DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

Medical Device Tracking Order

Ms. April Lavender
Vice President Regulatory Affairs
Cook, Inc.
Post Office Box 489
Bloomington, Indiana 47402-0489

MAY 23 2003

RE: Endovascular Graft (P020018)

Dear Ms. Lavender:

You are notified by this letter of your obligation to adopt a method of tracking for the devices referenced above, as authorized by section 519(e) of the Federal Food, Drug, and Cosmetic Act, (the Act) as amended by section 211 of the Food and Drug Administration Modernization Act of 1997 (FDAMA). The implementation of section 519(e) of the Act, as amended, requires the Food and Drug Administration (FDA) to issue an order to manufacturers when FDA determines that a person who manufactures and distributes a device meets the relevant statutory requirements and tracking is required to protect the public health. This order is effective immediately.

Section 519(e) of the Act, as amended, states that FDA, "...may by order require a manufacturer to adopt a method of tracking a class II or class III device—

(A) the failure of which would be reasonably likely to have serious adverse health consequences; or

(B) which is—

(i) intended to be implanted in the human body for more than one year, or

(ii) a life sustaining or life supporting device used outside a device user facility."

As you know, the corresponding medical device tracking regulations, found in Title 21 Code of Federal Regulations (CFR) Part 821, are intended to ensure that tracked devices can be traced from the device manufacturing facility to the person by whom the device is intended to be used when patient notification (under section 518(a) of the act) or device recall (under section 518(e) of the act) actions are ordered by the agency. The device tracking requirements for exemptions and variances, system and content requirements of tracking, the obligations of persons other than device manufacturers, such as distributors, records and inspection requirements, confidentiality, and record retention requirements, which were published in the **Federal Register** on August 16, 1993, remain in effect. (21 CFR sections 821.2, 821.25, 821.30, 821.50, 821.55 and 821.60, copy enclosed.)

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This order to adopt a tracking method does not change your obligations concerning other existing FDA regulations affecting your device. FDA published in the **Federal Register** on February 28, 2002, an amendment to the final rule to revise the scope of the regulation and add certain patient confidentiality requirements, and non-substantive changes to remove outdated references and simplify terminology. (67 FR 6943) Please contact Chet Reynolds in the Office of Compliance at (301) 594-4618 if you need specific guidance. Other general information on your responsibilities under the Act, or more specific information, such as non-binding guidance on medical device tracking, may be obtained from the Division of Small Manufacturers, International, and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597, or at the internet address www.fda.gov/cdrh.

Sincerely yours,

for Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

Enclosure

Summary of Safety and Effectiveness Data

1. General Information

Device Generic Name:	Endovascular Graft and Delivery System
Device Trade Name:	Zenith® AAA Endovascular Graft with the H&L-B One-Shot™ Introduction System
Applicant's Name and Address:	Cook Incorporated 750 North Daniels Way Bloomington, Indiana 47404
Date of Panel Recommendation:	April 10, 2003
Premarket Approval (PMA) Application Number:	P020018
Date of Notice of Approval to Applicant:	May 23, 2003

2. Indications and Usage

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

Adequate iliac/femoral access compatible with the required introduction systems

Non-aneurysmal infrarenal aortic segment (neck) proximal to the aneurysm:

- with a length of at least 15 mm,
- with a diameter measured outer wall to outer wall of no greater than 28 mm and no less than 18 mm,
- with an angle less than 60 degrees relative to the long axis of the aneurysm, and
- with an angle less than 45 degrees relative to the axis of the suprarenal aorta.

Iliac artery distal fixation site greater than 10 mm in length and 7.5-20 mm in diameter (measured outer wall to outer wall).

3. Contraindications

There are no known contraindications.

4. Warnings and Precautions

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

5. Device Description

The Cook Zenith® AAA Endovascular Graft (Zenith) is a modular system of components consisting of multiple endovascular graft configurations and additional ancillary pieces. All components in this system use common self-expanding Z-stents sewn to traditional, currently marketed Dacron graft material using currently marketed braided polyester and monofilament polypropylene suture materials.

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

5.1. Zenith Main Endovascular Graft

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

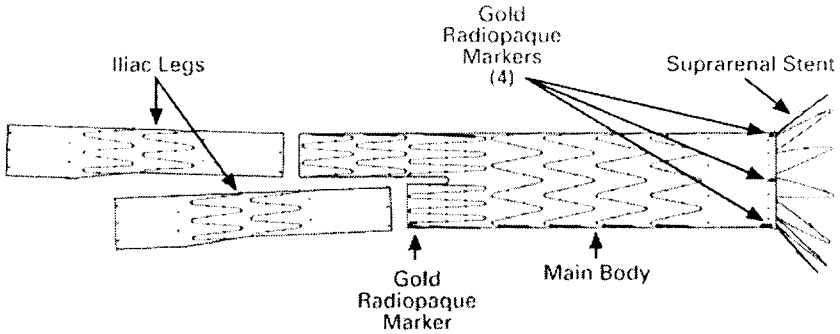

Figure 5.1-1. Zenith® AAA Endovascular Graft

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

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ipsilateral iliac artery. (The aortic main body extensions and iliac leg extensions described in Section 5.2 can be used to provide additional length to their respective portions of the endovascular graft.)

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

22 mm	24 mm	26 mm	28 mm	30 mm	32 mm
TFB-22-74	TFB-24-74	TFB-26-74	TFB-28-74	TFB-30-74	TFB-32-74
TFB--22-88	TFB-24-88	TFB-26-88	TFB-28-88	TFB-30-88	TFB-32-88
TFB-22-103	TFB-24-103	TFB26-103	TFB-28-103	TFB-30-103	TFB-32-103
TFB22-117	TFB-24-117	TFB-26-117	TFB-28-117	TFB-30-117	TFB-32-117
TFB-22-132	TFB-24-132	TFB-26-132	TFB28-132	TFB-30-132	TFB-32-132

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

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

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

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

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

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

5.2. Zenith® AAA Endovascular Graft Ancillary Components

The Zenith® AAA Endovascular Graft ancillary components consist of aortic main body extensions, iliac leg extensions, converters and occluders. The aortic main body extensions and iliac leg extensions can be used to provide additional length to their respective portions of the endovascular graft. The converters and occluders can be used to convert a bifurcated graft into an aorto-uniiliac graft, if necessary (e.g. cases of Type 3 endoleak, limb occlusion, or unattainable contralateral limb cannulation). Examples of each ancillary component are shown in Figure 5.2-1.

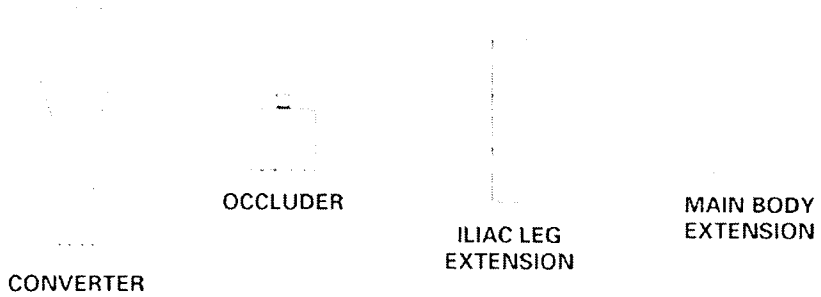

Figure 5.2-1. Zenith Ancillary Components

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

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

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

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

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

The Zenith® AAA Endovascular Graft is shipped preloaded onto the H&L-B One-Shot™ Introduction System. It has a simple sequential deployment method with built-in features to provide continuous control of the endovascular graft throughout the deployment procedure. The H&L-B One-Shot™ Introduction System enables precise positioning and has the ability to readjust the final graft position before deploying the barbed suprarenal Z-stent.

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

5.3.1. 18 Fr and 20 Fr Delivery Systems Description

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

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

H&L-B One-Shot™ Introduction System	Main Body[1]				
	74 mm	88 mm	103 mm	117 mm	132 mm
18 Fr System	TFB-22-74 TFB-24-74 TFB-26-74	TFB-22-88 TFB-24-88 TFB-26-88	TFB-22-103 TFB-24-103 TFB-26-103	TFB-22-117 TFB-24-117 TFB-26-117	TFB-22-132 TFB-24-132 TFB-26-132
20 Fr System	TFB-28-74 TFB-30-74 TFB-32-74	TFB-28-88 TFB-30-88 TFB-32-88	TFB-28-103 TFB-30-103 TFB-32-103	TFB-28-117 TFB-30-117 TFB-32-117	TFB-28-132 TFB-30-132 TFB-32-132

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

Table 5.3.1-2 lists the catalog/reorder numbers of the main body extensions and converters deployed using these two sizes of H&L-B One-Shot™ Introduction Systems. Zenith® AAA Endovascular Graft main body extensions and converters ranging in diameter from 22 - 26 mm

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are deployed using the 18 Fr system. Zenith® AAA Endovascular Graft main body extensions and converters ranging in diameter from 28 - 32 mm are deployed using the 20 Fr system. In addition, Table 5.3.1-2 lists the iliac leg extensions deployed with the 18 Fr delivery system.

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

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

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

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

When configured for main body deployment, these systems contain sideports for angiography using contrast injection through the hub, dual trigger-wire release mechanisms with safety locks, a top cap assembly coupled with the dilator tip (covered by sheath in Figure 5.3.1-1), and a bottom cap assembly (covered by sheath in Figure 5.3.1-1). These features lock the Zenith main body onto the delivery system at both ends of the component, giving the physician both longitudinal and rotational control of the endovascular graft after sheath retraction. Therefore, accurate positioning relative to the renal arteries and appropriate orientation of the contralateral limb are possible.

