manufactured from the same material and is the same design as the segment of the Zenith Alignment Stent intended for vessel contact. The leveraged testing included genotoxicity, ISO muscle implantation,

and plasma recalcification time coagulation. Compared to the Formula Balloon-Expandable Stent, the delivery system for the Zenith Alignment Stent utilizes different color additives for the balloon catheter tip and shaft, which contact the body for a limited period of time and were shown to be biocompatible based on the results from testing described in Table 4.

Table 4. Summary of biocompatibility testing – Zenith Alignment Stent and delivery system

Test Type	Purpose	Acceptance Criteria	Result
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
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
In vivo Thrombo-resistance Study (carotid artery)	Determine whether the device triggers thrombus formation	The device/ material shall be considered thrombo-resistant and there shall be no evidence of thrombus formation	Pass
In vitro Hemolysis Study (modified ASTM-extraction method)	Determine whether extracts would cause hemolysis *in vitro*	The device/ material shall be considered nonhemolytic (hemolytic index 0-2%)	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
ISO Maximization Sensitization Study (extract)	Evaluate the potential for delayed dermal contact sensitization	The device/ material shall show no evidence of causing delayed dermal contact sensitization	Pass

B. Laboratory (*in vitro*) Studies

As a product line extension, much of the testing previously performed on the Zenith Flex AAA Endovascular Graft is applicable to the Zenith Fenestrated AAA Endovascular Graft. A comprehensive preclinical testing plan was conducted to evaluate any differences in design and verify that the performance attributes of the Fenestrated Graft System are acceptable. All testing was conducted in accordance with national and international standards and guidance

documents. The results obtained from *in vitro* testing provided evidence supporting safety and effectiveness of the Fenestrated Graft System

1. Zenith Fenestrated AAA Endovascular Graft

The results of *in vitro* bench testing performed on the Zenith Fenestrated AAA Endovascular Graft (implant) are summarized in Table 5.

Table 5. Results of testing performed for the implant

Test Method	Purpose	Acceptance Criteria	Result
Dimensional verification	Determine the outer diameters and lengths of the endovascular prosthesis in the deployed state for verification to design specifications	• Length must be ± 5% of the nominal length; • The diameter of the proximal vessel seal site (D1) must be ± 5% of the nominal outer diameter (NOD); • D2 (maximum measured outer diameter) < D3 (minimum measured outer diameter) + 1.432 mm; • D3 (minimum measured outer diameter) > D2 (maximum measured outer diameter) - 1.432 mm; • D4 (maximum measured outer diameter) < iliac leg graft (minimum measured outer diameter) + 1.34 mm; and • The diameter of the distal vessel seal site (D5) must be ± 10% of the nominal diameter (NOD) for nominal diameters < 20 mm or ± 5% of the nominal diameter for nominal diameters ≥ 20 mm	Pass
Flex/kink	Determine the minimum radius that the endovascular prosthesis can accommodate without kinking	Maximum kink radius must be < 50.8 mm	Pass
Pull test for modular components	Determine the force required to separate the modular components of an endovascular prosthesis or to separate overlapping endoprostheses in the deployed state	Separation force must be ≥ 5.1 N	Pass

Test Method	Purpose	Acceptance Criteria	Result
Radial Force	Demonstrate that when grafts are sized correctly, the z-stents are expected to exert a radial force sufficient enough to maintain graft patency and apposition to the vessel wall without causing vessel damage	Radial force must be between 7.7 N and 14.3 N.	Pass
Fatigue & durability (pulsatile)	Evaluate the fatigue life of the Fenestrated Graft in combination with Alignment Stent during physiologic pulsatile loading for 400 million cycles (10 year simulated fatigue)	• No stent fractures; • External stents must not have more than six suture attachment failures in a row; • Internal stents must not completely separate from the graft; • Graft material wear around a small fenestration and at the graft to fenestration stent interface shall not show any opening up of the weave construction that is wider than the stent wire at that location; • Nitinol ring shall remain in location around the small fenestration and shall not develop fractures leading to a free floating piece of wire; • Fenestration ring retention sutures shall not develop a suture fracture(s) leading to a free floating detached suture after 10-year time-accelerated radial fatigue test; • Zenith Alignment Stent must maintain position within the fenestrated stent-graft such that the cross-sectional area of the orifice is reduced by no more than 60%; and • Zenith Alignment Stent must not have any fractures not present in the non-Cook stents tested.	Pass

Test Method	Purpose	Acceptance Criteria	Result
Fatigue and durability (bending)	Evaluate the fatigue life of the Fenestrated Graft in combination with Alignment Stent during simulated respiration for 85 million cycles (10 year simulated fatigue)	• Graft material wear around a small fenestration, and the graft to fenestration stent interface shall not show any opening up of the weave construction that is wider than the stent wire at that location • Nitinol ring shall remain in location around the small fenestration and shall not develop fractures leading to a free floating piece of wire • Fenestration ring retention sutures shall not develop a suture fracture(s) leading to a free floating detached suture after 10-year time accelerated respiratory motion test • Zenith Alignment Stent must not have any fractures not present in the non-Zenith stents tested	Pass
Stress/strain analysis	To determine and locate the maximum stresses and strains in the implant when subjected to worst-case catheter loading, deployment, and physiological pulsatile loading	The fatigue safety factors must be >1.0	Pass

The results of *in vitro* bench testing performed on the Zenith Fenestrated AAA Endovascular Graft H&L-B One Shot Introduction System (delivery system/complete assembly) are summarized in Table 6.

Table 6. Results of testing performed for the delivery system/complete assembly

Test Method	Purpose	Acceptance Criteria	Result
Simulated use models (deployment)	Demonstrate that the Zenith® Fenestrated AAA Endovascular Graft and delivery system perform as intended with respect to dimensional compatability, trackability, pushability, torquability, and deployability in a simulated use model	100% success for each of the deployment parameters assessed	Pass

Test Method	Purpose	Acceptance Criteria	Result
Visibility	Demonstrate that the Zenith® Fenestrated AAA Endovascular Graft and delivery system perform as intended with respect to visibility in a simulated use model	100% success for each of the visibility parameters assessed	Pass
Force to deploy	The purpose of this test is to determine the force to deploy the endovascular prostheses, including the force necessary for sheath retraction, trigger wire withdrawal, and top cap advancement	• Sheath retraction must be < 100 N • Trigger wire withdrawal must be < 35 N • Top cap advancement must be < 15 N	Pass
Bond strength	Determine tensile characteristics of the delivery system using a tensile testing machine	• Inner cannula/dilator tip must be ≥ 60.4 N • Hub/inner cannula must be ≥ 60.4 N • Pin vise handle/dilator must be ≥ 60.4 N • Valve/sheath must be ≥ 100 N • Trigger wire/trigger knob ≥ 35 N	Pass
Torsional bond strength	Determine the maximum torque required to cause failure of the delivery system components	• Needle hub/threaded cannula must be > 0.02 N•m; • Threaded dilator tip/threaded cannula must be > 0.068 N•m; • Threaded dilator tip/threaded cap must be > 0.068 N•m; • Pin vise handle/dilator must be > 0.068 N•m	Pass

2. Zenith Alignment Stent

The results of *in vitro* bench testing performed on the Zenith Alignment Stent (implant) are summarized in Table 7.

Table 7. Results of testing performed for the implant

Test Method	Purpose	Acceptance Criteria	Result
Stent Corrosion Resistance	Evaluate the susceptibility of the metallic components of the stent to corrosion in a simulated physiological environment	The mean breakdown potential of the Zenith Alignment Stent shall be ≥ 586 mV_{SCE}	Pass

Test Method	Purpose	Acceptance Criteria	Result
Foreshortening	Determine the amount a stent will foreshorten upon deployment	For the non-flarable (arterial) region of the stent, the calculated maximum length change between the expanded (post-deployed) stent length and crimped (undeployed) stent length must be less than 5%	Pass
Dimensional Verification	Determine the outer diameter of the stent in the deployed state	On an expanded stent, $O.D._{max} - O.D._{min}$ must be less than or equal to 0.5 mm for the non-flarable segment of the stent	Pass
Recoil for Balloon Expandable Stents	Determine the amount of elastic recoil after the deployment of a balloon-expandable stent	For the arterial segment of the stent, the stent recoil must be less than 6%	Pass
Stent Integrity	Evaluate the integrity of the stent following deployment	There must be no microscopic evidence of structural deficiency at 50-63X magnification after deployment	Pass
Percent Surface Area	Determine the percentage of vessel surface area covered by the stent struts (abluminal surface area) when the stent is expanded to its nominal diameter	No acceptance criteria - for characterization of stent design criteria	Surface area was between 13.11% and 21.31% depending on stent size
Radial Stiffness and Radial Strength	Determine the ability of a stent to withstand deformation due to external radial forces.	Radial strength > $\pi \times D_{Nom} \times 0.02133$ N/mm^2 and radial stiffness >0.134 N/mm^2	Pass
Crush Resistance	Determine the crush resistance of the Zenith Alignment Stent when subjected to external focal loading	The shear force required to reduce the cross-sectional area of the 6, 7, and 8 mm diameter stents by 60% must be >2.37 N. Testing of 3, 4, and 5 mm diameter stents was performed for characterization purposes only.	Pass
Shelf Life	Establish an expiration period for the product	No sign of stent fractures at a magnification of 50x following balloon burst testing after aging	Pass

Test Method	Purpose	Acceptance Criteria	Result
Stress/strain Analysis	To determine and locate the maximum stresses and strains in the implant after crimping, deployment, and physiological pulsatile loading, bending loading, and combined (pulsatile and bending) loading	The fatigue safety factors must be >1.0	Pass
Fatigue and Durability (pulsatile)	Evaluate the fatigue life of the stent by subjecting it to time-accelerated, physiologically modeled, controlled displacement pulsatile loading for 400 million cycles	No stent fractures	Pass
Fatigue and Durability (bending)	To determine the bending fatigue endurance limit of the stent, defined as the bending angle/radius of curvature at which six out of six test articles achieved run-out to 85 million cycles without fracture	The endurance limit radius of curvature must be less than the physiologically relevant curvature during respiration	Pass

The results of *in vitro* bench testing performed on the Zenith Alignment Stent Balloon Catheter (balloon catheter/complete assembly) are summarized in Table 8.

Table 8. Results of testing performed for the balloon catheter/complete assembly

Test Method	Purpose	Acceptance Criteria	Result
Crossing profile	Determine the undeployed stent outer diameters	No acceptance criteria – for characterization of sheath compatibility	Stents will fit in specified sheaths
Balloon profile	Determine the undeployed balloon outer diameters	No acceptance criteria – for characterization of sheath compatibility	Stents will fit in specified sheaths
Stent Diameter vs. Balloon Pressure (Compliance Chart)	The purpose of this test was to determine the relationship between stent diameter and balloon inflation pressure	At nominal inflation pressure (8 atm), stent inner diameter must equal the labeled diameter ± 10% with a confidence interval of 95% and a reliability interval of 99%	Pass

Test Method	Purpose	Acceptance Criteria	Result
Balloon Rated Burst Pressure	Determine the rated burst pressure (RBP) of the delivery system balloon	• With the stent mounted on the balloon, 99.9% of balloons must survive at least 12 atm of pressure (the labeled rated burst pressure) with a confidence of 95%; • Balloon failure must occur linearly and not at the balloon bond sites; and • There must be no microscopic evidence of structural deficiency of the stent at 50-63X magnification after balloon burst	Pass
Deployment and Sheath Compatibility Testing	Evaluate performance of the endovascular system using a model that simulates deployment under the intended use conditions	100% success for all deployment parameters assessed	Pass
Dogboning. Measurement	Evaluate the diameter of the balloon at rated burst pressure compared to the diameter of the stent during deployment	No acceptance criteria - for characterization related to geometry and deployment of the stents	Balloon diameter is smaller than the outer diameter of the stents
Balloon Fatigue	Determine the ability of the balloon to withstand repeated inflation cycles.	All test samples must inflate to 12 atm and deflate 10 times without bursting	Pass
Catheter Bond Strength	Determine the longitudinal strength of various joints/subassemblies used in the delivery system	All bonds must have a strength $\geq$ 10 N	Pass
Balloon Inflation and Deflation Time	Determine the time required to inflate the balloon to the maximum recommended inflation pressure, volume, or diameter, and to measure the time required to deflate the balloon	Each balloon must be inflated with a 1:1 mixture of contrast and saline within 30 seconds, and each balloon must be evacuated of the same mixture within 30 seconds of a negative pressure being applied to the balloon	Pass

Test Method	Purpose	Acceptance Criteria	Result
Stent Securement for Unsheathed Stents	Determine if the stent will become displaced or dislodged from the balloon and to determine the force required to displace or dislodge the stent from the balloon	The device must be able to pass through an anatomical model, an appropriately sized sheath, and a simulated stricture without the stent being dislodged or displaced so that it is no longer between the markers on the balloon catheter. The force to dislodge the stent was measured for characterization only	Pass
Shelf Life	Establish an expiration period for the product	• All bonds must have a strength ≥ 10 N after aging • Balloons must survive at least 12 atm of pressure	Pass

C. Animal Studies

1. Zenith Fenestrated AAA Endovascular Graft

Considerable *in vivo* testing addressing patency, histopathology, and survival at 1, 3, and 6 months of the Zenith® AAA Endovascular Graft in animal models has been previously reported to the Agency. The need for animal studies to assess deployability and biological response to the Zenith® Fenestrated AAA Endovascular Graft was considered during development of the *in vitro* bench testing and non-clinical studies testing plan. However, based on several factors (i.e., similarities in materials of construction with other devices, limitations of appropriate animal models, and extensive clinical experience); animal studies specific to the Zenith® Fenestrated AAA Endovascular Graft were considered not necessary.

