Zenith® AAA Endovascular Graft Annual Clinical Update

Abstract

On May 23, 2003, the Zenith® AAA Endovascular Graft received FDA approval based upon results of the U.S. clinical study, which included 351 patients. These data provided a prospective evaluation of clinical and radiographic performance related to safety and effectiveness. The study examined freedom from mortality, rupture, and open surgical conversion. In addition, the study examined aneurysm size change, rates of device migration, endoleak, patency, and device integrity. The long-term results from those patients who agreed to participate beyond two years continue to support the safety and effectiveness of the device and the need for annual clinical and imaging follow-up for detection of disease progression, aneurysm growth, endoleak, loss of patency, and device integrity.

Device Description

The Zenith® AAA Endovascular Graft is a modular system of primary and ancillary components that combine to form multiple endovascular graft configurations. All components in this system use self-expanding Cook-Z® stents sewn to traditional, currently marketed Dacron® graft material with currently marketed suture material. The Zenith® AAA Endovascular Graft has a bare suprarenal stent at the proximal end of the graft containing 10 or 12 barbs designed for additional proximal fixation to resist migration. Distal to the bare suprarenal stent, a self-expanding stent inside the proximal end of the graft material is designed to provide a seal with the aorta to minimize type I endoleak. Radiopaque markers are placed along the top of the graft to enable accurate placement below the renal arteries. Additional radiopaque markers along the contralateral limb guide rotational alignment to facilitate cannulation of the contralateral limb. The main body is long and designed to bifurcate just above the aortic bifurcation to aid in stability. The iliac legs taper or expand to accommodate a wide range of iliac diameters. The introduction system has a top cap and trigger wires designed for precise, controlled placement of the endograft. Knowledge of the device provides a helpful framework within which to understand the clinical results reported in the following six sections.

Introduction

This report is a clinical update on the performance of the Zenith® AAA Endovascular Graft. This report is intended to provide up-to-date quantitative performance data on the clinical use of this device. The summary of clinical data (Section I) presents the results through five years from the U.S. clinical study of the Zenith® AAA Endovascular Graft – this study is complete and the follow-up data are unchanged from the previous clinical update, but are being reproduced for completeness. Data presented include the safety endpoints of freedom from mortality, freedom from rupture, and freedom from conversion to open repair. Also presented are the effectiveness endpoints of freedom from endoleak, freedom from aneurysm growth, freedom from device migration, and endograft patency. This section also includes a summary of Clinical Events Committee (CEC) confirmed device integrity events that have been observed by the core lab. The five-year results from the pivotal clinical study are positive. Importantly, the Zenith® AAA Endovascular Graft was not associated with migration > 10 mm and there were no unexplained cases of late aneurysm growth according to adjudicated core lab results from the pivotal study at five years.

Five-year results included Kaplan-Meier estimates for freedom from rupture (99.7%), freedom from conversion (97.8%), freedom from AAA-related mortality including all-cause mortality within 30 days of the procedure (98.9% for standard risk, 93.8% for high risk), and freedom from all-cause mortality (83.1% for standard risk, 57.8% for high risk). Aneurysm size was stable or decreased, changing the natural history of aneurysm disease in 91.0% of patients; aneurysm growth was observed only in association with endoleak (primarily type II) or graft infection. At five years, no proximal type I, III, or IV endoleaks were observed. Migration > 10 mm was 0%; migration > 5 mm was 4.9% through five years with no clinical sequelae and no secondary interventions for migration. No new cases of limb occlusion were detected between one and five years, overall. Prior to one year, 1.4% of patients received femoral bypasses for limb occlusion. No radiographic evidence of graft material rupture was noted and barb separation was noted in some patients, but was not clinically significant. Single stent fracture was identified in six patients without clinical sequelae. In three patients an extension was placed for graft-to-leg separation without sequelae and in one patient, a body extension with suprarenal stent was placed prophylactically for partial separation of the top stent (attachment design prior to commercial distribution). In a second patient, partial separation of the top stent (attachment design prior to commercial distribution) remained untreated. Of note, the suture attachment to the suprarenal stent was strengthened prior to market release. Annual imaging follow-up is recommended to detect progression of the disease and ensure aneurysm stabilization and device integrity.