Figure 5.3.1-1 depicts this configuration. The top cap assembly constrains the barbed, uncovered, suprarenal Z-stent until: 1) removal of its corresponding trigger-wire (black trigger-wire release); and 2) release of the Z-stent from within the cap which is achieved by loosening the pin vise and advancing the top cap inner cannula. The bottom cap assembly and its corresponding trigger-wire constrain the ipsilateral limb of the main body until removal of its trigger-wire (white trigger-wire release).

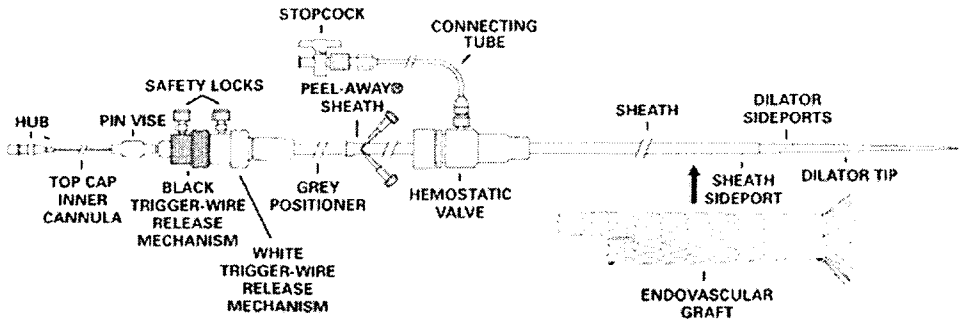

Figure 5.3.1-1. H&L-B One-Shot™ Introduction System (Main Body)

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

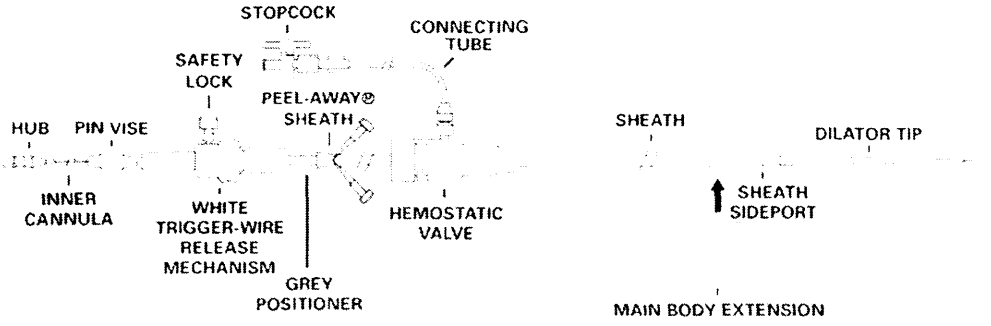

Figure 5.3.1-2. H&L-B One-Shot™ Introduction System (Main Body Extender)

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

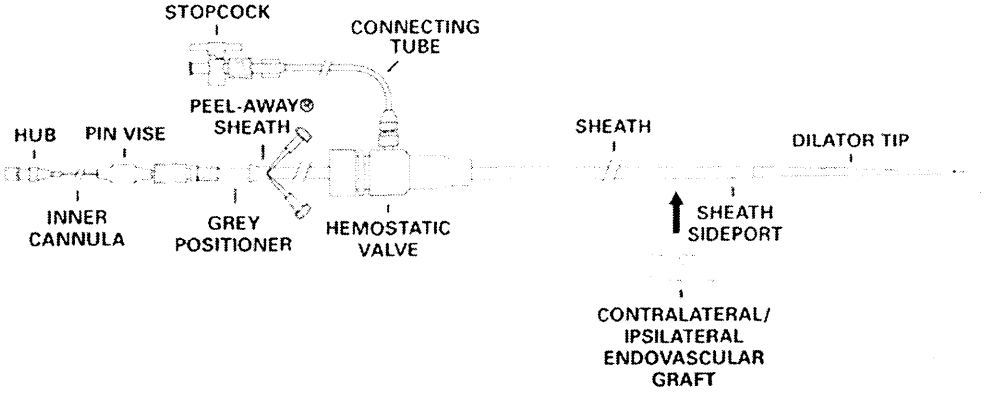

Figure 5.3.1-3. H&L-B One-Shot™ Introduction System (Iliac Leg)

5.3.2. 14 Fr and 16 Fr delivery systems description

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

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

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

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

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

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

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

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

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

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5.3.3. Occluder Cartridge Description

A delivery sheath is used together with a preloaded cartridge (transfer capsule) for occluder deployment. Table 5.3.3-1 lists the catalog/reorder numbers of the occluders deployed using the delivery sheath. All Zenith® AAA Endovascular Graft occluders are deployed using an 18 Fr sheath.

Table 5.3.3-1. Zenith occluders deployed with 18 Fr systems

Delivery Sheath	Occluders [1]
18 Fr System	ESP-14-20 ESP-16-20
	ESP-20-20 ESP-24-20

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

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

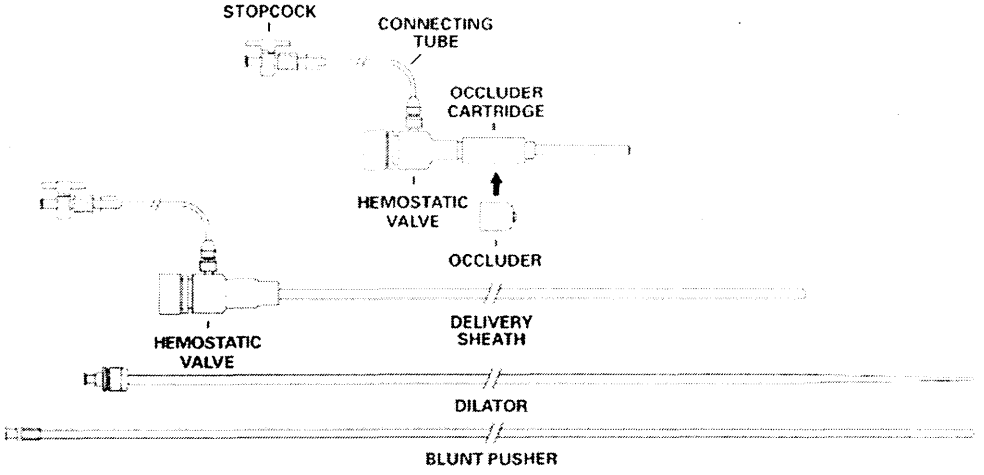

Figure 5.3.3-1. Zenith® AAA Endovascular Graft Occluder Cartridge System

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6. Alternate Practices and Procedures

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

Patients who are unacceptable surgical or anesthesia candidates may be medically managed and closely monitored or recommended for endovascular repair.

7. Marketing History

The Zenith® AAA Endovascular Graft with the H&L-B One-Shot™ Introduction System is currently available throughout the world including European countries (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, and the United Kingdom), Argentina, Australia, Brazil, Canada, Chile, China, Hong Kong, India, Israel, Lebanon, Malaysia, New Zealand, Saudi Arabia, Singapore, and South Africa. The Zenith® AAA Endovascular Graft with the H&L-B One-Shot™ Introduction System has not been withdrawn from marketing for any reason relating to safety and effectiveness.

8. Adverse Events

8.1. Observed Adverse Events

A U.S. multicenter, prospective study conducted at 15 centers which included 352 endovascular patients (200 standard risk, 100 high risk and 52 roll-in) and 80 control patients provide the basis of the observed adverse event rates in Table 8.1-1.

Table 8.1-1. Death and rupture from clinical study

Death and rupture	Zenith Standard Risk[1]	Surgical Standard Risk	*P* value	Zenith High Risk	Zenith Roll-in
All death (0-30 days)[2]	0.5% (1/199)	2.5% (2/80)	.20	2.0% (2/100)	1.9% (1/52)
(31-365 days)[2, 3]	3.0% (6/198)	1.3% (1/78)	.68	7.1% (7/98)	9.8% (5/51)
AAA-related	0.0% (0/198)	1.3% (1/78)	.29	3.1% (3/98)	0.0% (0/51)
Non-AAA-related	3.0% (6/198)	0.0% (0/78)	.19	4.1% (4/98)	9.8% (5/51)
(0-365 days)[2, 3, 4]	3.5% (7/199)	3.8% (3/80)	>.99	9.0% (9/100)	11.5% (6/52)
AAA-related	0.5% (1/199)	3.8% (3/80)	.07	5.0% (5/100)	1.9% (1/52)
Non-AAA-related	3.0% (6/199)	0.0% (0/80)	.19	4.0% (4/100)	9.6% (5/52)
Rupture (0-30 days)	0.0% (0/199)	n/a	n/a	0.0% (0/100)	0.0% (0/52)
(31-365 days)	0.0% (0/198)	n/a	n/a	1.0% (1/98)	0.0% (0/51)
(0-365 days)	0.0% (0/199)	n/a	n/a	1.0% (1/100)	0.0% (0/52)

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

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

3 Of the deaths (31-365 days), four were considered AAA related: 1 surgical (septic shock from ischemic colitis) and 3 high risk (pancreatitis with renal failure and sepsis, hemorrhage from upper abdominal aneurysm [not treated AAA], and multiple system failure).