2. Zenith Alignment Stent

The purpose of the animal study (summarized in Table 9) was to evaluate the functional biocompatibility and safety of Zenith Alignment Stents. Up to four prototype stents were implanted in each domestic pig, one each, in the left and right renal arteries, celiac artery and superior mesenteric artery (SMA) for one month. Primary safety endpoints included quantitative angiographic evaluation of early (immediately after implant) and late (at one-month follow-up) patency of the stented arteries as well as qualitative histopathologic evaluation and

quantitative histomorphometric analysis of the stented arteries characterizing the response of the stented vessels to the stents. A one-month follow-up time point is supported based on the demonstrated safety and effectiveness of the Formula Balloon-Expandable Renal Stent (P100028), which is the same design as the segment of the Zenith Alignment Stent intended for vessel contact. Secondary endpoints in the study included a qualitative evaluation of the performance characteristics of the delivery system. Performance parameters evaluated included preparation, introduction, pushability, trackability, flexibility, radiopacity and appearance on inspection. The Zenith Alignment Stent was evaluated under conditions that simulated the intended clinical use of the device. The animal testing complied with 21 CFR 58, Good Laboratory Practices (GLP).

Table 9. Animal testing summary for the Zenith Alignment Stent

One-Month Study of Balloon Expandable Fenestration Stents in Domestic Swine Arteries		
Study Objectives	**Number of Animals** **Timepoints** **Devices Tested**	**Relevant Findings**
Evaluate the functional biocompatibility and safety of Zenith Alignment Stents under conditions that simulated the intended clinical use of the device	• 9 pigs • 1 month • 16 stents evaluated	• All animals were healthy at 1 month follow up • Performance of stent delivery systems was rated as "adequate" or better for all parameters • Stented vessels remained widely patent throughout the study. • Stented vessels appeared to be healing adequately at 1 month. • No stent fractures were observed 1 month following implantation.

The animal study revealed no safety problems or negative sequelae associated with the Zenith Alignment Stent following a 1 month implantation period.

D. Sterilization, Packaging and Shelf Life

The Zenith Fenestrated AAA Endovascular Graft and H&L-B One-Shot Introduction System is sterilized by a validated ethylene oxide (EtO) sterilization process to achieve a minimal sterility assurance level (SAL) of 10^{-6}. The Zenith Fenestrated AAA Endovascular Graft system is packaged in the same packaging system that is currently used for other marketed products produced by Cook Incorporated and William Cook Australia. The shelf life studies on file for these

packaging materials reveal that the package configuration and materials provide an acceptable bacterial barrier and that three years is an appropriate sterility expiration period. The Zenith Fenestrated AAA Endovascular Graft and H&L-B One-Shot Introduction System is constructed from identical materials using similar manufacturing processes as the Zenith Flex AAA Endovascular Graft and H&L-B One-Shot Introduction System which previously performed as intended following 3-years aging, supporting a 3-year shelf life for the Zenith Fenestrated AAA Endovascular Graft.

The Zenith Alignment Stent is sterilized by a validated ethylene oxide (EtO) sterilization process to achieve a minimal sterility assurance level (SAL) of 10^{-6}. The Zenith Alignment Stent is packaged in the same packaging system that is currently used for the Formula Stent produced by Cook Incorporated. The shelf life studies on file for these packaging materials reveal that the package configuration and materials provide an acceptable bacterial barrier and that 3 years is an appropriate sterility expiration period. The additional shelf life studies referred to in Tables 7 and 8 further support a 3 year shelf life for the Zenith Alignment Stent.

X. SUMMARY OF CLINICAL STUDY

The applicant performed a clinical study in the US under G040063 to help establish a reasonable assurance of safety and effectiveness of the Zenith Fenestrated AAA Endovascular Graft for the endovascular treatment of abdominal aortic or aorto-iliac aneurysms. Data from the pivotal clinical study support the PMA approval decision.

The study was initially approved for 30 patients and use of available balloon-expandable stents in combination with the Fenestrated Graft. Following completion of the initial 30 patient enrollment, the study hypothesis and requirements for approval were agreed upon. The study was then expanded to include the Zenith Alignment Stent and enrollment of 12 additional patients, thus providing 42 total patients, which was the pre-specified study sample size.

A summary of the clinical study is presented below.

A. Clinical Study Design

Patients were treated between January 2005 and August 2010. The database for this PMA supplement reflected data collected through June 2011 and included 42 patients. There were 7 investigational sites.

The study was a prospective, multi-center, two-armed clinical study. One study arm consisted of investigational patients implanted with the Zenith Fenestrated AAA Endovascular Graft and the second arm consisted of historical, case-matched controls treated with the standard Zenith AAA Endovascular Graft (identified from patients treated with the Zenith AAA Endovascular Graft under G990135).

Taking into consideration the Zenith AAA study results, expected attrition, and a goal of achieving at least a minimum of 80% statistical power at a significance level of 5%, a sample size of 42 subjects was considered sufficient using a 10% margin. Propensity score methods with a pre-specified matching algorithm were used to select the control patients from the Zenith AAA endovascular cohorts. The covariates for matching were pre-specified and included the following relevant demographic, comorbid, and anatomic characteristics, all of which were comparable between the two groups: age, gender, height, weight, arrhythmia, cancer, chronic heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, diabetes, hypertension, previous diagnosis of systemic infection, previous myocardial infarction, peripheral vascular disease, previous surgeries at access site, thromboembolic event, maximum aneurysm diameter, minimum aneurysm diameter, and neck diameter.

Patient imaging underwent independent core laboratory analysis. All patient deaths and any associated adverse events were adjudicated by an independent clinical events committee (CEC). The clinical trial was monitored by an independent data safety monitoring board (DSMB) according to an established safety monitoring plan.

1. Inclusion and Exclusion Criteria

Enrollment in clinical study was limited to patients who met the following selection criteria:

- Aortic or aortoiliac aneurysm with diameter ≥5 cm; or
- Aortic or aortoiliac aneurysm with a history of growth ≥0.5 cm per year, or clinical indication for AAA repair

Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

General Exclusion Criteria

- Less than 18 years of age
- Life expectancy less than 2 years
- Pregnant or breastfeeding
- Unwilling to comply with the follow-up schedule
- Inability or refusal to give informed consent

Medical Exclusion Criteria

- Baseline creatinine >2.0 mg/dl
- Cultural objection to receipt of blood or blood products
- Allergy to stainless steel, polyester, solder, gold, or nitinol
- Anaphylactic reaction to contrast that cannot be adequately pre-medicated
- Leaking/ruptured or symptomatic aneurysm
- Uncorrectable coagulopathy
- Previous stent in any renal or visceral artery to be accommodated with a small fenestration

Anatomical Exclusion Criteria

- Significant occlusive disease, tortuosity, or calcification
- Proximal neck <4 mm, or ≥15 mm in length unless otherwise compromised to preclude seal (i.e., unsuitable for a non-fenestrated graft)
- Proximal neck, measured outer wall to outer wall on a sectional image (CT), >31 mm in diameter or <19 mm in diameter
- Proximal neck angulated more than 45 degrees relative to the long axis of the aneurysm
- Immediate suprarenal neck angulated more than 45 degrees relative to the immediate infrarenal neck
- Proximal neck diameter change over the length of the proximal seal zone ≥4 mm
- Proximal seal site with circumferential thrombus/atheroma above the renal arteries
- Iliac artery diameter, measured inner wall to inner wall on a sectional image (CT), <7.5 mm at any point along access length (prior to deployment)
- Ipsilateral iliac artery fixation site diameter, measured inner wall to inner wall on a sectional image (CT), <9.0 mm (prior to deployment)
- Iliac artery diameter, measured outer wall to outer wall on a sectional image (CT), >21 mm at distal fixation site

- Iliac artery distal fixation site <30 mm in length
- Inability to maintain at least one patent hypogastric artery
- Renal artery stenosis >50%
- Non-bifurcated segment of any artery to be stented <15 mm in length
- Artery to be stented with a maximum diameter <3 mm or >8 mm at the vessel ostium
- Unsuitable arterial anatomy

2. Study Follow-up Schedule

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

3. Clinical Endpoints

The primary safety and effectiveness endpoint was based on treatment success, which is defined as technical success (i.e., successful access of the aneurysm site and deployment of the Zenith Fenestrated AAA Endovascular Graft in the intended location, with all vessels targeted by fenestrations patent at the completion of the procedure) plus freedom from the following at 6 months: Type I and Type III endoleak, aneurysm growth >0.5 cm, any AAA-related serious adverse event (death, rupture, conversion), and any AAA-related major complication (Q-wave MI; congestive heart failure; cardiac ischemia requiring intervention; renal failure requiring permanent dialysis; bowel obstruction, ischemia, or fistula; stroke with permanent deficit; paralysis).

The study results for the primary endpoint, 6-month treatment success, were explored in patients treated with the Zenith Fenestrated AAA Endovascular Graft and in matched patients treated with the standard Zenith AAA Endovascular Graft. The study additionally provided for assessment of morbidity, mortality, aneurysm size change, endoleak, migration, device integrity, and secondary interventions.

B. <u>Patient Accountability</u>

Of 42 patients enrolled in the clinical study, 95% (40) were evaluable for the primary endpoint analysis. The 42 patient cohort, combines patient data from the feasibility study (n = 30; implanted device between January 2005 – January 2006) with pivotal study data (n = 12). Table 10 reports the patient accountability for study follow-up as of the database lock.

The data in the follow-up accountability table is site reported and reflects data available for endpoints that are assessed with imaging. As such, denominators for core lab reported analyses and for events that are not imaging dependant in the results tables below may differ from the information in this table.