Section I also presents results from physician experience with the 36 mm diameter Zenith Flex® AAA Endovascular Graft. Follow-up data collection is complete. Approval to add the 36 mm diameter Zenith Flex® AAA Endovascular Graft to the existing Zenith Flex® AAA Endovascular Graft product line was granted by the FDA on September 7, 2006. The product line was expanded to include 36 mm diameter sizes for use in the treatment of patients with AAA that have larger infrarenal neck diameters of up to 32 mm. The results presented in this report reiterate that the outcomes associated with clinical use of the 36 mm diameter Zenith Flex® AAA Endovascular Graft appear comparable to those of the pivotal clinical trial. In addition, these data provide confirmatory evidence that supports the continued safety and effectiveness of the 36 mm diameter Zenith Flex® AAA Endovascular Graft.

Section II reports commercial experience with the Zenith® AAA Endovascular Graft. A total of 159,200 bifurcated Zenith® AAA Endovascular Grafts have been distributed worldwide. Distribution outside of the U.S. over the last twelve years totals 87,826 bifurcated endografts. Since FDA approval on May 23, 2003, 275,895 components (e.g., main body components, iliac leg components, and ancillary components) comprising 71,372 Zenith® AAA Endovascular Grafts have been sold in the U.S. Also during this time period, 67 deaths within 30 days, 16 post procedural aneurysm ruptures and 118 open surgical conversions have been reported through the Company's complaint system in the U.S. Post-market surveillance has confirmed factors in the IFU that mitigate the risk of limb thrombosis including recognizing patient anatomy that is not consistent with the IFU, properly planning and sizing graft components, removing any stiff wire guide before recording a final angiogram, and considering adjunctive procedures when unexpected severe iliac tortuosity causes kinking of the graft.

The Zenith Renu® AAA Ancillary Graft, which was approved by FDA on June 9, 2005, is intended to be used as a bailout device for situations in which a previously implanted AAA stent graft does not provide adequate proximal fixation or seal. Registry results show that the Renu device has been used primarily to treat pre-existing grafts with proximal type I endoleak or migration, although additional failure modes were also reported. Low incidences of mortality, conversion, and rupture continue to support the safety and effectiveness of the Zenith Renu® AAA Ancillary Graft. Annual imaging follow-up remains recommended to detect progression of disease and to ensure aneurysm stabilization and device integrity.

Finally, Section II provides a summary of device improvements. The company has been proactive in making minor modifications to the device to further improve device performance and mitigate potential risks as much as possible. Additional improvements are anticipated as a result of the company's commitment to the evolving innovation of the Zenith® AAA Endovascular Graft.

Section III provides a summary of explant analyses from the U.S. multi-center clinical study (pivotal and continued access) and worldwide commercial experience. Explants included complete grafts, parts of grafts, and graft fragments that have been analyzed using high resolution X-ray, gross examination, light microscopy, and scanning electron microscopy. A total of 36 explants have undergone analysis, including 8 from the multi-center study. Isolated cases of graft material wear have been noted on the explanted grafts. Isolated suture breaks were observed upon explant; however, these isolated observations are consistent with radiographic or clinical evidence suggesting that broken sutures have been rarely observed in clinical use. Damaged or broken stents and/or barbs have also been observed upon explant. There were no adverse sequelae associated with the explant observations from multi-center study cases; limited information was available regarding the cases of explant from outside the multi-center study. While damage from surgical instruments during explantation was sometimes obvious, it was not always possible to determine if observations occurred before explantation or if the explantation process contributed to, or caused, the observations. Results of the explant analyses further support the device integrity of the Zenith® AAA Endovascular Graft.

Section IV provides a brief summary of this report, highlighting the safety and effectiveness results from the U.S. pivotal clinical study of the Zenith® AAA Endovascular Graft as well as the results from commercial experience with the Zenith® AAA Endovascular Graft, 36 mm diameter Zenith Flex® AAA Endovascular Graft, and Zenith Renu® AAA Ancillary Graft.

Section V (Notes to Clinicians) is reserved for any new notes or general instructions to clinicians, of which there are none at this time beyond those already covered as part of the indications, warnings, and precautions from the IFU.