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

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Table 8.1-2. Adverse events[1] in clinical study

	Zenith Standard Risk	Surgical Standard Risk	*P* value	Zenith High Risk	Zenith Roll-in
Freedom from Morbidity (0-30 days)	80% (160/200)	58% (46/80)	<.001	68% (68/100)	73% (38/52)
Cardiovascular [2]	3.0% (6/200)	11% (9/80)	.02	14% (14/100)	1.9% (1/52)
Pulmonary [3]	1.0% (2/200)	15% (12/80)	<.001	2.0% (2/100)	0.0% (0/52)
Renal [4,9]	2.5% (5/200)	10% (8/80)	.01	6.0% (6/100)	5.8% (3/52)
Bowel [5]	1.0% (2/200)	3.8% (3/80)	.14	1.0% (1/100)	1.9% (1/52)
Wound [6]	4.5% (9/200)	7.5% (6/80)	.38	2.0% (2/100)	3.8% (2/52)
Neurologic [7]	0.0% (0/200)	2.5% (2/80)	.08	0.0% (0/100)	0.0% (0/52)
Vascular [8,11]	11% (21/200)	31% (25/80)	<.001	20% (20/100)	19% (10/52)
Freedom from Morbidity (31-365 days)	91% (181/198)	86% (67/78)	.25	79% (77/98)	86% (44/51)
Cardiovascular[2]	2.5% (5/198)	3.8% (3/78)	.69	5.1% (5/98)	2.0% (1/51)
Pulmonary [3]	0.5% (1/198)	1.3% (1/78)	.49	4.1% (4/98)	0.0% (0/51)
Renal [4,10]	0.5% (1/198)	0.0% (0/78)	>.99	3.1% (3/98)	0.0% (0/51)
Bowel [5]	0.5% (1/198)	1.3% (1/78)	.49	0.0% (0/98)	0.0% (0/51)
Wound [6]	2.0% (4/198)	5.1% (4/78)	.23	3.1% (3/98)	2.0% (1/51)
Neurologic [7]	1.0% (2/198)	0.0% (0/78)	>.99	1.0% (1/98)	3.9% (2/51)
Vascular [8]	3.0 % (6/198)	3.8% (3/78)	.72	8.2% (8/98)	5.9 % (3/51)
Freedom from Morbidity (0-365 days)	76% (151/200)	49% (39/80)	<.001	55% (55/100)	62% (32/52)
Cardiovascular[2]	5.0% (10/200)	14% (11/80)	.02	19% (19/100)	3.8% (2/52)
Pulmonary [3]	1.5% (3/200)	16 % (13/80)	<.001	6.0 % (6/100)	0.0% (0/52)
Renal [4,9,10]	2.5% (5/200)	10% (8/80)	.01	9.0% (9/100)	5.8% (3/52)
Bowel [5]	1.5% (3/200)	3.8% (3/80)	.36	1.0% (1/100)	1.9% (1/52)
Wound [6]	5.5% (11/200)	13% (10/80)	.08	5.0% (5/100)	5.8% (3/52)
Neurologic [7]	1.0% (2/200)	2.5% (2/80)	.32	1.0% (1/100)	3.8% (2/52)
Vascular [8,11]	12% (24/200)	33% (26/80)	<.001	25% (25/100)	23% (12/52)

1 From the morbidity index.

2 Cardiovascular included: Q-wave and non-Q-wave myocardial infarctions, congestive heart failure, arrhythmias requiring new medication or treatment, cardiac ischemia requiring intervention, inotropic support, medically intractable hypertension.

3 Pulmonary included: reintubation or ventilation >24 hours, pneumonia requiring antibiotics, supplemental oxygen at discharge.

4 Renal included: dialysis in patients with normal preoperative renal function, creatinine rise >30% from baseline on two or more follow-up tests.

5 Bowel included: bowel obstruction, bowel ischemia, aorto-enteric fistula, paralytic ileus >4 days.

6 Wound included: infection requiring antibiotic treatment, hernia, lymph fistula, dehiscence, necrosis requiring debridement.

7 Neurological includes: stroke, TIA, spinal cord ischemia/paralysis.

8 Vascular included: limb thrombosis, distal embolization resulting in tissue loss or requiring intervention, transfusion post-procedure (resulting from pseudoaneurysm, vascular injury, aneurysm leak or other procedure-related causes), pseudoaneurysm, vascular injury (such as inadvertent occlusion, dissection or other procedure related causes), aneurysm leak or rupture, increase in aneurysm size by more than 0.5 cm relative to the smallest of any prior measurement.

9 Investigators reported one additional high risk patient to have occlusion of an accessory renal artery and one additional high risk patient to have chronic renal insufficiency as "other" adverse events.

10 Investigators reported one additional roll-in patient to have renal insufficiency and one additional surgical patient to have renal insufficiency as "other" adverse events.

11 Investigators reported one additional roll-in patient to have experienced intraoperative aortic plaque rupture resulting in renal artery occlusion as an "other" adverse event.

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Table 8.1-3. Other complications to 12 months

	Zenith Standard Risk	Surgical Standard Risk	*P* value	Zenith High Risk	Zenith Roll-in
Other (0 to 30 days)	15% (30/200)	38% (30/80)	<.001	16% (16/100)	31% (16/52)
Other (31-365 days)	8.1% (16/198)	7.7% (6/78)	>.99	11% (11/98)	12% (6/51)
Other (0 to 365 days)	22% (43/200)	40% (32/80)	<.01	25% (25/100)	35% (18/52)

Investigators reported the following as "other" adverse events (surgical and endovascular arms, surgical listed in italics), that is, events not identified and defined prospectively as reportable events for the study: abdominal pain (3), *abnormal wound healing (e.g., wound drainage)*, acute respiratory distress, anemia (4), angina (2), anorexia, *anxiety*, appendiceal adenocarcinoma, atelectasis, atheroembolic event, back pain (3), bilateral ecchymosis, bladder tumor (3), *blindness in right eye*, *bradycardia (treated by holding medication)*, bronchitis, *candida in urine (prolonged ICU stay)*, carcinoma of the iliocecal junction, cardiomyopathy, carotid stenosis (2), chest pain (2, *1*), chronic lower extremity pain, claudication (3, *1*), confusion (1, *1*), *congestive heart failure exacerbation*, constipation (2, *1*), COPD exacerbation, deep vein thrombosis (3, *1*), dehydration (3, *1*), difficile colitis, difficulty urinating, difficulty with blood pressure management, duodenal ulcer, edema, *elevation of liver enzymes*, embolization without tissue loss, enlarged heart, fatigue, fever (3, *1*), foot pain, gastroenteritis, gout, hematuria (1, *1*), hemoglobin volume depletion, hepatocellular carcinoma, *hyperkeratotic wound*, hypertension, hypoglycemic episode, hypotension, *impotence (2)*, *incisional pain*, left ventricular thrombus, lost pedal pulse, lymphocele, mitral regurgitation, neurological changes, neuropathy, numbness in groin, *oral thrush*, pancreatitis (1, *1*), paresthesia of lower extremity, *PEG tube placement*, *pleural effusion*, *positive blood culture*, pressure sore, prolonged intubation (<24 hours), pulmonary edema (1, *1*), pulmonary embolism, purpura, reaction to transfusion, *respiratory distress*, respiratory insufficiency (1, *1*), *retrograde ejaculation*, scrotal/penile swelling, *sepsis*, seroma, shingles (2), shortness of breath, *sinus surgery*, *splenectomy*, stroke induced dysphagia, syncopal episode, testicular infarction, testicular pain (2), testicular swelling, thrombocytopenia, *thrombus in distal lower extremity (treated with embolectomy)*, *tracheobronchitis*, *tracheostomy*, upper GI bleed (2), urinary frequency (2), urinary retention (2), urinary tract infection (2, *1*), urosepsis, ventricular tachycardia (asymptomatic, not requiring treatment), vomiting/nausea (3), *winged scapula*, wound slough with debridement, *yeast in urinary tract*.

8.2. Potential Adverse Events

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 thrombosis and/or pseudoaneurysm
- Arteriovenous fistula
- Bleeding, hematoma, or coagulopathy
- Bowel (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
- Endoleak
- Endoprosthesis: improper component placement; incomplete component deployment; component migration, suture break; occlusion; infection; stent fracture; graft material wear, dilatation, erosion, puncture, perigraft flow, barb separation and corrosion
- Fever and localized inflammation
- Genitourinary complications and subsequent attendant problems (e.g., ischemia, erosion, fistula, incontinence, hematuria, infection)
- Graft or native vessel occlusion
- Hepatic failure

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- 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., stroke, transient ischemic attack, paraplegia, paraparesis, paralysis)
- Occlusion of device or native vessel

- Pulmonary/respiratory complications and subsequent attendant problems (e.g., pneumonia, respiratory failure, prolonged intubation)
- Renal complications and subsequent attendant problems (e.g., artery occlusion, contrast toxicity, insufficiency, failure)
- Surgical conversion to open repair
- Vascular access site complications, including infection, pain, hematoma, pseudoaneurysm, arterio-venous fistula
- Vessel damage
- Wound complications and subsequent attendant problems (e.g., dehiscence, infection)
- Vascular spasm or vascular trauma (e.g., ilio-femoral vessel dissection, bleeding, rupture, death)

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9. Summary of Pre-Clinical Results

9.1. Biocompatibility

Toxicology and biocompatibility testing was conducted for materials in the Zenith® AAA Endovascular Graft and the H&L-B One-Shot™ Introduction System by an independent laboratory (NAMSA, Northwood, OH). Testing was conducted in accordance with Federal Good Laboratory Practices per 21 CFR §58. The Zenith® AAA Endovascular Graft was classified per ISO 10993-1 Biological Evaluation of Medical Device as an implant device with permanent contact. The H&L-B One-Shot™ Introduction System was classified as an externally communicating device with limited exposure (≤ 24 hr). Table 9.1-1 summarizes biocompatibility testing for the implant. Table 9.1-2 summarizes biocompatibility testing for the delivery system.

Table 9.1-1. Summary of Biocompatibility Tests for the Zenith® AAA Endovascular Graft, All With Acceptable Results

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

Table 9.1-2. Summary of Biocompatibility Tests for the H&L-B One-Shot™ Delivery System, All With Acceptable Results.

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

9.2. Product Testing

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

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

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

The express intent of this *in vitro* testing was to verify that the performance attributes of the Zenith® AAA Endovascular Graft and the H&L-B One-Shot™ Introduction System are sufficient to minimize adverse events under anticipated clinical conditions.