Table 10. Follow-up compliance

		Percent of Data Available[1]			Adequate Imaging to Assess the Parameter[2]				Events Occurring Before Next Interval				
Follow-up Visit	Patients Eligible for Follow-up[3]	Clinical	X-ray	CT	Size Increase	Endoleak	Migration	Fracture	Death	Conversion	Lost to Follow-up (LTF) or Withdrawal	Refused Consent for 3-5 Year Follow-up[4]	Not Due for Next Visit
Pre-discharge	42 (0)	100.0% (42/42)	95.2% (40/42)	95.2% (40/42)	95.2% (40/42)	92.9% (39/42)	95.2% (40/42)	100.0% (42/42)	0	0	0	0	0
30-day	42 (0)	97.6% (41/42)	88.1% (37/42)	97.6% (41/42)	97.6% (41/42)	92.9% (39/42)	95.2% (40/42)	97.6% (41/42)	1	0	1	0	0
6-month	40 (0)	97.5% (39/40)	95.0% (38/40)	95.0% (38/40)	95.0% (38/40)	87.5% (35/40)	95.0% (38/40)	97.5% (39/40)	0	0	1	0	4
12-month	35 (3)	91.4% (32/35)	82.9% (29/35)	88.6% (31/35)	82.9% (29/35)	80.0% (28/35)	82.9% (29/35)	82.9% (29/35)	1	0	0	0	7
24-month	27 (0)	96.3% (26/27)	85.2% (23/27)	96.3% (26/27)	96.3% (26/27)	81.5% (22/27)	96.3% (26/27)	96.3% (26/27)	1	0	0	6	0
3-year	20 (0)	90.0% (18/20)	70.0% (14/20)	90.0% (18/20)	75.0% (15/20)	70.0% (14/20)	80.0% (16/20)	75.0% (15/20)	0	0	1	0	0
4-year	19 (0)	94.7% (18/19)	73.7% (14/19)	89.5% (17/19)	84.2% (16/19)	63.2% (12/19)	84.2% (16/19)	89.5% (17/19)	0	0	2	0	0
5-year	17 (0)	100.0% (17/17)	70.6% (12/17)	82.4% (14/17)	64.7% (11/17)	52.9% (9/17)	64.7% (11/17)	64.7% (11/17)	0	0	0	0	0

[1]Site submitted data.
[2]Based on core lab analysis – does not include imaging exams received by the core lab for analysis, but that have not yet been analyzed.
[3]Number in parenthesis indicates the number of patients without submitted data who are still eligible for follow-up.
[4]Initial cohort of 30 patients consented only for 2-year follow-up and therefore were asked to reconsent for 3-5 year follow-up.

38

C. Study Population Demographics and Baseline Parameters

Table 11 summarizes the demographics and patient characteristics for the Zenith Fenestrated group.

Table 11. Demographics and patient characteristics

Demographic	Result[1]
Age (years)	75.3 ± 7.4 (58 - 86), 42
Gender	
Male	78.6% (33/42)
Female	21.4% (9/42)
Ethnicity	
White	92.9% (39/42)
Hispanic or Latino	2.4% (1/42)
Black or African American	0.0% (0/42)
American Indian or Alaska Native	2.4% (1/42)
Asian	2.4% (1/42)
Native Hawaiian or other Pacific Islander	0.0% (0/42)
Other	0.0% (0/42)
Height (in)	67.5 ± 4.4 (51 - 74), 41
Weight (lbs)	190.6 ± 46.9 (110 - 342), 42
Body mass index	28.7 ± 4.8 (19.5 - 40.8), 41

[1] Mean values +/- the standard deviation, with the range of values shown in parentheses, followed by the number of patients evaluated

Table 12 presents the medical history of patients in the Zenith Fenestrated group.

Table 12. Pre-existing comorbid medical conditions

Medical History	Percent Patients (number/total number)
Cardiovascular	
Previous myocardial infarction	23.8% (10/42)
Previous diagnosis of symptomatic congestive heart failure	9.5% (4/42)
Previous diagnosis of coronary artery disease	52.4% (22/42)
Previous diagnosis of cardiac arrhythmia	40.5% (17/42)
Vascular	
Thromboembolic event	11.9% (5/42)
Peripheral vascular disease	23.8% (10/42)
Family history of aneurysmal disease	14.3% (6/42)[1]
Hypertension	92.9% (39/42)

Medical History	Percent Patients (number/total number)
Pulmonary	
Chronic obstructive pulmonary disease	33.3% (14/42)
Renal	
Diagnosis of renal failure requiring dialysis	0.0% (0/42)
Renal insufficiency	9.5% (4/42)
GFR ≤ 60 ml/min/1.73 m^2	21.4% (9/42)
Endocrine	
Diabetes	26.2% (11/42)
Infectious disease	
Previous diagnosis of sepsis	7.1% (3/42)
Gastrointestinal	
Gastrointestinal disease	40.5% (17/42)
Hepatobiliary	
Previous diagnosis of liver disease	2.4% (1/42)
Neoplasms	
Previous diagnosis of cancer	35.7% (15/42)
Neurologic	
Previous diagnosis of cerebrovascular disease	16.7% (7/42)
Previous endarterectomy	2.4% (1/42)
Substance use	
Excessive alcohol use	0.0% (0/42)
Tobacco use: currently smokes	28.6% (12/42)
quit smoking	57.1% (24/42)
never smoked	14.3% (6/42)
Access site	
Previous surgery at the intended access site	11.9% (5/42)[2]
Previous radiation at the intended access site	0.0% (0/42)

[1] In 11.9% (5/42) of patients family history of aneurysmal disease was reported as unknown.
[2] In 2.4% (1/42) of patients previous surgery at intended access site was reported as unknown.

Table 13 lists the anatomical characteristics of patients in the Zenith Fenestrated group, as assessed by the core lab.

Table 13. Presenting anatomical dimensions, as assessed by core lab

Measure	Mean ± S.D. (range), N=42
Aortic diameters (mm)	
Diameter at celiac artery	28.2 ± 3.2 (21.2 - 35.9)
Diameter at SMA	28 ± 3.5 (22.3 - 39.8)
Diameter at lowest patent renal artery	25.7 ± 3.2 (19.2 - 33.2)
Diameter at midpoint of renal arteries	25.5 ± 5.1 (0.0 - 32.2)
Maximum aneurysm diameter – long axis	61.1 ± 10.9 (45.2 - 94.2)
Maximum aneurysm diameter – short axis	56.8 ± 10.3 (43.4 - 90.4)
Proximal neck length (mm)	9.7 ± 3.5 (2.4 - 19.1)
Angles (°)	
Angle between immediate suprarenal neck and immediate infrarenal neck	15.9 ± 9.6 (2 - 40)
Angle between the proximal neck and the longitudinal axis of the aneurysm	34 ± 14.2 (7 - 57)
Diameter of renal artery ostia (mm)	
Right renal artery	6.5 ± 1.2 (4.6 - 8.9)
Left renal artery	6.8 ± 1.3 (4.0 - 9.4)

D. Devices Implanted

1.0 Stent-graft Components

Table 14 reports the type of stent-graft components that were deployed during the index procedure. All but one patient received the standard 3-piece system (proximal graft, distal graft, contralateral leg) – one patient received only a proximal graft, which landed in a previous open surgical graft and thus did not require a distal graft or contralateral leg.

Table 14. Stent-graft components deployed

Type	Percent Patients (number/total number)
Proximal graft	100% (42/42)
Distal graft	97.6% (41/42)[1]
Contralateral leg	97.6% (41/42)[1]
Ancillary components	
Main body extension	0.0% (0/42)
Additional iliac leg	7.1% (3/42)
Ipsilateral iliac leg extension	2.4% (1/42)
Contralateral iliac leg extension	7.1% (3/42)
Occluder	0.0% (0/42)
Converter	0.0% (0/42)

[1]One patient that had undergone prior open surgical AAA repair received only the proximal fenestrated component

Table 15 reports the sizes (diameters and lengths) of the proximal grafts used during the initial implant procedure. The full range of available graft diameters and lengths was utilized.

Table 15. Proximal graft sizes used

Diameter (mm)	Length (mm)					Total
	97	107	109	122	124	
24	0	0	0	0	2	2
26	0	0	4	0	0	4
28	1	0	7	0	4	12
30	1	0	6	0	9	16
32	0	0	1	0	2	3
34	0	2	0	2	0	4
36	0	0	0	1	0	1
Total	2	2	18	3	17	42

Table 16 reports the sizes (diameters and lengths) of the distal grafts used during the initial implant procedure. The full range of available graft diameters and lengths was utilized.

Table 16. Distal graft sizes used

Diameter (mm)	Length (mm)							Total
	119	121	136	138	151	153	168	
12	0	2	2	1	0	3	0	8
16	0	2	3	4	2	2	4	17
20	1	0	1	3	1	5	3	14
24	0	0	1	0	1	0	0	2
Total	1	4	7	8	4	10	7	41

Table 17 reports the sizes (diameters and lengths) of the contralateral leg grafts used during the initial implant procedure.

Table 17. Contralateral leg sizes used

Diameter (mm)	Length (mm)						Total
	54	56	71	73	88	90	
12	3	1	2	0	0	0	6
14	1	0	10	0	1	0	12
16	3	0	3	1	0	0	7
18	6	0	3	0	1	0	10
20	0	0	3	0	0	1	4
22	0	0	1	0	0	0	1
24	0	0	1	0	0	0	1
Total	13	1	23	1	2	1	41

The location of the most proximal graft margin relative to the renal arteries, SMA, and celiac artery is provided in Table 18. The proximal margin of the graft was above the renal arteries in all patients.

Table 18. Graft location

Location of proximal graft margin relative to specified vessel		Percent Patients (number/total number)
Renal arteries	Above	100.0% (42/42)
	Below	0.0% (0/42)
SMA	Above	66.7% (28/42)
	Below	33.3% (14/42)
Celiac	Above	0.0% (0/42)
	Below	100.0% (42/42)

The specific graft fenestration/scallop configurations that were utilized to accommodate the vessels intended to remain patent are provided in Table 19. The most commonly used configuration was 2 fenestrations and 1 scallop.

Table 19. Fenestrated configurations used

Configurations	% (n/N)
1 scallop	9.5% (4/42)
1 small fenestration and 1 scallop	11.9% (5/42)
2 small fenestrations	4.8% (2/42)
2 small fenestrations and 1 scallop	69.0% (29/42)
2 small fenestrations and 1 large fenestration	4.8% (2/42)

2.0 Fenestration Stents

Table 20 provides the total number of each stent type used during the initial implant procedure. Eleven (11) patients received a Zenith Alignment Stent.

Table 20. Type and number of fenestration stents used

Stent type/description	(n)
Zenith Alignment Stent (uncovered, balloon-expandable, 316 L stainless steel)	22
Uncovered, balloon-expandable, 316L stainless steel biliary stent	28
Uncovered, balloon-expandable, 316L stainless steel biliary/iliac stent	20
Uncovered, balloon-expandable, 316L stainless steel biliary/renal stent	8
Covered, balloon-expandable, 316L stainless steel tracheobronchial stent	2

Table 21 indicates which vessels were targeted by either a fenestration or scallop and were either stented or unstented. All vessels accommodated by a small fenestration were stented.

Table 21. Fenestration and vessel stenting

Vessel	Small fenestration		Large fenestration		Scallop		Total
	Stented	Unstented	Stented	Unstented	Stented	Unstented	
Celiac	0	0	0	0	0	0	0
SMA	0	0	0	2	0	29	31
Right renal	35	0	0	0	3	0	38
Left renal	36	0	0	0	4	2	42
Accessory	0	0	0	0	0	0	0
Total	71	0	0	2	7	31	111

E. Safety and Effectiveness Results

The analysis of safety and effectiveness was based on the cohort of 42 patients/procedures, etc available for 6 month evaluations. The primary safety and effectiveness endpoints are based on treatment success, plus freedom from the following at 6 months: Type I and Type III endoleak, aneurysm growth >0.5 cm, any AAA-related serious adverse event (death, rupture, conversion), and any AAA-related major complication (Q-wave MI; congestive heart failure; cardiac

Comment [dxh1]: Incorporated template language-

ischemia requiring intervention; renal failure requiring permanent dialysis; bowel obstruction, ischemia, or fistula; stroke with permanent deficit; paralysis).

The study results for the primary endpoint, 6-month treatment success, were explored in patients treated with the Zenith Fenestrated AAA Endovascular Graft and in matched patients treated with the standard Zenith AAA Endovascular Graft. The study additionally provided for assessment of morbidity, mortality, aneurysm size change, endoleak, migration, device integrity, and secondary interventions.

The key safety and effectiveness outcomes for this study are presented below in tables 22-33.