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9.2.1. Delivery System Test Results Summary

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

Table 9.2.1-1. Summary of Results Related to H&L-B One-Shot™ Introduction System Functionality

In Vitro Test	Relevant Functional Requirement	Summary of Test Result
Tensile/ Bond Strength	• Ability to access the intended location • Ability to deploy the implant • Ability to withdraw the delivery system	The tensile strengths of the bonds and joints of the H&L-B One-Shot™ Introduction System were determined. A total of 220 catheter bonds were tested and shown to have tensile strengths between 10.6 and 73.2 lbf. Results indicate that there is at least a 95% confidence level that the minimum tensile strength of each catheter bond will exceed the established acceptance criterion.
Torsional Bond Strength	• Ability to access the intended location • Ability to deploy the implant	The torsional strengths of the bonds and joints of the H&L-B One-Shot™ Introduction System were determined. A total of 130 catheter bonds were tested and shown to have torque strengths between 11.7 and 58.1 in.-oz. Mean bond strength met the acceptance criterion for each joint tested.
Dimensional Verification	• Ability to access the intended location • Ability to deploy the implant	Dimensional checks are part of internal QC records verifying conformance to design specifications for each device.
Crossing Profile	• Ability to access the intended location • Ability to deploy the implant • Ability to withdraw the delivery system • Hemostasis of the delivery system	Crossing profile was analyzed for all four delivery system sizes (14, 16, 18, and 20 Fr) and shown to range between 5.4 and 7.8 mm. All delivery systems passed the established acceptance criterion, demonstrating the delivery systems are capable of being inserted into the vasculature during clinical use.

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In Vitro Test	Relevant Functional Requirement	Summary of Test Result
Top Cap Microscopic Inspection	• Ability to deploy the implant • Ability to withdraw the delivery system	A total of 10 top caps were split in half and microscopically examined. Inspection of the lumens revealed only slight surface scratches which could be attributed to manufacturing, loading, or deployment. There was no evidence of pitting or gouging of the top cap material by the suprarenal stent barbs. Results of microscopic examination demonstrate that the top cap of the H&L-B One-Shot™ Introduction System is unlikely to pit or gouge during deployment of the barbed suprarenal Z-stent.
Deployment Test	• Ability to access the intended location • Ability to deploy the implant • Ability to withdraw the delivery system	Comprehensive evaluation of *in vitro* deployment was conducted in a clinically relevant model. A total of 113 finished sterilized devices were tested with 100% deployment success. Results of deployment testing demonstrate the ability of all four sizes (14, 16, 18, and 20 Fr) of the H&L-B One-Shot™ Introduction System to deliver the Zenith in a safe, consistent and accurate manner. Delivery systems are capable of deploying all modular components (main bodies, main body extensions, iliac legs, iliac leg extensions, converters, and occluders) in the entire product line. The deployment mechanisms of the delivery systems functioned to release the pre-loaded endovascular graft components. After release, each component expanded in the intended deployment location, and the delivery system was withdrawn successfully.
Minimum Bend Radius Test	• Ability to access the intended location • Ability to deploy the implant • Ability to withdraw the delivery system	A total of 108 delivery systems (all four sizes: 14, 16, 18, and 20 Fr) containing the largest and smallest diameters of main bodies, main body extensions, iliac legs, iliac leg extensions, converters and occluders were passed through a clinically-relevant model mimicking percutaneous introduction and then deployed. 100% successful deployment was achieved for all components. All delivery systems passed the established acceptance criterion, demonstrating the Zenith components may be deployed after worst case (percutaneous introduction) insertion into patient vasculature.
Catheter Body Maximum Pressure Test	• Ability to deploy accurately	The lower bound of catheter body maximum pressure was calculated to be 58.6 ksi, considerably higher than that expected from a typical power contrast injector. Therefore, the H&L-B One-Shot™ Introduction System is considered suitable for contrast injection.

The results of *in vitro* testing demonstrate that the Zenith® AAA Endovascular Graft has met the physical and mechanical design goals.

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9.2.2. Implant Test Results Summary

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

Table 9.2.2-1. Summary of Test Results Related to Zenith® AAA Endovascular Graft Functionality

In Vitro Test	Relevant Functional Requirement	Summary of Test Result
Graft Material Mechanical Properties Test	• Testing of the modularity of the endovascular system • Appropriate sizing of the implant • Durability and integrity of the implanted device	The full thickness Dacron graft material used in Zenith construction is a currently-marketed device (cleared for marketing by FDA in 1993). As such, base graft porosity, longitudinal tensile strength, circumferential tensile strength, probe burst strength, suture retention strength, kink radius, and wall thickness data obtained are consistent with vascular grafts.
Stainless Steel Material Analysis Test	• Durability and integrity of the implanted device	All sizes of stainless steel wire used in Zenith construction were chemically analyzed and quantified. The material analysis meets the manufacturing material specification.
Stainless Steel Mechanical Properties Test	• Durability and integrity of the implanted device	Tensile testing was performed on all three stent wire sizes to characterize the mechanical properties of the material. These properties include modulus of elasticity, yield strength, and ultimate strength. In addition, rotary beam fatigue testing was conducted on all three stent wire sizes (at three different stress levels) to characterize wire fatigue parameters. Results indicate the wire used in Zenith construction meets the manufacturing specification.
Solder Material Analysis	• Durability and integrity of the implanted device	The solder used in Zenith construction was chemically analyzed and quantified. The material analysis meets the manufacturing material specification.

In Vitro Test	Relevant Functional Requirement	Summary of Test Result
Time-Accelerated Corrosion Test	• Durability and integrity of the implanted device	A total of 12 stent samples were immersed in an accelerated corrosion bath for various periods of time and then removed for examination. The resistance of the stainless steel wire, solder, and gold markers to general, pitting, crevice, and galvanic corrosion was evaluated. There is a potential for solder loss due to corrosion, however, the loss in solder is not anticipated to be greater than 50% over 10 years and there is a redundancy in design intended to provide additional protection from migration as a result of barb slippage due to solder loss. Results demonstrate no apparent corrosion of the stainless steel wire and gold markers after 12 years of simulated implant time.
Barb Attachment Strength Test (after corrosion test)	• Durability and integrity of the implanted device	A total of 36 barbs were tensile tested after immersion in an accelerated corrosion bath. Mean barb attachment (shear) strength was approximately 6 times the acceptance criterion after 12 years of simulated implant (corrosion) time.
Cannula (portion of Z-stent) Tensile Test (after corrosion test)	• Durability and integrity of the implanted device	A total of 11 stent cannula were tensile tested after immersion in an accelerated corrosion bath. Minimum cannula tensile strength was approximately 6 times the acceptance criterion after 12 years of simulated implant (corrosion) time.
Stent Free-Area Percentage	• Patency of the implant	Stent free-area percentages were calculated for the stent configurations used in the suprarenal stent position. Free-area percentages for these Z-stents are 82% and 84% respectively, for the worst case (smallest aorta) conditions.
Radial Force Test	• Expansion and sealing effectiveness of the implant • Appropriate sizing of the implant • Patency of the implant	Radial force testing was performed on 45 samples of Z-stents, which included configurations used in the entire Zenith product line. Results demonstrate the ability of the Z-stent to exert an outward non-zero radial force on the graft material even under worst case (largest resting diameter) conditions allowing the Z-stents to expand and maintain an open lumen and provide sealing in a variety of patient anatomies.

In Vitro Test	Relevant Functional Requirement	Summary of Test Result
Time-Accelerated Pulsatile Fatigue Test (Three-piece bifurcated graft)	• Durability and integrity of the implanted device	Time-accelerated pulsatile fatigue testing was conducted on 31 bifurcated grafts to an equivalent of 10 years. At 10 years, there was no loss of device function, fragmentation, barb separation, suprarenal stent breaks, or cannula separations. No component separations, migrations, graft kinks, or graft twists were observed and all grafts were patent. A single Z-stent vertex break was observed. This test was not designed to assess suture and graft material abrasion, although it was noted. Binomial statistics demonstrate with at least 95% confidence that 99% of the Zenith stents will not fracture after 10 years of implant time meeting the acceptance criteria for this test.
Time-Accelerated Longitudinal Fatigue Test (Suprarenal Attachment)	• Durability and integrity of the implanted device • Fixation effectiveness of the implant	Time-accelerated longitudinal fatigue testing of the double-sutured suprarenal stent attachment site was conducted on 30 attachment sites to an equivalent of 10 years. At 10 years, there were no failures of the suprarenal attachment sutures or graft material at the suprarenal attachment sites. Therefore, fatigue failure is unlikely to occur under normal conditions, when the device is used in accordance with the IFU.
Finite Element Analysis	• Durability and integrity of the implanted device	Force versus diameter curves and maximum stress (in the loop or eye of the stent points) versus diameter curves were generated demonstrating the ability of the Z-stent to self-expand the graft during deployment. Fatigue analysis of the Z-stents and their barbs demonstrated that fatigue failure is unlikely to occur during the expected implant life of the Zenith under normal conditions, when the device is used in accordance with the IFU.
Magnetic Resonance Imaging Test	• MRI compatibility	The MR safety and compatibility of the Zenith® AAA Endovascular Graft has been evaluated through bench testing in MRI systems with static fields of ≤ 1.5 Tesla, gradient magnetic fields of ≤ 20 Tesla/second, and whole body averaged specific absorption rate (SAR) of 1.2 W/kg for 30 minutes of imaging. The Zenith® AAA Endovascular Graft was found to exhibit torque and deflection of the stainless steel metallic component of the endovascular graft and therefore did not meet standard 'MR Safe' bench test criteria. The Zenith® AAA Endovascular Graft may affect image quality (image artifact) depending on the pulse sequence that is used for MR imaging.

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In Vitro Test	Relevant Functional Requirement	Summary of Test Result
Dimensional Verification	• Ability to accurately deploy • Appropriate sizing of the implant	Records from work orders indicate that production processes are outlined sufficiently to enable repeatable dimensional characteristics from lot-to-lot of manufacturing.
Water Permeability Test	• Ability to exclude the aneurysm • Testing of the modularity of the endovascular system	Water permeability of the Zenith was determined to be 165.0±109.7 (ml/cm^2/min) using the methods defined in ANSI/AAMI VP:20 – 1994 using 9 samples containing sutures. Results of this test demonstrate that the addition of sutures, during Zenith manufacturing, does not significantly increase the mean permeability of the Zenith above that of the virgin graft material. Zenith samples met the acceptance criterion for this test.
Graft to Stent Attachment Strength Test (attaching suprarenal stent and body stents to graft)	• Durability and integrity of the implanted device	Mean attachment strength of 27 test sample sutures was determined to range between 4.98 and 6.15 lbf which is more than twice the acceptance criterion for attachment strength. Results indicate that detachment of the graft material from the Z-stents due to inadequate graft to stent attachment strength is unlikely.
Kink Radius Test	• Ability to accurately deploy • Fixation effectiveness of the implant • Patency of the implant	The radius at which component kinking occurs was measured for a total of 90 test samples. Acceptance criteria for the main body components are based upon the anatomical restrictions established for angulation between the aortic neck and the longitudinal axis of the aneurysm. Kink radius test results demonstrate the Zenith is expected to resist kinking when implanted within aortas having a degree of angulation ≤ 60°.
Migration Resistance Test	• Fixation effectiveness of the implant • Testing of the modularity of the endovascular system	Forces acting to cause migration *in vivo* were estimated using analytical and CFD methods. Migration resistance of the main body, ipsilateral leg, contralateral leg, main body extension, iliac leg extension, and occluder were compared to these estimates and found to meet the acceptance criteria established for this test. Based upon these results, component migration appears unlikely.

9.3. Shelf Life Testing

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

9.4. Animal Studies

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

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

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

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

10. Summary of Clinical Studies

10.1. Objectives

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

10.2. Zenith® AAA Endovascular Graft with the H&L-B One-Shot™ Introduction System Study Design

The clinical study was a multicenter, concurrently controlled study comparing standard risk endovascular patients having anatomy suitable for the Zenith® AAA Endovascular Graft with the H&L-B One-Shot™ Introduction System to a control group comprised of

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standard risk surgical patients. Two additional endovascular treatment groups, one which allowed high medical risk patients to be treated with the Zenith® AAA Endovascular Graft with the H&L-B One-Shot™ Introduction System , and the other a roll-in treatment group of initial cases. Fifteen centers enrolled 200 standard risk, 80 surgical control, 100 high risk, and 52 roll-in patients. Clinical and imaging follow-up were scheduled for post-procedure and 1 month, 6 months, 12 months, and annually thereafter. Patient follow-up and accountability at 1 month, 12 months, and 24 months are presented in Table 10.2-2 as these were the primary data analysis time points. Data provided in this summary are based on findings from an independent core lab that reviewed CT scans, abdominal x-rays, and ultrasound scans to assess aneurysm changes, device position and integrity, and endoleaks.

Table 10.2-2. Patient follow-up and accountability: standard risk and surgical patients

Treatment	Zenith Standard Risk			Surgical Standard Risk		
Interval	1 mo.	12 mo.	24 mo.	1 mo.	12 mo.	24 mo.
No Device	1	1[2]	1[2]	0	0	n/a
Conversion to Open Repair	0	2[2]	2[2]	n/a	n/a	n/a
Expired	1	7	17	2	3	n/a
Withdrawn/Lost to Follow-up	0	0	2	0	4	n/a
Available	198	190	178	78	73	n/a
Site CT Imaging	191	168	110	69	58	n/a
Core Lab CT Imaging	190	165	99	69	59	n/a
Site KUB Imaging	179	153	108	n/a	n/a	n/a
Core Lab KUB Imaging	178	149	93	n/a	n/a	n/a
Site Evaluated for Endoleak	187	163	107	n/a	n/a	n/a
Core Lab Evaluated for Endoleak	161	148	92	n/a	n/a	n/a
Site Evaluated for Aneurysm Enlargement	n/a	149	104	n/a	n/a	n/a
Core Lab Evaluated for Aneurysm Enlargement	n/a	151	94	n/a	n/a	n/a

1 Data analysis sample size varies for each of the timepoints above and in the following tables. This variability is due to patient availability for follow-up, as well as, quantity and quality of images available from specific timepoints for evaluation. For example, the number and quality of images available for evaluation of endoleak at 12 months is different than the number and quality of images available at 24 months due to variation in the number of image exams performed, the number of images provided from the clinical site to the Core Lab, and/or the number of images with acceptable evaluation quality. Totals at time points are not cumulative, unless otherwise noted.

2 Totals at time points are cumulative.

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10.3. Patient Demographics

Tables 10.3-1 and 10.3-2 tabulate patient demographics and comorbid conditions and present the distribution of initial aneurysm diameters for the four study groups.

Table 10.3-1. Patient Demographics and Comorbid Conditions

Item	Zenith Standard Risk	Surgical Standard Risk	*P* value	Zenith High Risk	Zenith Roll-in
Age (years)	71 ± 7	69 ± 7	.03	77 ± 7	74 ± 8
Gender male	94% (187/200)	89% (71/80)	.22	92% (92/100)	90% (47/52)
Current medical conditions					
Peripheral vasc. disease	16% (31/195)	25% (19/76)	.12	24% (23/96)	9.6% (5/52)
Hypertension	64% (127/200)	83% (65/78)	.001	68% (67/99)	67% (35/52)
Renal failure	0.0% (0/197)	0.0% (0/79)	>.99	5.2% (5/97)	1.9% (1/52)
COPD	20% (39/199)	18% (14/78)	.87	34% (33/98)	22% (11/51)
Thromboembolic event	4.5% (9/199)	7.7% (6/78)	.38	7.1% (7/99)	1.9% (1/52)
Liver disease	2.1% (4/192)	5.1% (4/79)	.24	1.0% (1/99)	1.9% (1/52)
Diabetes Mellitus	12% (24/199)	15% (12/79)	.55	17% (17/99)	14% (7/51)
Insulin-dependent	17% (4/24)	8.3% (1/12)	.65	24% (4/17)	43% (3/7)
Previous medical conditions					
MI	39% (74/192)	29% (23/80)	.13	35% (34/98)	35% (18/52)
Congestive heart failure	5.0% (10/199)	12% (9/78)	.07	16% (16/100)	10% (5/50)
Angina	49% (98/198)	39% (31/79)	.14	45% (44/98)	44% (23/52)
Arrhythmia	20% (40/197)	22% (17/78)	.87	28% (27/98)	24% (12/51)
Cerebrovascular disease	9.5% (19/199)	16% (13/79)	.14	20% (20/99)	9.8% (5/51)
Systemic infection	1.0% (2/196)	0.0% (0/78)	>.99	3.1% (3/97)	0.0% (0/49)
Cancer	22% (43/200)	19% (15/80)	.74	31% (31/99)	29% (15/51)
Family history of aneurysmal disease	16% (24/150)	27% (17/63)	.09	14% (11/77)	26% (10/38)
Previous surgery at site	10% (20/200)	15% (12/79)	.22	10% (10/99)	14% (7/51)
Previous radiation at site	0.5% (1/197)	0.0% (0/79)	>.99	2.0% (2/100)	2.0% (1/51)
Excessive alcohol use	3.6% (7/193)	10% (8/77)	.04	3.1% (3/96)	4.0% (2/50)
Tobacco use			.03		
Never smoked	10% (20/193)	5.0% (4/80)		14% (13/96)	24% (12/49)
Past smoker	69% (133/193)	60% (48/80)		69% (66/96)	57% (28/49)
Still smokes	21% (40/193)	35% (28/80)		18% (17/96)	18% (9/49)

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Table 10.3-2. Aneurysm Diameter Distribution

Diameter Range	Zenith Standard Risk	Surgical Standard Risk	Zenith High Risk	Zenith Roll-in
< 30 mm	0.0% (0/199)	0.0% (0/78)	0.0% (0/100)	0.0% (0/52)
30-39 mm	0.5% (1/199)	0.0% (0/78)	1.0% (1/100)	0.0% (0/52)
40-49 mm	23% (45/199)	7.7% (6/78)	15% (15/100)	13% (7/52)
50-59 mm	48% (95/199)	33% (26/78)	47% (47/100)	40% (21/52)
60-69 mm	24% (47/199)	29% (23/78)	27% (27/100)	42% (22/52)
70-79 mm	3.0% (6/199)	21% (16/78)	5.0% (5/100)	1.9% (1/52)
80-89 mm	2.5% (5/199)	6.4% (5/78)	1.0% (1/100)	0.0% (0/52)
≥ 90 mm	0.0% (0/199)	2.6% (2/78)	1.0% (1/100)	0.0% (0/52)

Aneurysm diameter distribution was not assessed in three high and one roll-in patient.

10.4. Results

10.4.1. Devices Implanted

Table 10.4.1-1 lists the devices implanted in the U.S. pivotal trial. Devices were implanted intraoperatively unless otherwise noted.

Table 10.4.1-1. Devices implanted

Item	Zenith Standard Risk	Zenith High Risk	Zenith Roll-in
Main body and legs	99.5% (199/200)*	100% (100/100)[1]	100% (52/52)
Main body extension[2]	1.5% (3/199)	1% (1/100)	5.8% (3/52)
Ipsilateral iliac leg extension[3,5]	9.5% (19/199)	11% (11/100)	0% (0/52)
Contralateral iliac leg extension[4,5]	11% (21/199)	11% (11/100)	13.5% (7/52)
Converter	0.5% (1/199)**	0% (0/100)	0% (0/52)
Occluder	0% (0/199)	0% (0/100)	0% (0/52)

* One standard risk patient did not receive a device due to tortuosity and calcification of the access vessel.