1.0 Technical Success

Technical success is defined as successful access of the aneurysm site and deployment of the Zenith Fenestrated AAA Endovascular Graft in the intended location, with all vessels targeted by fenestrations patent at the completion of the procedure. Table 22 reports the technical success results for the Zenith Fenestrated AAA Endovascular Graft.

Table 22. Technical success

Measure	Percent (n/N)
Technical success	100.0% (42/42)

2.0 6-month Treatment Success (Primary Endpoint)

Treatment success is defined as technical success plus freedom from the following at 6 months: Type I and Type III endoleak, aneurysm growth >0.5 cm, any AAA-related serious adverse event (death, rupture, conversion), and any AAA-related major complication (Q-wave MI; congestive heart failure; cardiac ischemia requiring intervention; renal failure requiring permanent dialysis; bowel obstruction, ischemia, or fistula; stroke with permanent deficit; paralysis). Of 42 patients enrolled in the clinical study, 40 were evaluable for the primary endpoint analysis (two patients were lost to follow-up). Table 23 reports the 6-month treatment success for the Zenith Fenestrated AAA Endovascular Graft, as compared to the matched patients treated with the standard Zenith AAA Endovascular Graft. Propensity score methods with a pre-specified one-to-one global matching algorithm were used to select patients from the Zenith AAA Endovascular Graft multicenter study. The 6-month treatment success was 97.5%

in the Fenestrated endovascular treatment group compared to 95% in the matched Zenith AAA cohort.

Table 23. Results for 6-month treatment success

Measure	Zenith Fenestrated	Zenith AAA
Treatment success	97.5% (39/40)[1]	95.0% (38/40)[2]

[1]Failure due to bowel ischemia
[2]Failure due to congestive heart failure in one and congestive heart failure as well as cardiac ischemia requiring intervention in another

3.0 Adverse Events

3.1 Major Adverse Events

Table 24 reports the Kaplan-Meier survival estimates for freedom from major adverse events (MAE) within 30 days (death, Q-wave MI, bowel ischemia, paralysis, stroke, reintubation, renal failure requiring dialysis). One Zenith Fenestrated patient experienced a major adverse event within 30 days (bowel ischemia, which resolved with antibiotics and IV fluids). There were no MAEs in the Zenith AAA group within 30 days.

Table 24. Results from Kaplan-Meier analysis for freedom from 30-day MAE

Event	Parameter	Zenith Fenestrated
Any MAE	Number at risk	41
	Cumulative events	1
	Cumulative censored	0
	Kaplan-Meier estimate	0.976
	Standard error	0.024
Death	Number at risk	42
	Cumulative events	0
	Cumulative censored	0
	Kaplan-Meier estimate	1.000
	Standard error	0.000
Q-wave MI	Number at risk	42
	Cumulative events	0
	Cumulative censored	0
	Kaplan-Meier estimate	1.000
	Standard error	0.000
Bowel ischemia	Number at risk	41
	Cumulative events	1
	Cumulative censored	0
	Kaplan-Meier estimate	0.976
	Standard error	0.024
Paralysis	Number at risk	42

Event	Parameter	Zenith Fenestrated
	Cumulative events	0
	Cumulative censored	0
	Kaplan-Meier estimate	1.000
	Standard error	0.000
Stroke	Number at risk	42
	Cumulative events	0
	Cumulative censored	0
	Kaplan-Meier estimate	1.000
	Standard error	0.000
Re-intubation	Number at risk	42
	Cumulative events	0
	Cumulative censored	0
	Kaplan-Meier estimate	1.000
	Standard error	0.000
Renal failure requiring dialysis	Number at risk	42
	Cumulative events	0
	Cumulative censored	0
	Kaplan-Meier estimate	1.000
	Standard error	0.000.

3.2 Serious Adverse Events

Table 25 provides the Kaplan-Meier estimates for freedom from death (all-cause and AAA-related , which was defined as any death occurring within 30 days of the initial implant procedure or secondary intervention, or any death determined by an independent clinical events committee (CEC) to be related to the AAA repair), rupture, and conversion. The cause of death was unknown in one patient from the Zenith Fenestrated group, which the CEC was therefore unable to adjudicate – this was the only patient death counted as AAA-related in the Zenith Fenestrated group. No aneurysm ruptures or conversions to open repair where reported in the Zenith Fenestrated group.

Table 25. Results from Kaplan-Meier analysis for serious adverse events

Event	Group	Parameter	30 Days	365 Days	730 Days	1095 Days	1460 Days	1825 Days
All-cause mortality	Zenith Fenestrated	Number at risk	42	36	27	20	19	14
		Cumulative events	0	1	2	4	4	4
		Cumulative censored	0	5	13	18	19	24
		Kaplan-Meier estimate	1.000	0.976	0.943	0.861	0.861	0.861
		Standard error	0.000	0.024	0.040	0.066	0.066	0.066
	Zenith AAA	Number at risk	33	32	30	30	28	17
		Cumulative events	0	0	2	2	2	2
		Cumulative censored	0	1	1	1	3	14
		Kaplan-Meier estimate	1.000	1.000	0.938	0.938	0.938	0.938
		Standard error	0.000	0.000	0.043	0.043	0.043	0.043

Event	Group	Parameter	30 Days	365 Days	730 Days	1095 Days	1460 Days	1825 Days
AAA-related mortality	Zenith Fenestrated	Number at risk	42	36	27	20	19	14
		Cumulative events	0	0	0	1[1]	1	1
		Cumulative censored	0	6	15	21	22	27
		Kaplan-Meier estimate	1.000	1.000	1.000	0.955	0.955	0.955
		Standard error	0.000	0.000	0.000	0.044	0.044	0.044
	Zenith AAA	Number at risk	33	32	30	30	28	17
		Cumulative events	0	0	0	0	0	0
		Cumulative censored	0	1	3	3	5	16
		Kaplan-Meier estimate	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
Rupture	Zenith Fenestrated	Number at risk	42	37	28	21	21	18
		Cumulative events	0	0	0	0	0	0
		Cumulative censored	0	5	14	21	21	24
		Kaplan-Meier estimate	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
	Zenith AAA	Number at risk	33	32	30	30	28	17
		Cumulative events	0	1	1	1	1	1
		Cumulative censored	0	0	2	2	4	15
		Kaplan-Meier estimate	1.000	0.970	0.970	0.970	0.970	0.970
		Standard error	0.000	0.030	0.030	0.030	0.030	0.030
Conversion	Zenith Fenestrated	Number at risk	42	37	28	21	21	18
		Cumulative events	0	0	0	0	0	0
		Cumulative censored	0	5	14	21	21	24
		Kaplan-Meier estimate	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
	Zenith AAA	Number at risk	33	32	30	30	28	17
		Cumulative events	0	1	1	1	1	1
		Cumulative censored	0	0	2	2	4	15
		Kaplan-Meier estimate	1.000	0.970	0.970	0.970	0.970	0.970
		Standard error	0.000	0.030	0.030	0.030	0.030	0.030

[1] 1 case of death that the CEC was unable to adjudicate, which was conservatively counted as AAA-related for the purpose of analysis.

3.3 Pre-specified Adverse Events by Organ System

Table 26 reports the Kaplan-Meier survival estimates for freedom from pre-specified cardiovascular, pulmonary, renal, GI, wound, neurologic, and vascular events reported by the investigative sites. The procedure-related incidence (i.e., within 30 days) of cardiovascular, pulmonary, gastrointestinal, wound, and neurologic events appeared comparable between Zenith Fenestrated and Zenith AAA, and the occurrence of events in these categories beyond 30 days was not surprising given the pre-existing comorbid conditions of the patient populations. The percent of patients experiencing renal events or vascular events within 30 days trended higher for Zenith Fenestrated compared to Zenith AAA patients, the details of which are discussed further in Sections 3.4 and 3.5, respectively.

Table 26. Kaplan-Meier estimates (freedom from morbidity, by category)

Category	Group	Parameter	30 Days	365 Days	730 Days	1095 Days	1460 Days	1825 Days
Cardiovascular[1]	Zenith Fenestrated	Number at risk	40	30	21	15	15	10
		Cumulative events	2	6	7	8	8	10
		Cumulative censored	0	6	14	19	19	22
		Kaplan-Meier estimate	0.952	0.854	0.817	0.766	0.766	0.656
		Standard error	0.033	0.055	0.064	0.078	0.078	0.098
	Zenith AAA	Number at risk	29	27	24	24	23	14
		Cumulative events	4	5	6	6	6	6
		Cumulative censored	0	1	3	3	4	13
		Kaplan-Meier estimate	0.879	0.848	0.817	0.817	0.817	0.817
		Standard error	0.057	0.062	0.068	0.068	0.068	0.068
Pulmonary[2]	Zenith Fenestrated	Number at risk	41	32	24	18	17	12
		Cumulative events	1	4	4	5	5	6
		Cumulative censored	0	6	14	19	20	24
		Kaplan-Meier estimate	0.976	0.903	0.903	0.855	0.855	0.798
		Standard error	0.024	0.046	0.046	0.064	0.064	0.081
	Zenith AAA	Number at risk	33	32	29	29	28	17
		Cumulative events	0	0	1	1	1	1
		Cumulative censored	0	1	3	3	4	15
		Kaplan-Meier estimate	1.000	1.000	0.969	0.969	0.969	0.969
		Standard error	0.000	0.000	0.031	0.031	0.031	0.031
Renal[3]	Zenith Fenestrated	Number at risk	37	30	21	15	14	10
		Cumulative events	5	6	8	9	10	10
		Cumulative censored	0	6	13	18	18	22
		Kaplan-Meier estimate	0.881	0.856	0.791	0.742	0.692	0.692
		Standard error	0.050	0.054	0.067	0.079	0.088	0.088
	Zenith AAA	Number at risk	33	31	29	29	27	16
		Cumulative events	0	1	1	1	1	1
		Cumulative censored	0	1	3	3	5	16
		Kaplan-Meier estimate	1.000	0.970	0.970	0.970	0.970	0.970
		Standard error	0.000	0.030	0.030	0.030	0.030	0.030
GI[4]	Zenith Fenestrated	Number at risk	40	33	25	20	19	14
		Cumulative events	2	2	2	2	2	2
		Cumulative censored	0	7	15	20	21	26
		Kaplan-Meier estimate	0.952	0.952	0.952	0.952	0.952	0.952
		Standard error	0.033	0.033	0.033	0.033	0.033	0.033
	Zenith AAA	Number at risk	33	32	30	30	28	17
		Cumulative events	0	0	0	0	0	0
		Cumulative censored	0	1	3	3	5	16
		Kaplan-Meier estimate	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
Wound[5]	Zenith Fenestrated	Number at risk	41	32	24	19	18	13
		Cumulative events	1	3	3	3	3	3
		Cumulative censored	0	7	15	20	21	26
		Kaplan-Meier estimate	0.976	0.927	0.927	0.927	0.927	0.927
		Standard error	0.024	0.041	0.041	0.041	0.041	0.041
	Zenith AAA	Number at risk	32	31	29	29	26	15
		Cumulative events	1	1	1	1	2	2
		Cumulative censored	0	1	3	3	5	16
		Kaplan-Meier estimate	0.970	0.970	0.970	0.970	0.936	0.936
		Standard error	0.030	0.030	0.030	0.030	0.044	0.044

Category	Group	Parameter	30 Days	365 Days	730 Days	1095 Days	1460 Days	1825 Days
Neurologic[6]	Zenith Fenestrated	Number at risk	42	35	26	19	18	13
		Cumulative events	0	0	0	1	1	1
		Cumulative censored	0	7	16	22	23	28
		Kaplan-Meier estimate	1.000	1.000	1.000	0.950	0.950	0.950
		Standard error	0.000	0.000	0.000	0.049	0.049	0.049
	Zenith AAA	Number at risk	33	32	28	28	26	15
		Cumulative events	0	0	2	2	2	2
		Cumulative censored	0	1	3	3	5	16
		Kaplan-Meier estimate	1.000	1.000	0.934	0.934	0.934	0.934
		Standard error	0.000	0.000	0.045	0.045	0.045	0.045
Vascular[7]	Zenith Fenestrated	Number at risk	34	28	20	17	16	10
		Cumulative events	8	8	8	8	8	9
		Cumulative censored	0	6	14	17	18	23
		Kaplan-Meier estimate	0.810	0.810	0.810	0.810	0.810	0.759
		Standard error	0.061	0.061	0.061	0.061	0.061	0.075
	Zenith AAA	Number at risk	30	28	26	26	23	13
		Cumulative events	3	4	4	4	5	5
		Cumulative censored	0	1	3	3	5	15
		Kaplan-Meier estimate	0.909	0.879	0.879	0.879	0.845	0.845
		Standard error	0.050	0.057	0.057	0.057	0.064	0.064