** Converter was used without occluder

[1] One device was custom.

[2] Two standard risk and one high risk patient received main body extensions post-procedure; one standard risk patient received two main body extensions.

[3] Two standard risk and one high risk patient received ipsilateral leg extensions post-procedure.

[4] Four standard risk, two high risk and one roll-in patient received contralateral leg extensions post-procedure.

[5] Three standard risk and three high risk patients received both ipsilateral and contralateral extensions during the procedure; one standard risk received both ipsilateral and contralateral extensions post-procedure.

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10.4.2. Primary Results

Measures of mortality, rupture, conversion and adverse events are presented in Table 10.4.2-1. and Figures 10.4.2-1 and 10.4.2-2. Where available, 24-month data are provided. Control patients were not followed beyond 12 months and some data have not yet been adjudicated beyond 12 months. Therefore, some results are presented to 12 months while other results are presented to 24 months in this section. Figures 10.4.2-1 and 10.4.2-2 depict all-cause and AAA-related survival, respectively. An independent clinical events committee adjudicated all deaths for possible relationship to aneurysm repair. All early deaths (0-30 days) were considered AAA-related. Deaths after 30 days were considered AAA-related if AAA disease or device involvement was confirmed. Zenith® AAA Endovascular Graft patients exhibited no significant differences between males and females for survival and freedom from major adverse events. (Error bars in Figures 10.4.2-1, 10.4.2-2 and 10.4.2-3 represent 95% confidence limits.) Table 10.4.2-3. presents success measures.

Table 10.4.2-1. Principal safety results

Item	Zenith Standard Risk[1]	Surgical Standard Risk	*P* value	Zenith High Risk	Zenith Roll-in
All death (0-30 days)[2]	0.5% (1/199)	2.5% (2/80)	.20	2.0% (2/100)	1.9% (1/52)
All death (31-365 days)[2, 3]	3.0% (6/198)	1.3% (1/78)	.68	7.1% (7/98)	9.8% (5/51)
AAA-related	0.0% (0/198)	1.3% (1/78)	.29	3.1% (3/98)	0.0% (0/51)
Non-AAA-related	3.0% (6/198)	0.0% (0/78)	.19	4.1% (4/98)	9.8% (5/51)
All death (0-365 days)[2, 3, 4]	3.5% (7/199)	3.8% (3/80)	>.99	9.0% (9/100)	11.5% (6/52)
AAA-related	0.5% (1/199)	3.8% (3/80)	.07	5.0% (5/100)	1.9% (1/52)
Non-AAA-related	3.0% (6/199)	0.0% (0/80)	.19	4.0% (4/100)	9.6% (5/52)
Rupture (0-30 days)	0.0% (0/199)	n/a	n/a	0.0% (0/100)	0.0% (0/52)
Rupture (31-365 days)	0.0% (0/198)	n/a	n/a	1.0% (1/98)	0.0% (0/51)
Rupture (0-365 days)	0.0% (0/199)	n/a	n/a	1.0% (1/100)	0.0% (0/52)
Conversion (0-30 days)	0.0% (0/199)	n/a	n/a	0.0% (0/100)	0.0% (0/52)
Conversion (31-365 days)[5]	1.0% (2/199)	n/a	n/a	1.0% (1/100)	0.0% (0/52)
Conversion (0-365 days)[5]	1.0% (2/199)	n/a	n/a	1.0% (1/100)	0.0% (0/52)
Adverse Events (0-30 days)[6]	20% (40/200)	43% (34/80)	<.001	32% (32/100)	27% (14/52)
Adverse Events (31-365 days)[6]	8.6%(17/199)	14% (11/78)	.25	21% (21/98)	14% (7/51)
Adverse Events (0-365 days)[6]	25% (49/200)	51% (41/80)	<.001	45% (45/100)	38% (20/52)

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

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

3 Of the deaths (31-365 days), four were considered AAA related: 1 surgical (septic shock from ischemic colitis) and 3 high risk (pancreatitis with renal failure and sepsis, hemorrhage from upper abdominal aneurysm [not treated AAA], and multiple system failure).

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

5 Standard risk patients underwent conversions due to a persistent, proximal Type I endoleak and a new suprarenal aortic aneurysm. Three surgical patients had massive hemorrhages, of which 2 required re-operation and one died.

6 Adverse events included in the morbidity index

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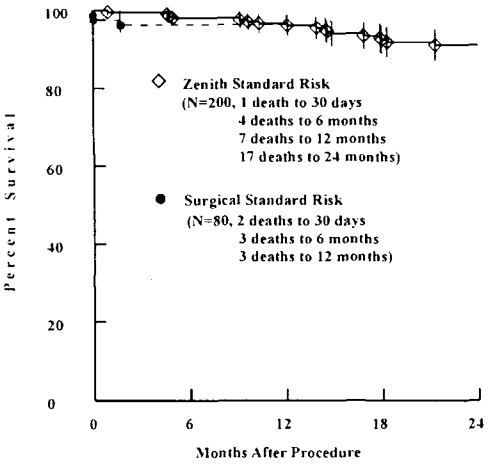
Figure 10.4.2-1 presents all-cause survival to 24 months. The accompanying table presents the Kaplan-Meier analysis at 1, 6, 12, and 24 months.

Figure 10.4.2-1. Survival at 24 Months

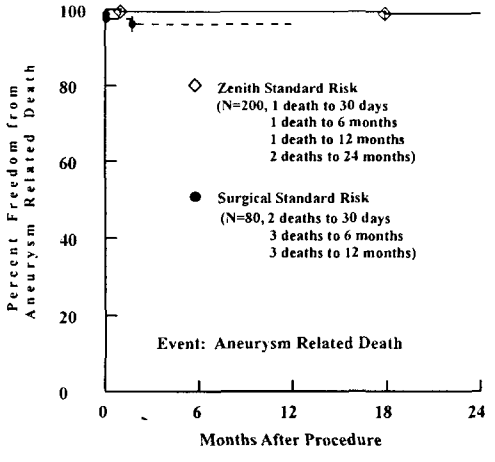


	1 month		6 months		12 months		24 months	
	n	% survival	n	% survival	n	% survival	n	% survival
Zenith Standard Risk	198	99.5	194	98.0	190	96.5	97	90.9
Surgical Standard Risk	78	97.5	73	96.2	67	96.2	n/a	n/a

n= patients alive and available for follow-up at the end of the interval
P=.81

Figure 10.4.2-2 presents AAA-related survival (determined by Clinical Events Committee) to 24 months. The accompanying table presents the Kaplan-Meier analysis at 1, 6, 12, and 24 months.

Figure 10.4.2-2. AAA-related Survival at 24 Months



	1 month		6 months		12 months		24 months	
	n	% survival	n	% survival	n	% survival	n	% survival
Zenith Standard Risk	198	99.5	194	99.5	190	99.5	97	99.0
Surgical Standard Risk	78	97.5	73	96.2	67	96.2	n/a	n/a

n= patients alive and available for follow-up at the end of the interval
P=.04

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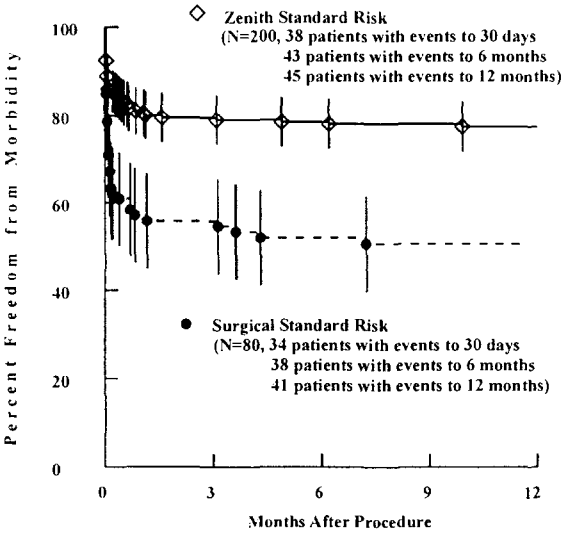
Table 10.4.2-3. Success Measures

Item	Zenith Standard Risk	Surgical Standard Risk	Zenith High Risk	Zenith Roll-In
Technical success[1]	99.5% (199/200)	98.8% (79/80)	100% (100/100)	100% (52/52)
Procedural success at 30 days[2]	95.1% (155/163)	88% (60/68)	86% (70/81)	91% (30/33)
Treatment success at 12 months[3]	89% (122/137)	85% (52/61)	70% (44/63)	87% (26/30)

[1]Patent graft following deployment.
[2]Technical success with no major complications, patent graft and no Type I or Type III endoleaks at 30 days.
[3]Procedural success extended to 12 months with no aneurysm enlargement (>5 mm).

Figure 10.4.2-3 presents freedom from morbidity (events in the morbidity index). The accompanying table presents the Kaplan-Meier analysis at 1, 6, and 12 months.

Figure 10.4.2-3. Freedom from Morbidity (0-365 days)



	1 month		6 months		12 months	
	n	%	n	%	n	% survival
Zenith Standard Risk	162	81.0	154	78.5	133	77.4
Surgical Standard Risk	45	57.1	39	52.0	33	47.8

n= patients alive and free of morbidity at the end of the interval
P<.001

Tables 10.4.2-4 through 10.4.2-7 describe results of the Zenith® AAA Endovascular Graft subjects as reported by the Core Lab. Device performance factors analyzed by the Core Lab include device integrity (Table 10.4.2-4), device patency (Table 10.4.2-5), migration (Table 10.4.2-6), and limb separation (Table 10.4.2-7).

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Table 10.4.2-4. Abdominal Radiographic Findings - Device Integrity

Item		Zenith Standard Risk		Zenith High Risk		Zenith Roll-In	
Stent Fractures[1]	Pre-discharge	0.0%	(0/172)	0.0%	(0/81)	0.0%	(0/39)
	30 day	0.0%	(0/172)	0.0%	(0/83)	0.0%	(0/43)
	6 month	0.0%	(0/166)	0.0%	(0/78)	0.0%	(0/35)
	12 month	0.0%	(0/148)	0.0%	(0/60)	0.0%	(0/28)
	24 month	0.0%	(0/93)	0.0%	(0/42)	0.0%	(0/19)
Barb Separation[2]	Pre-discharge	0.0%	(0/176)	0.0%	(0/86)	0.0%	(0/39)
	30 day	0.0%	(0/178)	0.0%	(0/86)	0.0%	(0/43)
	6 month	1.2%	(2/167)	2.5%	(2/80)	0.0%	(0/35)
	12 month	2.0%	(3/149)	1.7%	(1/60)	0.0%	(0/28)
	24 month	1.1%	(1/93)	0.0%	(0/42)	0.0%	(0/19)
Graft material rupture	Pre-discharge	0.0%	(0/176)	0.0%	(0/86)	0.0%	(0/39)
	30 day	0.0%	(0/178)	0.0%	(0/86)	0.0%	(0/43)
	6 month	0.0%	(0/167)	0.0%	(0/80)	0.0%	(0/35)
	12 month	0.0%	(0/149)	0.0%	(0/60)	0.0%	(0/28)
	24 month	0.0%	(0/93)	0.0%	(0/42)	0.0%	(0/19)

[1]Stent fracture percentages are for main body. There were also no right iliac leg, left iliac leg, occluder, converter, left iliac extension, right iliac extension, or main body extension fractures observed by the core lab.
[2]Patients with separation of 1 or 2 barbs (of 10 or 12 total); no adverse clinical sequelae.

Table 10.4.2-5. CT Findings – Graft Patency

Item		Zenith Standard Risk		Zenith High Risk		Zenith Roll-In	
Graft patency	30 day	100%	(185/185)	99%	(85/86)	100%	(47/47)
	6 month	99%	(183/184)	100%	(74/74)	100%	(39/39)
	12 month	99%	(153/155)	100%	(62/62)	100%	(30/30)
	24 month	100%	(96/96)	100%	(33/33)	100%	(25/25)

Table 10.4.2-6. CT Findings – Graft (Main Body) Migration

Item	Zenith Standard Risk		Zenith High Risk		Zenith Roll-In	
Graft migration (>5 mm) at 12 months with clinical sequelae[1] or intervention	0.0%	(0/162)	0.0%	(0/71)	0.0%	(0/34)
without clinical sequelae[1] or intervention	2.5%	(4/162)	2.8%	(2/71)	0.0%	(0/34)
Graft migration (>10 mm)	0.0%	(0/162)	0.0%	(0/71)	0.0%	(0/34)

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

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Table 10.4.2-7. Abdominal Radiograph Findings – Limb Separation

Item		Zenith Standard Risk		Zenith High Risk		Zenith Roll-In	
Limb separation	Pre-discharge	0.0%	(0/176)	0.0%	(0/86)	0.0%	(0/39)
	30 day	0.0%	(0/178)	0.0%	(0/86)	0.0%	(0/43)
	6 month	0.0%	(0/167)	0.0%	(0/80)	0.0%	(0/35)
	12 month	0.0%	(0/149)	0.0%	(0/60)	0.0%	(0/28)
	24 month	0.0%	(0/93)	0.0%	(0/42)	0.0%	(0/19)

Table 10.4.2-8 presents the incidence of endoleaks by evaluation interval, as identified by the Core Lab for the standard risk, high risk, and roll-in patients, respectively.

Table 10.4.2-8. Endoleaks (all types, new and persistent)

	Zenith Standard Risk	Zenith High Risk	Zenith Roll-in
Endoleaks			
Pre-discharge	15% (23/153)	14% (11/78)	12% (3/26)
30 day[1]	9.9% (16/161)	12% (9/75)	6.3% (2/32)
6 month[1]	8.7% (15/172)	11% (8/70)	8.6% (3/35)
12 month[1]	7.4% (11/148)	8.8% (5/57)	3.4% (1/29)

[1]Includes both persistent endoleaks and new observations

Tables 10.4.2-9 – 10.4.2-11 present the incidence of first occurrence of an endoleak according to evaluation interval, as identified by the Core Lab at or before the 30 day, 6 month, and 12 month exams for the standard risk, high risk, and roll-in patients, respectively. The number of patients who are leak-free thereafter is also given.

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Table 10.4.2-9. First occurrence of endoleak[1] for standard risk patients

Item	To One Month Exam N=179			Six Month Exam N=172			Twelve Month Exam[3] N=148		
	%	Endo-leak[1]	Leak-free there-after[2]	%	Endo-leak[1]	Leak-free there-after[2]	%	Endo-leak[1]	Leak-free there-after[2]
Endoleaks	17	31	17	2.3	4	3	3.4	5	2
Proximal Type I	2.8	5	4	0.0	0	0	0.0	0	0
Distal Type I	1.7	3	1	0.0	0	0	0.7	1	1
Type II	9.5	17	9	2.3	4	3	1.4	2	1
Type III	1.1	2	2	0.0	0	0	0.7	1	0
Type IV	0.0	0	0	0.0	0	0	0.0	0	0
Multiple	1.1	2	1	0.0	0	0	0.0	0	0
Unknown	1.1	2	0	0.0	0	0	0.7	1	0

[1]Identified by Core Lab
[2]Subsequent endoleaks may have been of difference type than original
[3]Only 2 patients had new endoleaks after 12 months; follow-up after 24 months not available

Table 10.4.2-10. First occurrence of endoleak[1] for high risk patients

Item	To One Month Exam N=88			Six Month Exam N=70			Twelve Month Exam[3] N=57		
	%	Endo-leak[1]	Leak-free there-after[2]	%	Endo-leak[1]	Leak-free there-after[2]	%	Endo-leak[1]	Leak-free there-after[2]
Endoleaks	18	16	6	2.9	2	0	3.5	2	1
Proximal Type I	2.3	2	1	0.0	0	0	0	0	0
Distal Type I	1.1	1	1	0.0	0	0	0	0	0
Type II	9.1	8	3	1.4	1	0	1.8	1	0
Type III	0.0	0.0	0	1.4	1	0	1.8	1	1
Type IV	0.0	0.0	0	0.0	0	0	0.0	0	0
Multiple	4.5	4	0	0.0	0	0	0.0	0	0
Unknown	1.1	1	1	0.0	0	0	0.0	0	0

[1]Identified by Core Lab
[2]Subsequent endoleaks may have been of difference type than original
[3]No endoleaks after 12 months; follow-up after 24 months not available

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Table 10.4.2-11. First occurrence of endoleak[1] for roll-in patients

Item	To One Month Exam N=36			Six Month Exam N=35			Twelve Month Exam[3] N=29		
	%	Endo-leak[1]	Leak-free there-after[2]	%	Endo-leak[1]	Leak-free there-after[2]	%	Endo-leak[1]	Leak-free there-after[2]
Endoleaks	11	4	2	2.9	1	0	0.0	0	0
Proximal Type I	0.0	0	0	0.0	0	0	0.0	0	0
Distal Type I	0.0	0	0	0.0	0	0	0.0	0	0
Type II	5.6	2	1	2.9	1	0	0.0	0	0
Type III	2.8	1	0	0.0	0	0	0.0	0	0
Type IV	0.0	0	0	0.0	0	0	0.0	0	0
Multiple	0.0	0	0	0.0	0	0	0.0	0	0
Unknown	2.8	1	1	0.0	0	0	0.0	0	0

[1]Identified by Core Lab
[2]Subsequent endoleaks may have been of difference type than original
[3]No endoleaks after 12 months; follow-up after 24 months not available

Tables 10.4.2-12 – 10.4.2-14 present the change in aneurysm diameter for the endovascular patients, as identified by the Core Lab. Table 10.4.2-12 presents maximum aneurysm diameter change by interval. Tables 10.4.2-13 and 10.4.2-14 present aneurysm change and endoleak at 12 and 24 months respectively.

Table 10.4.2-12. Change in Maximum Aneurysm Diameter by Interval

Item		Zenith Standard Risk		Zenith High Risk		Zenith Roll-In	
From pre-discharge							
30-day	Decrease >5 mm	1.7%	(3/180)	4.8%	(4/84)	0.0%	(0/40)
	Unchanged	97%	(174/180)	94%	(79/84)	97.5%	(39/40)
	Increase >5 mm	1.7%	(3/180)	1.2%	(1/84)	2.5%	(1/40)
Change from pre-discharge							
6-month	Decrease >5 mm	36%	(63/173)	41%	(30/73)	49%	(18/37)
	Unchanged	62%	(108/173)	59%	(43/73)	51%	(19/37)
	Increase >5 mm	1.2%	(2/173)	0.0%	(0/73)	0.0%	(0/37)
Change from pre-discharge							
12-month	Decrease >5 mm	68%	(102/151)	63%	(39/62)	67%	(20/30)
	Unchanged	31%	(47/151)	35%	(22/62)	33%	(10/30)
	Increase >5 mm	1.3%	(2/151)	1.6%	(1/62)	0.0%	(0/30)
Change from pre-discharge							
24-month	Decrease >5 mm	78%	(74/94)	75%	(27/36)	71%	(17/24)
	Unchanged	19%	(18/94)	25%	(9/36)	25%	(6/24)
	Increase >5 mm	2.1%	(2/94)	0.0%	(0/36)	4.2%	(1/24)

Only includes subjects with interpretable films and measurements of aneurysm change

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Table 10.4.2-13. Change in Aneurysm Size and Endoleak at 12 Months

Item	Zenith Standard Risk N=140			Zenith High Risk N=53			Zenith Roll-In N=27		
Aneurysm size change from pre-discharge to 12 months		Endoleak			Endoleak			Endoleak	
	N	N	%	N	N	%	N	N	%
Decrease >5 mm	96	3	3	35	3	9	20	0	0
Unchanged	42	8	19	17	2	12	7	1	14
Increase >5 mm	2	0	0	1	0	0	0	0	0

Table 10.4.2-14. Change in Aneurysm Size and Endoleak at 24 Months

Item	Zenith Standard Risk N=90			Zenith High Risk N=31			Zenith Roll-In N=21		
Aneurysm size change from pre-discharge to 24 months		Endoleak			Endoleak			Endoleak	
	N	N	%	N	N	%	N	N	%
Decrease >5 mm	71	3	4	24	1	4	16	0	0
Unchanged	18	1	6	7	3	43	5	0	0
Increase >5 mm	1	1	100	0	0	0	0	0	0

AAA-related secondary interventions within the first year were performed in 11% of the Zenith Standard Risk, 13% Zenith High Risk and 5.8% Zenith Roll-in subjects as shown in Table 10.4.2-15. Greater than 50% of the secondary interventions involved catheterization to treat an endoleak. AAA-related secondary interventions within the second year were performed in 4.2% of the Zenith Standard Risk, 2.2% Zenith High Risk and 2.3% Zenith Roll-in subjects as shown in Table 10.4.2-16.