[1]Cardiovascular pre-specified events: cardiac ischemia requiring intervention, inotropic support, Q-wave MI, non-Q-wave MI, congestive heart failure (CHF), arrhythmia requiring intervention or new treatment, and medically intractable hypertension.
[2]Pulmonary pre-specified events: pneumonia requiring antibiotics, supplemental oxygen at discharge, ventilation (>24 hours and >72 hours), and re-intubation.
[3]Renal pre-specified events: renal failure requiring dialysis, renal insufficiency, renal infarct, and occlusion of fenestrated renal vessel.
[4]GI pre-specified events: bowel obstruction, bowel ischemia/mesenteric ischemia, paralytic ileus >4 days, and aorto-enteric fistula.
[5]Wound pre-specified events: incisional hernia, wound infection requiring antibiotic treatment, wound complication requiring return to the operating room (OR), seroma requiring treatment, lymph fistula, and wound breakdown requiring debridement.
[6]Neurologic pre-specified events: transient ischemic attack (TIA)/reversible ischemic neurological deficit (RIND), stroke, spinal cord ischemia/paralysis.
[7]Vascular pre-specified events: embolization resulting in tissue loss or requiring intervention; limb thrombosis, aneurysm leak/rupture, pseudoaneurysm, increase in aneurysm size by >0.5 cm, vascular injury, and post-procedure transfusion.

3.4 Renal Adverse Events

Given the involvement of the renal arteries in the repair with a fenestrated graft, there is an expected higher risk for renal adverse events as compared to use of a standard, non-fenestrated endograft. Renal morbidity was therefore closely monitored during the study by evaluating several pre-specified events (renal infarct, renal insufficiency, renal failure requiring dialysis, occlusion of a fenestrated renal vessel). Table 27 reports the Kaplan-Meier estimates for freedom from these pre-specified renal morbid events. Also included in Table 27 is the Kaplan-Meier estimate for freedom from stenosis/compression events that

required reintervention, as also counted (as device/renal stenosis) in Table 33 (Reasons for Secondary Intervention).

There were five incidental findings of renal infarct on imaging (without an associated clinical event). Each occurred in a patient from the Zenith Fenestrated group that had some degree of calcification/thrombus in the sealing zone (one also with a history of infarct and coverage of an accessory renal artery at the time of the procedure).

Renal insufficiency was observed in Zenith Fenestrated (n=3) as well as Zenith AAA (n=1) patients. One of the Zenith Fenestrated patients with renal insufficiency was also the only patient in either group to require dialysis, which the CEC judged to be unrelated to AAA repair due to underlying renal dysfunction. Renal insufficiency in one of the other patients from the Zenith Fenestrated group was also judged unrelated to AAA repair by the CEC due to underlying renal dysfunction.

There were two reports of renal occlusion in the Zenith Fenestrated group, neither of which was associated with graft migration. One required reintervention and occurred in a patient with suboptimal placement of the renal stent in the middle/upper portion of the fenestration.

There were seven patients with stenosis/compression events requiring secondary intervention (one associated with migration), four of which had a peak systolic velocity <280 cm/s prior to reintervention.

Table 27. Kaplan-Meier estimates for freedom from pre-specified renal events occurring in either Zenith Fenestrated or Zenith AAA (regardless of whether determined by the clinical events committee to be related or unrelated to AAA repair) and also stenosis/compression events requiring reintervention in Zenith Fenestrated

Category	Group	Parameter	30 Days	365 Days	730 Days	1095 Days	1460 Days	1825 Days
Renal infarct*	Zenith Fenestrated	Number at risk	37	31	24	19	18	14
		Cumulative events	5[1,2,3,4,5]	5	5	5	5	5
		Cumulative censored	0	6	13	18	19	23
		Kaplan-Meier estimate	0.881	0.881	0.881	0.881	0.881	0.881
		Standard error	0.050	0.050	0.050	0.050	0.050	0.050
	Zenith AAA	Number at risk	33	32	30	30	28	17
		Cumulative events	0	0	0	0	0	0
		Cumulative censored	0	1	3	3	5	16
		Kaplan-Meier estimate	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
Renal	Zenith	Number at risk	42	35	25	18	16	11

insufficiency** (on two or more follow-up tests)	Fenestrated	Cumulative events	0	0	1[6]	2[7]	3[8]	3
		Cumulative censored	0	7	16	22	23	28
		Kaplan-Meier estimate	1.000	1.000	0.963	0.912	0.862	0.862
		Standard error	0.000	0.000	0.036	0.060	0.075	0.075
	Zenith AAA	Number at risk	33	31	29	29	27	16
		Cumulative events	0	1	1	1	1	1
		Cumulative censored	0	1	3	3	5	16
		Kaplan-Meier estimate	1.000	0.970	0.970	0.970	0.970	0.970
		Standard error	0.000	0.030	0.030	0.030	0.030	0.030
Dialysis***	Zenith Fenestrated	Number at risk	42	35	26	20	18	13
		Cumulative events	0	0	0	0	1[8]	1
		Cumulative censored	0	7	16	22	23	28
		Kaplan-Meier estimate	1.000	1.000	1.000	1.000	0.947	0.947
		Standard error	0.000	0.000	0.000	0.000	0.051	0.051
	Zenith AAA	Number at risk	33	32	30	30	28	17
		Cumulative events	0	0	0	0	0	0
		Cumulative censored	0	1	3	3	5	16
		Kaplan-Meier estimate	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
Renal occlusion	Zenith Fenestrated	Number at risk	42	34	24	18	18	13
		Cumulative events	0	1[9]	2[10]	2	2	2
		Cumulative censored	0	7	16	22	22	27
		Kaplan-Meier estimate	1.000	0.975	0.945	0.945	0.945	0.945
		Standard error	0.000	0.025	0.038	0.038	0.038	0.038
	Zenith AAA	Number at risk	33	32	30	30	28	17
		Cumulative events	0	0	0	0	0	0
		Cumulative censored	0	1	3	3	5	16
		Kaplan-Meier estimate	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
Stenosis/ compression requiring reintervention	Zenith Fenestrated	Number at risk	41	33	24	18	16	11
		Cumulative events	1[11]	3[12,13]	4[14]	5[15]	6[2]	7[16]
		Cumulative censored	0	6	14	19	20	24
		Kaplan-Meier estimate	0.976	0.927	0.897	0.850	0.800	0.747
		Standard error	0.024	0.040	0.049	0.065	0.078	0.089

*As reported by sites, regardless of whether confirmed by core lab.
**Creatinine rise >2 mg/dl and >30% from baseline.
***Although dialysis in patients with a normal pre-operative renal function was pre-specified, the analysis was performed with consideration to dialysis in any patient.
[1](0111011) Incidental finding on imaging without an associated clinical event at the time of reporting; patient noted to have (mild) thrombus and calcification in the seal zone on pre-procedure imaging.
[2](0511009) Incidental finding on imaging without an associated clinical event at the time of reporting; patient noted to have (mild) thrombus and calcification in the seal zone on pre-procedure imaging; patient also with bilateral renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent) treated with bilateral angioplasty and stenting. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.
[3](0511010) Incidental finding on imaging without an associated clinical event at the time of reporting; patient noted to have (moderate) thrombus and (mild) calcification in the seal zone on pre-procedure imaging; patient also with hydronephrosis on POD# 237.
[4](1111002) Incidental finding on imaging without an associated clinical event at the time of reporting; patient noted to have (moderate) calcification in the seal zone as well as renal infarct on pre-procedure imaging, and also underwent intentional coverage of an accessory renal artery at the time of aneurysm repair.
[5](1111007) Incidental finding on imaging without an associated clinical event at the time of reporting; patient noted to have (mild) calcification in the seal zone on pre-procedure imaging;

52

patient also with renal insufficiency (creatinine rise >2 mg/dl and >30% from baseline) on a single follow-up (at POD# 424).
[6](0211010) Patient with a decrease in GFR >30% at the 24-month follow-up, but not on subsequent follow-up at 36 months. The patient underwent secondary intervention to treat a Type II endoleak (on POD# 239) and hospitalization for congestive heart failure treated with Lasix (on POD# 314), but there were no reports of renal artery stenosis or occlusion at any time point.
[7](0111006) Patient also with renal calculi noted on POD# 214; all events (renal calculi, renal insufficiency, and dialysis) were determined un-related to AAA repair by the CEC.
[8](0421001) Patient also with stenosis of an unstented renal artery proximal to the graft margin, which underwent stenting on POD# 1221; all events (renal insufficiency and stenosis) were determined un-related to AAA repair by the CEC.
[9](0211008) No evidence of graft migration, but with compression of the fenestration stent (uncovered, balloon-expandable 316L stainless steel biliary/renal stent), due likely to suboptimal deployment of the renal stent into the middle/upper portion of the fenestration; patient underwent secondary intervention (ilio-renal bypass).
[10](0611003) No evidence of graft migration or fenestration stent compression (uncovered, balloon-expandable 316L stainless steel biliary/iliac stent), suggesting occlusion likely resulted from the development and progression of thrombus or intimal hyperplasia within the stented vessel; patient did not undergo secondary intervention; patient also with site-reported atrophy of kidney (on POD# 177).
[11] (0211011) Angiography revealed that the right renal artery was severely stenosed. Attempted cannulation was unsuccessful, as the fenestration stent (Zenith® Alignment Stent) was not flared at the time of the initial implant procedure. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.
[12] (0111008) Right renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent) was treated by angioplasty and additional stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.
[13] (0111014) Bilateral renal artery stenoses (uncovered, balloon-expandable 316L stainless steel biliary stent) were treated by angioplasty and additional stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.
[14] (0211007) Right renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary/renal stent) was treated by angioplasty and additional stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.
[15] (0511006) Right renal artery stent compression and subsequent stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent) treated by angioplasty and stent placement. Compression of fenestration stent associated with graft migration (approximately 12 mm by 24 months) due likely to longitudinal progression of disease with further aortic neck dilatation.
[16] (0511003) Left renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent) from slight compression of fenestration stent (with no measurable graft movement > 5 mm) treated by angioplasty and stent placement.

3.5 Vascular Adverse Events

Table 28 provides the Kaplan-Meier estimates for freedom from pre-specified vascular events occurring in either the Zenith Fenestrated or Zenith AAA groups.

While the overall occurrence of vascular events trended higher in Zenith Fenestrated compared to Zenith AAA, this was due to a higher incidence of post-procedure transfusion in the Zenith Fenestrated group. A likely reason for the greater number of patients requiring a post-procedure transfusion in Zenith Fenestrated compared to Zenith AAA is the expected longer procedure times for Zenith Fenestrated (252.2 ± 75.5 minutes for Zenith Fenestrated vs. 160.6 ± 60.6 minutes for Zenith AAA) and correspondingly greater amount of procedural blood loss (537.4 ± 498.5 cc for Zenith Fenestrated vs. 281.2 ± 192.4 cc for Zenith AAA).

Table 28. Kaplan-Meier estimates for freedom from pre-specified vascular events occurring in either Zenith Fenestrated or Zenith AAA

Event	Group	Parameter	30 Days	365 Days	730 Days	1095 Days	1460 Days	1825 Days
Embolization resulting in tissue loss or requiring intervention	Zenith Fenestrated	Number at risk	41	34	25	19	18	13
		Cumulative events	1	1	1	1	1	1
		Cumulative censored	0	7	16	22	23	28
		Kaplan-Meier estimate	0.976	0.976	0.976	0.976	0.976	0.976
		Standard error	0.024	0.024	0.024	0.024	0.024	0.024
	Zenith AAA	Number at risk	33	32	30	30	28	17
		Cumulative events	0	0	0	0	0	0
		Cumulative censored	0	1	3	3	5	16
		Kaplan-Meier estimate	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
Limb thrombosis	Zenith Fenestrated	Number at risk	42	35	26	20	19	14
		Cumulative events	0	0	0	0	0	0
		Cumulative censored	0	7	16	22	23	28
		Kaplan-Meier estimate	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
	Zenith AAA	Number at risk	33	31	29	29	27	16
		Cumulative events	0	1	1	1	1	1
		Cumulative censored	0	1	3	3	5	16
		Kaplan-Meier estimate	1.000	0.970	0.970	0.970	0.970	0.970
		Standard error	0.000	0.030	0.030	0.030	0.030	0.030
Post-procedure transfusion	Zenith Fenestrated	Number at risk	34	28	20	17	16	10
		Cumulative events	8	8	8	8	8	9
		Cumulative censored	0	6	14	17	18	23
		Kaplan-Meier estimate	0.810	0.810	0.810	0.810	0.810	0.759
		Standard error	0.061	0.061	0.061	0.061	0.061	0.075
	Zenith AAA	Number at risk	30	29	27	27	24	14
		Cumulative events	3	3	3	3	4	4
		Cumulative censored	0	1	3	3	5	15
		Kaplan-Meier estimate	0.909	0.909	0.909	0.909	0.875	0.875
		Standard error	0.050	0.050	0.050	0.050	0.058	0.058

4.0 Device Performance

The following tables provide information regarding performance of the Zenith Fenestrated AAA Endovascular Graft in terms of aneurysm size change, endoleak, migration, integrity, and need for reintervention.

Table 29 reports the percent of patients with an increase (> 5 mm), decrease (> 5 mm), or no change (≤ 5 mm) in aneurysm size at each follow-up time point, as compared to pre-discharge based on the results from core lab analysis. There were two cases of aneurysm expansion, both of which occurred in patients with a persistent Type II endoleak.

Table 29. Change in aneurysm size based on results from core lab analysis[1]

Item	1-month	6-month	12-month	24-month	36-month	48-month	60-month
Increase (>5mm)	0.0% (0/39)	0.0% (0/38)	0.0% (0/29)	0.0% (0/26)	6.7% (1/15)[2]	6.3% (1/16)[3]	0.0% (0/11)
Decrease (>5mm)	2.6% (1/39)	50.0% (19/38)	69.0% (20/29)	69.2% (18/26)	73.3% (11/15)	75.0% (12/16)	72.7% (8/11)
No change (≤5mm)	97.4% (38/39)	50.0% (19/38)	31.0% (9/29)	30.8% (8/26)	20.0% (3/15)	18.8% (3/16)	27.3% (3/11)

[1] Core lab analysis, so the denominators are not consistent with the information provided in Table 10 that reports site submitted data.
[2] Patient 0511004 had a persistent Type II endoleak requiring secondary intervention at 1393 days post-procedure.
[3] Patient 0211010 had a persistent Type II endoleak requiring secondary intervention at 239 days post-procedure, but the Type II endoleak was still evident on the 48-month exam.

Table 30 reports endoleaks by type, as assessed by the core lab at each exam period. Except for two endoleaks of unknown type, all other reported endoleaks were Type II.

Table 30. Endoleak based on results from core lab analysis

Type	Pre-discharge	1-month	6-month	12-month	24-month	36-month	48-month	60-month
Any (new only)	32.5% (13/40)	2.4% (1/41)	5.3% (2/38)	0.0% (0/29)	0.0% (0/26)	0.0% (0/16)	0.0% (0/16)	0.0% (0/11)
Any (new and persistent)	32.5% (13/40)	22.0% (9/41)	23.7% (9/38)	27.6% (8/29)	15.4% (4/26)	12.5% (2/16)	12.5% (2/16)	0.0% (0/11)
Multiple	0.0% (0/40)	0.0% (0/41)	0.0% (0/38)	0.0% (0/29)	0.0% (0/26)	0.0% (0/16)	0.0% (0/16)	0.0% (0/11)
Proximal Type I	0.0% (0/40)	0.0% (0/41)	0.0% (0/38)	0.0% (0/29)	0.0% (0/26)	0.0% (0/16)	0.0% (0/16)	0.0% (0/11)
Distal Type I	0.0% (0/40)	0.0% (0/41)	0.0% (0/38)	0.0% (0/29)	0.0% (0/26)	0.0% (0/16)	0.0% (0/16)	0.0% (0/11)
Type II	30.0% (12/40)	22.0% (9/41)	21.1% (8/38)	27.6% (8/29)	15.4% (4/26)	12.5% (2/16)	12.5% (2/16)	0.0% (0/11)
Type III	0.0% (0/40)	0.0% (0/41)	0.0% (0/38)	0.0% (0/29)	0.0% (0/26)	0.0% (0/16)	0.0% (0/16)	0.0% (0/11)
Type IV	0.0% (0/40)	0.0% (0/41)	0.0% (0/38)	0.0% (0/29)	0.0% (0/26)	0.0% (0/16)	0.0% (0/16)	0.0% (0/11)
Unknown	2.5% (1/40)	0.0% (0/41)	2.6% (1/38)	0.0% (0/29)	0.0% (0/26)	0.0% (0/16)	0.0% (0/16)	0.0% (0/11)

Table 31 reports the percent of patients with CEC-confirmed radiographic migration (≥10 mm) or clinically significant migration (measurable movement of the stent-graft >5 mm and that developed a type I endoleak or renal stenosis/occlusion with demonstrable deformation of the mating renal stent by core lab) at each follow-up time point (date of first occurrence). There were two reports of migration, one of which required secondary intervention (due to associated renal stenosis). Neither case was associated with aneurysm growth or endoleak. Both cases of migration occurred in patients with evidence of disease progression at follow-up (without aneurysm pressurization).

Table 31. CEC-confirmed migration (date of first occurrence)

Item	1-month	6-month	12-month	24-month	36-month	48-month	60-month
Radiographic migration	0.0% (0/40)	0.0% (0/38)	0.0% (0/30)	3.6%[1] (1/28)	0.0% (0/16)	0.0% (0/16)	9.1%[2] (1/11)
Clinically significant migration	0.0% (0/40)	0.0% (0/38)	0.0% (0/30)	3.6%[1] (1/28)	0.0% (0/16)	0.0% (0/16)	0.0% (0/11)

[1] Patient 0511006 with renal stenosis from associated stent compression (uncovered, balloon-expandable 316L stainless steel biliary stent) requiring secondary intervention. Longitudinal

progression of disease with further aortic neck dilatation likely resulted in migration. There was no endoleak or increase in aneurysm size in this patient. The total amount of graft movement detected at the time of the clinically significant migration was approximately 12 mm (relative to the celiac).
[2]Patient 0511008 was without any associated renal stenosis requiring reintervention and additionally did not have any endoleak or increase in aneurysm size. Longitudinal progression of disease with further aortic neck dilatation likely resulted in migration. The total amount of graft movement was approximately 10 mm (relative to the celiac), which retrospectively occurred over 60 months. No interventions have been performed on this patient.

Device integrity observations are summarized in Table 32. Losses in device integrity included three patients with barb separation, one patient with possible fenestration stent fracture, and one patient with seal stent and fenestration stent fracture (who also had evidence of disease progression during follow-up in the absence of aneurysm pressurization). None of the integrity findings were associated with adverse clinical sequelae or the need for reintervention.

Although not associated with a device integrity loss (i.e., fracture), other observations included 4 cases with fenestration stent deformation/compression (1 also with migration, 3 without migration), 2 of which underwent reintervention to treat stenosis.

Table 32. Device integrity findings by core lab (time of first occurrence)

Finding	Pre-discharge	1-month	6-month	12-month	24-month	36-month	48-month	60-month
Stent-graft								
Barb separation	0.0% (0/42)	0.0% (0/41)	2.6% (1/39)[1]	3.4% (1/29)[2]	3.8% (1/26)[3]	0.0% (0/16)	0.0% (0/17)	0.0% (0/11)
Stent fracture (single)	0.0% (0/42)	0.0% (0/41)	0.0% (0/39)	3.4% (1/29)[4]	0.0% (0/26)	0.0% (0/16)	0.0% (0/17)	0.0% (0/11)
Stent fracture (multiple)	0.0% (0/42)	0.0% (0/41)	0.0% (0/39)	0.0% (0/29)	0.0% (0/26)	0.0% (0/16)	0.0% (0/17)	0.0% (0/11)
Component separation	0.0% (0/42)	0.0% (0/41)	0.0% (0/39)	0.0% (0/29)	0.0% (0/26)	0.0% (0/16)	0.0% (0/17)	0.0% (0/11)
Limb separation	0.0% (0/42)	0.0% (0/41)	0.0% (0/39)	0.0% (0/29)	0.0% (0/26)	0.0% (0/16)	0.0% (0/17)	0.0% (0/11)
Stent-to-graft separation	0.0% (0/42)	0.0% (0/41)	0.0% (0/39)	0.0% (0/29)	0.0% (0/26)	0.0% (0/16)	0.0% (0/17)	0.0% (0/11)
Other	0.0% (0/42)	0.0% (0/41)	0.0% (0/39)	0.0% (0/29)	0.0% (0/26)	0.0% (0/16)	0.0% (0/17)	0.0% (0/11)
Fenestration stent								

Fracture	0.0% (0/42)	0.0% (0/41)	2.6% (1/39)[5]	3.4% (1/29)[4]	0.0% (0/26)	0.0% (0/16)	0.0% (0/17)	0.0% (0/11)
Separation	0.0% (0/42)	0.0% (0/41)	0.0% (0/39)	0.0% (0/29)	0.0% (0/26)	0.0% (0/16)	0.0% (0/17)	0.0% (0/11)
Other	0.0% (0/42)	0.0% (0/41)	7.7% (3/39)[6,7,8]	3.4% (1/29)[9]	0.0% (0/26)	0.0% (0/16)	0.0% (0/17)	0.0% (0/11)

[1] Patient 0421003: Separation of a single fixation barb. No clinical sequelae related to the barb separation have been reported.
[2] Patient 0111009: Separation of a single fixation barb. No clinical sequelae related to the barb separation have been reported.
[3] Patient 0511008: Separation of two barbs. No clinical sequelae related to the barb separation have been reported, although radiographic migration (approximately 10 mm over 5 years) was observed and was due likely to longitudinal progression of disease with further aortic neck dilatation.
[4] Patient 0411001: Fracture of sealing stent (at the distal edge of the scallop fenestration) and left renal fenestration stent (uncovered, balloon-expandable 316L stainless steel biliary/iliac stent), but in a patient with progressive aneurismal disease within and proximal to the treated segment, which likely resulted in uncharacteristic tension/loading of the stents. No subsequent renal events, endoleak, or secondary interventions reported in this patient.
[5] Patient 0511010: Fracture of left renal fenestration stent (Zenith® Alignment Stent) not readily confirmed based on subsequent bench top CT imaging studies that showed the same appearance of fracture, but in an entirely intact stent.
[6] Patient 1111011: Deformation of fenenstration stent (Zenith® Alignment Stent) with no measurable graft movement > 5 mm and not requiring secondary intervention.
[7] Patient 0511003: Slight compression of fenestration stent (uncovered, balloon-expandable 316L stainless steel biliary stent) with no measurable graft movement > 5 mm. Angioplasty and stent placement was performed 1539 days post-procedure to treat stenosis.
[8] Patient 0511007: Slight compression of fenestration stent (uncovered, balloon-expandable 316L stainless steel biliary stent) with no measurable graft movement > 5 mm and not requiring secondary intervention.
[9] Patient 0511006: Compression of fenestration stent (uncovered, balloon-expandable 316L stainless steel biliary stent) associated with graft migration (approximately 12 mm by 24 months) due likely to longitudinal progression of disease with further aortic neck dilatation. Angioplasty and stent placement were performed 883 days post-procedure to treat stenosis.