Table 10.4.2-15. Secondary Interventions (to 12 Months)

Intervention	Zenith Standard Risk N=199		Zenith High Risk N=100		Zenith Roll-In N=52	
	N	%	N	%	N	%
Conversion to Open Repair	2	1	1	1	0	0
Subjects with ≥1 Intervention	21	11	13	13	3	5.8
Treat an Endoleak						
Embolization	5	2.5	3	3	1	2
Ancillary Component	6	3	4	4	1	2
Stent	1	0.5	0	0	0	0
Angioplasty	0	0	1	1	0	0
Treat an Aneurysm Increase Embolization	0	0	0	0	0	0
Treat a Limb Occlusion	1	0.5	3	3	1	2
Treat a Limb Stenosis	1	0.5	0	0	0	0
Treat a Renal Artery	5	2.5	0	0	0	0
Treat Infra-inguinal Ischemia	1	0.5	1	1	0	0
Treat Multiple Events	1	0.5	1	1	0	0

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Table 10.4.2-16. Secondary Interventions (>12 to 24 Months)

Intervention	Zenith Standard Risk N=190		Zenith High Risk N=90		Zenith Roll-In N=44	
	N	%	N	%	N	%
Conversion to Open Repair	1	0.5	1	1.1	0	0.0
Subjects with ≥1 Intervention	8	4.2	2	2.2	1	2.3
Treat an Endoleak						
Embolization	3[1]	1.6	0	0	1[2]	2.3
Ancillary Component	1	0.5	0	0	0	0
Stent	0	0	1	1.1	0	0
Angioplasty	0	0	0	0	0	0
Treat an Aneurysm Increase Embolization	1	0.5	0	0	1[2]	2.3
Treat a Limb Occlusion	1	0.5	0	0	0	0
Treat a Limb Stenosis	0	0	0	0	0	0
Treat a Renal Artery	0	0	1	1.1	0	0
Treat Infra-inguinal ischemia	1	0.5	0	0	0	0
Treat Multiple Events	1	0.5	0	0	0	0

[1] Patient also received ancillary component
[2] Patient underwent intervention to treat aneurysm increase and endoleak

10.4.3. Secondary Outcome Measures

As described in Table 10.4.3-1, treatment of AAA with the Zenith® AAA Endovascular Graft with the H&L-B One-Shot™ Introduction System compared to the surgical control group demonstrated significant benefits in recovery and quality of life measures. Secondary measures included anesthesia time, procedure time, blood bank products received and blood loss. In addition, clinical utility was assessed through a number of clinical measures obtained before hospital discharge, including days in the ICU, days to discharge, days to oral fluids, days to normal diet, days to normal bowel function, days to ambulation, hours of intubation, and maximum core body temperature.

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Table 10.4.3-1. Secondary Outcomes by Treatment Group

Item	Zenith Standard Risk	Surgical Standard Risk	*P* value	Zenith High Risk	Zenith Roll-in
Anesthesia time (min)	221.6 ± 67.3	304.5 ± 102.7	<.001	218.9 ± 69.6	213.9 ± 57.7
Procedure time (min)	153.2 ± 56.3	238.7 ± 92.2	<.001	153.5 ± 58.6	155.9 ± 43.2
Blood bank products received	5.0% (10/200)	84% (67/80)	<.001	12% (12/100)	3.8% (2/52)
Blood loss (cc)	299 ± 324	1676 ± 1676	<.001	356 ± 514	265 ± 226
Days in ICU	0.4 ± 0.9	3.4 ± 4.6	<.001	0.5 ± 1.2	0.5 ± 0.9
Days to discharge	2.6 ± 1.7	8.8 ± 5.6	<.001	3.0 ± 2.8	2.7 ± 1.5
Days to oral fluids	0.5 ± 0.8	3.9 ± 2.5	<.001	0.5 ± 0.6	0.7 ± 0.5
Days to normal diet	1.3 ± 1.2	6.6 ± 4.9	<.001	1.3 ± 0.8	1.1 ± 0.7
Days to normal bowel function	2.6 ± 1.4	4.2 ± 2.1	<.001	2.6 ± 1.5	2.0 ± 1.2
Days to ambulation	1.2 ± 0.7	3.5 ± 3.4	<.001	1.2 ± 0.7	1.2 ± 0.6
Hours of intubation	1.9 ± 2.2	11.7 ± 13.6	<.001	1.2 ± 1.7	2.6 ± 4.6
Maximum temperature	101.1 ± 1.3	100.7 ± 1.2	.06	100.8 ± 1.1	101.0 ± 1.2

10.4.4. Evaluation of Gender Bias

The occurrence of AAA disease is known to be higher in men than women and the ratio of men to women enrolled in this study reflects the general population. In order to more carefully evaluate possible gender based differences in outcomes of treatment with the Zenith® AAA Endovascular Graft with the H&L-B One-Shot™ Introduction System, Cook requested and was granted approval to establish a registry for the treatment of AAA disease in women with standard medical risk. Measures of survival, 30-day morbidity, conversion and death using these combined data sets are presented in Table 10.4.4-1 through Table 10.4.4-3.

Zenith® AAA Endovascular Graft subjects exhibited no significant differences between males and females for survival and 30-day morbidity (31 measures). No gender based differences were identified in AAA-related mortality after treatment with the Zenith® AAA Endovascular Graft with the H&L-B One-Shot™ Introduction System.

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Table 10.4.4-1. Kaplan-Meier AAA-related survival rates by gender: All Zenith pivotal + female, and surgical

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

Table 10.4.4-2. 30-day morbidity (31 measures) by gender: All Zenith pivotal + female, and surgical

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

Table 10.4.4-3. Conversion and death by gender: All Zenith pivotal + female, and surgical

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

[1]One patient did not receive a device

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

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11. Conclusions Drawn from Studies

The Zenith® AAA Endovascular Graft with the H&L-B One-Shot™ Introduction System has undergone pre-clinical testing and clinical evaluation in a prospective, multicenter U.S. trial. Study results met the five study hypotheses of a reduced 30-day morbidity, equivalent 30-day and 12-month survival rates, equivalent 12-month treatment success, and improved clinical utility for Zenith patients as compared to surgical controls. The additional clinical benefits associated with the Zenith® AAA Endovascular Graft with the H&L-B One-Shot™ Introduction System compared to open surgical repair include reducing the duration of intubation, reducing the number of days spent in the hospital, reducing the number of days spent in the ICU, reducing the number of days to the resumption of oral fluids, diet, and normal bowel functions, reducing the number of days to ambulation, reducing anesthesia time, reducing procedural time, reducing procedural blood loss and the need for blood products. Most aneurysms (68%) had decreased in size or remained stable (31%) at 12 months. Very low incidence of aneurysm rupture and conversion to open repair were observed. Adequate device integrity was also demonstrated, although isolated observations illustrate the importance of periodic imaging follow-up.

12. Panel Recommendation

The Zenith® AAA Endovascular Graft with the H&L-B One-Shot™ Introduction System was presented to the Circulatory System Device Panel on April 10, 2003. The Panel recommended approving the device with conditions. The Panel's conditions included revisions to the intended use of the device, removing references to isolated iliac aneurysm from the indications for use, stressing the importance in the labeling of lifelong clinical follow-up of patients following endograft placement, and a post approval study as outlined in the PMA for follow-up of patients in the pivotal study for 5 years. The Panel also recommended modifications to the device labeling.

13. FDA Decision

FDA reviewed portions of the premarket application approval (PMA) application under the modular PMA process (M010038). All of the modules were incorporated into the review of the PMA (P020018).

FDA concurred with the Circulatory System Device Panel recommendations of April 10, 2003. To address these conditions, Cook Incorporated agreed to conduct a post approval study in order to gather 5-year follow-up data on patients enrolled in the pivotal study

and to revise the labeling to address the concerns raised by the Panel, which was reviewed by FDA and found acceptable.

The sponsor also agreed to provide a clinical update to physicians annually on the performance of the device due to the number of problems which historically have occurred with these types of device. This condition is consistent with conditions of approval issued by FDA for other marketed endovascular graft devices. During December 3-10, 2002, the sponsor's manufacturing facilities were inspected and found to be in compliance with the Quality System Regulation (21 CFR 820).

FDA issued an approval order for P020018 on:	May 23, 2003

14. Approval Specifications

Directions for Use:	See labeling
Hazards to Health from Use of the Device:	See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the Labeling
Post-approval Requirements, Restrictions:	See approval order

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