Table 33 summarizes the site reported reasons for secondary intervention. Of the 11 patients who underwent a secondary intervention, 7 did so because of renal stenosis (1 associated with graft migration and stent deformation, 1 associated with stent deformation without migration). In 4 patients, the peak systolic velocity was <280 cm/s prior to reintervention. The other reported reasons for reintervention included renal occlusion in 1, Type II endoleak in 2, and suspected Type I endoleak in 1 (ruled out by angiogram).

Table 33. Reasons for secondary intervention (as reported by site)

Reason	0-30 Days	31-365 Days	366-730 Days	731-1095 Days	1096-1460 Days	1461-1825 Days

Reason	0-30 Days	31-365 Days	366-730 Days	731-1095 Days	1096-1460 Days	1461-1825 Days
Aneurysm rupture	0	0	0	0	0	0
Symptoms	0	0	0	0	0	0
Device/renal stenosis	1[1]	2[5,6]	1[7]	1[8]	1[9]	1[11]
Device migration	0	0	0	0	0	0
Device separation	0	0	0	0	0	0
Occlusion	0	1[2]	0	0	0	0
Device kink	0	0	0	0	0	0
Infection	0	0	0	0	0	0
Endoleak						
Type I proximal	0	1[3]	0	0	0	0
Type I distal	0	0	0	0	0	0
Type IIA (vessel perfusion)	0	1[4]	0	0	1[10]	0
Type IIB (vessel perfusion)	0	0	0	0	0	0
Type III (graft overlap joint)	0	0	0	0	0	0
Type IV (through graft body)	0	0	0	0	0	0
unknown	0	0	0	0	0	0
Other	0	0	0	1[8]	1[10]	0

[1] Patient 0211011: Angiography revealed that the right renal artery was severely stenosed. Attempted cannulation was unsuccessful, as the fenestration stent (Zenith® Alignment Stent) was not flared at the time of the initial implant procedure. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.
[2] Patient 0211008: Angiogram demonstrated occluded left renal artery with proximal compression of the left renal stent (uncovered, balloon-expandable 316L stainless steel biliary/renal stent), which was treated with iliorenal bypass. Compression without evidence of migration due likely to suboptimal deployment of the renal stent into the middle/upper portion of the fenestration
[3] Patient 0411004: Selective left renal angiography was performed for suspected Type I endoleak. No type I endoleak was identified; however, Type II endoleak was identified but not treated.
[4] Patient 0211010: Persistent Type II endoleak was treated by coil embolization.
[5] Patient 0111008: Right renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent) was treated by angioplasty and additional stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.
[6] Patient 0111014: Bilateral renal artery stenoses (uncovered, balloon-expandable 316L stainless steel biliary stent) were treated by angioplasty and additional stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.
[7] Patient 0211007: Right renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary/renal stent) was treated by angioplasty and additional stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.
[8] Patient 0511006: Right renal artery stent compression and subsequent stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent) treated by angioplasty and stent placement. Compression of fenestration stent associated with graft migration (approximately 12 mm by 24 months) due likely to longitudinal progression of disease with further aortic neck dilatation.
[9] Patient 0511009: Bilateral renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent) was treated by bilateral angioplasty and stenting. No evidence of graft

migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.
[10] Patient 0511004: Underwent diagnostic angiogram for suspect Type IIa and Type III endoleak, which were not detected at 1137 days post-procedure; additional intervention performed 1393 days post-procedure, involving laparotomy, suture ligation of IMA, and exploration of aneurysm sac as treatment for Type II endoleak with aneurysm growth.
[11] Patient 0511003: Left renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent) from slight compression of fenestration stent (with no measurable graft movement > 5 mm) treated by angioplasty and stent placement.

5.0 Gender Subset Analysis

Cook evaluated possible sex/gender based differences in outcome following treatment with the Fenestrated Graft. Table 34 shows the results of this subset analysis for the primary endpoint (6-month treatment success). The ability to draw conclusions from this analysis is limited given the small number of females in the study, which is consistent with the expected demographics distribution for patients with abdominal aortic aneurysms.

Table 34. 6-month treatment success by gender in the Zenith Fenestrated treatment group and Zenith AAA control group

Sex	Zenith Fenestrated	Zenith AAA
Female	87.5% (7/8)[a]	100% (8/8)
Male	100% (32/32)	93.8% (30/32)[b]

[a]One failure due to bowel ischemia – patient recovered with antibiotics and IV fluids.
[b]Failure due to congestive heart failure in one and congestive heart failure as well as cardiac ischemia requiring intervention in another

XI. Summary of Supplemental Clinical Information

Over 200 patients have been treated with the Zenith Fenestrated AAA Endovascular Graft, beginning in 2001, as part of a single-center Cook-sponsored study and a physician-sponsored study. For the physician-sponsored study, follow-up was originally planned for 2 years, with 2-year study data available for 121 patients. Longer-term data were provided for patients agreeing to return for additional follow-up.

While not observed in the multi-center study, there were six patients with component separation (one resulting in rupture), each occurring on or after the 2-year follow-up and requiring reintervention. There have since been no reports of component separation in patients treated with graft component lengths that were selected to preserve a minimum 2-stent overlap over time.

As with component separation, and with consideration to patients treated with either a fenestrated or visceral branch endovascular graft, there have been reports of problems

involving renal/visceral stents. Occlusion occurred in 3.5% (18/518) of stents placed. Stenosis occurred in 6.9% (36/518) of stents placed, of which 19.4% (7/36) required reintervention. The incidence of stent fracture requiring reintervention was 66.7% (8/12). Overall, there appeared no unique safety or effectiveness concerns based on the supplemental information from these sources.

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

XIII. Conclusions Drawn from Preclinical and Clinical Studies

A. Preclinical Conclusions

Comprehensive preclinical bench testing was performed on the Zenith Fenestrated AAA Endovascular Graft with the H&L-B One-Shot Introduction System and Zenith Alignment Stent in accordance with national and international standards and guidance documents. The testing demonstrated that the Zenith Fenestrated AAA Endovascular Graft with the H&L-B One-Shot Introduction System and Zenith Alignment Stent each met the respective performance and design specifications.

Preclinical *in vivo* animal testing was considered unnecessary for the Zenith Fenestrated AAA Endovascular Graft due to the similarities in the materials of construction with other Zenith devices tested previously, limitations of appropriate animal models, and extensive clinical experience. Preclinical *in vivo* animal testing was conducted on 9 domestic pigs, using prototypes of the Zenith Alignment Stent, in order to evaluate acute and chronic performance of the stent. The study was performed to evaluate functional biocompatibility and safety of the stents in porcine models for 1 month. The results support the safety and expected clinical performance of the Zenith Alignment Stent.

Biocompatibility testing was leveraged for the Zenith Fenestrated AAA Endovascular Graft with the H&L-B One-Shot Introduction System based on use of the same materials

in other Zenith devices that were tested previously. Shorter-term biocompatibility testing for the Zenith Alignment Stent was performed in accordance with applicable standards, while longer-term biocompatibility testing for the Zenith Alignment Stent was leveraged from the Cook Formula Balloon-Expandable Renal Stent. All testing met the requirements as specified in the applicable standard, ensuring the finished devices are biocompatible.

Sterilization, packaging, and shelf life for the Zenith Fenestrated AAA Endovascular Graft and Zenith Alignment Stent were leveraged from related Cook products, with additional testing performed specific to the Zenith Alignment Stent. The combination of testing (leveraged and new) demonstrated that the Zenith Fenestrated AAA Endovascular Graft with the H&L-B One-Shot Introduction System and Zenith Alignment Stent will maintain a Sterility Assurance Level of 10^{-6}. The results from the leveraged and newly performed shelf life testing and packaging testing confirm that the devices will perform as intended throughout the 3-year shelf life.

B. Safety and Effectiveness Conclusions

The primary endpoint for the pivotal clinical study was a combined safety and effectiveness endpoint based on treatment success. The Fenestrated Graft was successfully placed in all patients, and all vessels accommodated by a fenestration or scallop were patent at the completion of the procedure. The primary safety and effectiveness data showed that the 6-month treatment success rate for Zenith Fenestrated (97.5%) was similar to that for matched patients treated with Zenith AAA (95%).

There were no ruptures or conversions following treatment with Zenith Fenestrated at any time point. Only one death was counted as AAA-related because the cause was unknown and the CEC was therefore unable to adjudicate it – all other deaths in the Zenith Fenestrated group (3) were determined unrelated to AAA-repair by the CEC.

Pre-specified renal adverse events included renal infarct, renal insufficiency, renal failure requiring dialysis, and occlusion of a fenestrated renal vessel. There were five patients with renal infarct (none were associated with a clinical event), each of which occurred in a patient with some degree of either thrombus or calcification in the seal zone (as well as a history of infarct and coverage of an accessory renal in one). Two of three patients with renal insufficiency in the Zenith Fenestrated group had renal dysfunction prior to treatment and were considered unrelated to AAA-repair by the CEC, one of which was also the only patient in the Zenith Fenestrated group requiring dialysis (also unrelated

according to the CEC). Two patients developed occlusion of a fenestrated renal vessel (neither was associated with graft migration), one of which had evidence of fenestration stent compression (from suboptimal stent placement in the mid/upper portion of the fenestration) that required reintervention.

There were no reports of Type I or Type III endoleak, and the only reports of aneurysm growth (2) occurred in patients with a Type II endoleak. There were 2 reports of migration, both in patients with evidence of disease progression at follow-up (without aneurysm pressurization), one of which had associated fenestration stent compression requiring secondary intervention. One patient was noted to have fracture of a fenestration stent as well as the seal stent on the Fenestrated Graft, neither of which resulted in endoleak, a clinical renal event, or the need for secondary intervention. This patient also exhibited disease progression at follow-up in the absence of aneurysm pressurization. A possible second patient with fenestration stent fracture was identified without a subsequent clinical renal event or need for reintervention.

The majority of patients who underwent reintervention following treatment with the Zenith Fenestrated Graft (7 of 11) did so for renal stenosis. There was evidence of fenestration stent deformation in 2 of 7 patients that underwent reintervention for renal stenosis (1 from suboptimal stent placement in the mid/upper portion of the fenestration, and 1 from migration due to progression of disease at follow-up in the absence of aneurysm pressurization).

C. Overall Conclusion

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The above outcomes were considered reasonable for the subjects requiring treatment with a fenestrated endovascular graft. As expected, there were more renal events with the fenestrated device as compared to the standard version of the endovascular graft. The risks associated with renal events can be greatly diminished with adequate patient selection and follow-up.

XIV. CDRH DECISION

CDRH issued an approval order on April 4, 2012. The final conditions of approval cited in the approval order.

4 April 2012

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

Fracture	0.0% (0/42)	0.0% (0/41)	2.6% (1/39)[5]	3.4% (1/29)[4]	0.0% (0/26)	0.0% (0/16)	0.0% (0/17)	0.0% (0/11)
Separation	0.0% (0/42)	0.0% (0/41)	0.0% (0/39)	0.0% (0/29)	0.0% (0/26)	0.0% (0/16)	0.0% (0/17)	0.0% (0/11)
Other	0.0% (0/42)	0.0% (0/41)	7.7% (3/39)[6,7,8]	3.4% (1/29)[9]	0.0% (0/26)	0.0% (0/16)	0.0% (0/17)	0.0% (0/11)

[1] Patient 0421003: Separation of a single fixation barb. No clinical sequelae related to the barb separation have been reported.
[2] Patient 0111009: Separation of a single fixation barb. No clinical sequelae related to the barb separation have been reported.
[3] Patient 0511008: Separation of two barbs. No clinical sequelae related to the barb separation have been reported, although radiographic migration (approximately 10 mm over 5 years) was observed and was due likely to longitudinal progression of disease with further aortic neck dilatation.
[4] Patient 0411001: Fracture of sealing stent (at the distal edge of the scallop fenestration) and left renal fenestration stent (uncovered, balloon-expandable 316L stainless steel biliary/iliac stent), but in a patient with progressive aneurismal disease within and proximal to the treated segment, which likely resulted in uncharacteristic tension/loading of the stents. No subsequent renal events, endoleak, or secondary interventions reported in this patient.
[5] Patient 0511010: Fracture of left renal fenestration stent (Zenith® Alignment Stent) not readily confirmed based on subsequent bench top CT imaging studies that showed the same appearance of fracture, but in an entirely intact stent.
[6] Patient 1111011: Deformation of fenenstration stent (Zenith® Alignment Stent) with no measurable graft movement > 5 mm and not requiring secondary intervention.
[7] Patient 0511003: Slight compression of fenestration stent (uncovered, balloon-expandable 316L stainless steel biliary stent) with no measurable graft movement > 5 mm. Angioplasty and stent placement was performed 1539 days post-procedure to treat stenosis.
[8] Patient 0511007: Slight compression of fenestration stent (uncovered, balloon-expandable 316L stainless steel biliary stent) with no measurable graft movement > 5 mm and not requiring secondary intervention.
[9] Patient 0511006: Compression of fenestration stent (uncovered, balloon-expandable 316L stainless steel biliary stent) associated with graft migration (approximately 12 mm by 24 months) due likely to longitudinal progression of disease with further aortic neck dilatation. Angioplasty and stent placement were performed 883 days post-procedure to treat stenosis.

Table 33 summarizes the site reported reasons for secondary intervention. Of the 11 patients who underwent a secondary intervention, 7 did so because of renal stenosis (1 associated with graft migration and stent deformation, 1 associated with stent deformation without migration). In 4 patients, the peak systolic velocity was <280 cm/s prior to reintervention. The other reported reasons for reintervention included renal occlusion in 1, Type II endoleak in 2, and suspected Type I endoleak in 1 (ruled out by angiogram).

Table 33. Reasons for secondary intervention (as reported by site)

Reason	0-30 Days	31-365 Days	366-730 Days	731-1095 Days	1096-1460 Days	1461-1825 Days

Reason	0-30 Days	31-365 Days	366-730 Days	731-1095 Days	1096-1460 Days	1461-1825 Days
Aneurysm rupture	0	0	0	0	0	0
Symptoms	0	0	0	0	0	0
Device/renal stenosis	1[1]	2[5,6]	1[7]	1[8]	1[9]	1[11]
Device migration	0	0	0	0	0	0
Device separation	0	0	0	0	0	0
Occlusion	0	1[2]	0	0	0	0
Device kink	0	0	0	0	0	0
Infection	0	0	0	0	0	0
Endoleak						
Type I proximal	0	1[3]	0	0	0	0
Type I distal	0	0	0	0	0	0
Type IIA (vessel perfusion)	0	1[4]	0	0	1[10]	0
Type IIB (vessel perfusion)	0	0	0	0	0	0
Type III (graft overlap joint)	0	0	0	0	0	0
Type IV (through graft body)	0	0	0	0	0	0
unknown	0	0	0	0	0	0
Other	0	0	0	1[8]	1[10]	0

[1] Patient 0211011: Angiography revealed that the right renal artery was severely stenosed. Attempted cannulation was unsuccessful, as the fenestration stent (Zenith® Alignment Stent) was not flared at the time of the initial implant procedure. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.

[2] Patient 0211008: Angiogram demonstrated occluded left renal artery with proximal compression of the left renal stent (uncovered, balloon-expandable 316L stainless steel biliary/renal stent), which was treated with iliorenal bypass. Compression without evidence of migration due likely to suboptimal deployment of the renal stent into the middle/upper portion of the fenestration

[3] Patient 0411004: Selective left renal angiography was performed for suspected Type I endoleak. No type I endoleak was identified; however, Type II endoleak was identified but not treated.

[4] Patient 0211010: Persistent Type II endoleak was treated by coil embolization.

[5] Patient 0111008: Right renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent) was treated by angioplasty and additional stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.

[6] Patient 0111014: Bilateral renal artery stenoses (uncovered, balloon-expandable 316L stainless steel biliary stent) were treated by angioplasty and additional stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.

[7] Patient 0211007: Right renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary/renal stent) was treated by angioplasty and additional stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.

[8] Patient 0511006: Right renal artery stent compression and subsequent stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent) treated by angioplasty and stent placement. Compression of fenestration stent associated with graft migration (approximately 12 mm by 24 months) due likely to longitudinal progression of disease with further aortic neck dilatation.

[9] Patient 0511009: Bilateral renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent) was treated by bilateral angioplasty and stenting. No evidence of graft

migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment.
[10] Patient 0511004: Underwent diagnostic angiogram for suspect Type IIa and Type III endoleak, which were not detected at 1137 days post-procedure; additional intervention performed 1393 days post-procedure, involving laparotomy, suture ligation of IMA, and exploration of aneurysm sac as treatment for Type II endoleak with aneurysm growth.
[11] Patient 0511003: Left renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent) from slight compression of fenestration stent (with no measurable graft movement > 5 mm) treated by angioplasty and stent placement.

5.0 Gender Subset Analysis

Cook evaluated possible sex/gender based differences in outcome following treatment with the Fenestrated Graft. Table 34 shows the results of this subset analysis for the primary endpoint (6-month treatment success). The ability to draw conclusions from this analysis is limited given the small number of females in the study, which is consistent with the expected demographics distribution for patients with abdominal aortic aneurysms.

Table 34. 6-month treatment success by gender in the Zenith Fenestrated treatment group and Zenith AAA control group

Sex	Zenith Fenestrated	Zenith AAA
Female	87.5% (7/8)[a]	100% (8/8)
Male	100% (32/32)	93.8% (30/32)[b]

[a]One failure due to bowel ischemia – patient recovered with antibiotics and IV fluids.
[b]Failure due to congestive heart failure in one and congestive heart failure as well as cardiac ischemia requiring intervention in another

XI. Summary of Supplemental Clinical Information

Over 200 patients have been treated with the Zenith Fenestrated AAA Endovascular Graft, beginning in 2001, as part of a single-center Cook-sponsored study and a physician-sponsored study. For the physician-sponsored study, follow-up was originally planned for 2 years, with 2-year study data available for 121 patients. Longer-term data were provided for patients agreeing to return for additional follow-up.

While not observed in the multi-center study, there were six patients with component separation (one resulting in rupture), each occurring on or after the 2-year follow-up and requiring reintervention. There have since been no reports of component separation in patients treated with graft component lengths that were selected to preserve a minimum 2-stent overlap over time.

As with component separation, and with consideration to patients treated with either a fenestrated or visceral branch endovascular graft, there have been reports of problems

involving renal/visceral stents. Occlusion occurred in 3.5% (18/518) of stents placed. Stenosis occurred in 6.9% (36/518) of stents placed, of which 19.4% (7/36) required reintervention. The incidence of stent fracture requiring reintervention was 66.7% (8/12). Overall, there appeared no unique safety or effectiveness concerns based on the supplemental information from these sources.

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

XIII. Conclusions Drawn from Preclinical and Clinical Studies

A. Preclinical Conclusions

Comprehensive preclinical bench testing was performed on the Zenith Fenestrated AAA Endovascular Graft with the H&L-B One-Shot Introduction System and Zenith Alignment Stent in accordance with national and international standards and guidance documents. The testing demonstrated that the Zenith Fenestrated AAA Endovascular Graft with the H&L-B One-Shot Introduction System and Zenith Alignment Stent each met the respective performance and design specifications.

Preclinical *in vivo* animal testing was considered unnecessary for the Zenith Fenestrated AAA Endovascular Graft due to the similarities in the materials of construction with other Zenith devices tested previously, limitations of appropriate animal models, and extensive clinical experience. Preclinical *in vivo* animal testing was conducted on 9 domestic pigs, using prototypes of the Zenith Alignment Stent, in order to evaluate acute and chronic performance of the stent. The study was performed to evaluate functional biocompatibility and safety of the stents in porcine models for 1 month. The results support the safety and expected clinical performance of the Zenith Alignment Stent.

Biocompatibility testing was leveraged for the Zenith Fenestrated AAA Endovascular Graft with the H&L-B One-Shot Introduction System based on use of the same materials

in other Zenith devices that were tested previously. Shorter-term biocompatibility testing for the Zenith Alignment Stent was performed in accordance with applicable standards, while longer-term biocompatibility testing for the Zenith Alignment Stent was leveraged from the Cook Formula Balloon-Expandable Renal Stent. All testing met the requirements as specified in the applicable standard, ensuring the finished devices are biocompatible.

Sterilization, packaging, and shelf life for the Zenith Fenestrated AAA Endovascular Graft and Zenith Alignment Stent were leveraged from related Cook products, with additional testing performed specific to the Zenith Alignment Stent. The combination of testing (leveraged and new) demonstrated that the Zenith Fenestrated AAA Endovascular Graft with the H&L-B One-Shot Introduction System and Zenith Alignment Stent will maintain a Sterility Assurance Level of 10^{-6}. The results from the leveraged and newly performed shelf life testing and packaging testing confirm that the devices will perform as intended throughout the 3-year shelf life.

B. Safety and Effectiveness Conclusions

The primary endpoint for the pivotal clinical study was a combined safety and effectiveness endpoint based on treatment success. The Fenestrated Graft was successfully placed in all patients, and all vessels accommodated by a fenestration or scallop were patent at the completion of the procedure. The primary safety and effectiveness data showed that the 6-month treatment success rate for Zenith Fenestrated (97.5%) was similar to that for matched patients treated with Zenith AAA (95%).

There were no ruptures or conversions following treatment with Zenith Fenestrated at any time point. Only one death was counted as AAA-related because the cause was unknown and the CEC was therefore unable to adjudicate it – all other deaths in the Zenith Fenestrated group (3) were determined unrelated to AAA-repair by the CEC.

Pre-specified renal adverse events included renal infarct, renal insufficiency, renal failure requiring dialysis, and occlusion of a fenestrated renal vessel. There were five patients with renal infarct (none were associated with a clinical event), each of which occurred in a patient with some degree of either thrombus or calcification in the seal zone (as well as a history of infarct and coverage of an accessory renal in one). Two of three patients with renal insufficiency in the Zenith Fenestrated group had renal dysfunction prior to treatment and were considered unrelated to AAA-repair by the CEC, one of which was also the only patient in the Zenith Fenestrated group requiring dialysis (also unrelated

according to the CEC). Two patients developed occlusion of a fenestrated renal vessel (neither was associated with graft migration), one of which had evidence of fenestration stent compression (from suboptimal stent placement in the mid/upper portion of the fenestration) that required reintervention.

There were no reports of Type I or Type III endoleak, and the only reports of aneurysm growth (2) occurred in patients with a Type II endoleak. There were 2 reports of migration, both in patients with evidence of disease progression at follow-up (without aneurysm pressurization), one of which had associated fenestration stent compression requiring secondary intervention. One patient was noted to have fracture of a fenestration stent as well as the seal stent on the Fenestrated Graft, neither of which resulted in endoleak, a clinical renal event, or the need for secondary intervention. This patient also exhibited disease progression at follow-up in the absence of aneurysm pressurization. A possible second patient with fenestration stent fracture was identified without a subsequent clinical renal event or need for reintervention.

The majority of patients who underwent reintervention following treatment with the Zenith Fenestrated Graft (7 of 11) did so for renal stenosis. There was evidence of fenestration stent deformation in 2 of 7 patients that underwent reintervention for renal stenosis (1 from suboptimal stent placement in the mid/upper portion of the fenestration, and 1 from migration due to progression of disease at follow-up in the absence of aneurysm pressurization).

C. Overall Conclusion

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The above outcomes were considered reasonable for the subjects requiring treatment with a fenestrated endovascular graft. As expected, there were more renal events with the fenestrated device as compared to the standard version of the endovascular graft. The risks associated with renal events can be greatly diminished with adequate patient selection and follow-up.

XIV. CDRH DECISION

CDRH issued an approval order on April 4, 2012. The final conditions of approval cited in the approval order.

4 April 2012

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.