Lastly, Section VI provides a brief summary of indications, warnings, and precautions for the Zenith® AAA Endovascular Graft as outlined in the Instructions for Use (IFU).

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Section I – Clinical Study Experience

U.S. Clinical Trial Update

On May 23, 2003, the Zenith® AAA Endovascular Graft received FDA approval based upon the results of the U.S. clinical study. The clinical study was concurrently controlled, comparing 200 standard risk endovascular patients with anatomy suitable for endovascular repair with the Zenith® AAA Endovascular Graft to a control group comprised of 80 standard risk open surgical patients. The study met its hypotheses, demonstrating that endovascular repair with the Zenith® AAA Endovascular Graft compares favorably to open surgery for repair of abdominal aortic and aorto-iliac aneurysms. Results from this study supported a determination of a reasonable assurance of safety and effectiveness for the Zenith® AAA Endovascular Graft, resulting in its approval.

One of the conditions of device approval was that Cook institute longer-term follow-up of the endovascular patients at 3, 4, and 5 years. Following IRB approval, all eligible endovascular patients were informed about the opportunity to participate in the study and encouraged to voluntarily provide informed consent. A summary of the U.S. clinical study results through 5 years is presented in this section. Results to date continue to support the longer-term safety and effectiveness of the Zenith® AAA Endovascular Graft.

The U.S. study was a 2-year trial. Between January 2000 and July 2001, 352 endovascular patients were enrolled at 15 centers throughout the United States. In addition to 200 standard risk endovascular patients and 80 open surgical patients, the study included a roll-in group of 52 patients and a high risk group of 100 patients. Centers without previous Zenith® AAA Endovascular Graft experience were required to implant Zenith® AAA Endovascular Grafts (with proctoring) in a minimum of two patients, who were assigned to the roll-in group, prior to enrolling patients into other arms. The pathophysiology of patients in the roll-in group included both standard and high risk.

Patients were enrolled into a high risk arm if they did not meet the pathophysiological criteria for standard risk, but were suitable for endografting. In addition, criteria for iliac anatomy were less restrictive with respect to thrombus and calcification.

Clinical and imaging follow-up (CT and KUB) were obtained at post-procedure, 30 days, 6, 12, 24, 36, 48 and 60 months. Paired CT films with and without contrast were used to identify endoleaks. In cases where renal function precluded contrast administration for CT, duplex ultrasound was used. A single central core lab performed the image analyses

(The Cleveland Clinic Foundation, Cleveland, OH), which ensured the use of uniform morphologic and morphometric methods.

An independent CEC was established (Harvard Clinical Research Institute, Boston, MA) to examine patient deaths, aneurysm ruptures, conversions to open surgical repair, and other adverse events, and to determine if the events were associated with the patient's aneurysm. In addition, the CEC reviewed device integrity including suspected separation or breakage of components, and migration based upon reports by the angiographic core laboratory and the site. Furthermore, this study was overseen by a Data Safety Monitoring Board (DSMB), which regularly reviewed adverse events across institutions in the study for trends to assure acceptable patient safety.

Patient Accountability

Of the 352 patients enrolled for endovascular treatment, 351 patients received the device. In one standard risk patient, implantation was precluded by extensive plaque in the femoral and iliac arteries. The patient was treated conservatively, and was not converted to open surgical repair.

Table 1 presents patient accountability by endovascular study group; standard risk, roll-in, and high risk through 2 years for all patients enrolled in the study, and at 3, 4, and 5 years for those patients that volunteered to participate in the longer-term, post-approval follow-up. Good participation in the longer-term follow-up phase was achieved, considering that the approval process for this additional follow-up was not completed before expiration of initial study consent and the first long-term follow-up study time point.

Table 1. Patient Follow-up and Accountability[1]

Time of Visit	Eligible for Visit	Clinical Exam n (%)	Imaging		Clinical, CT, or KUB n (%)	Patients with Adequate Imaging to Assess				Patients Lost to Future Follow-up[5]		
			CT n (%)	KUB n (%)		Size Change n (%)	Endoleak Analysis[3] n (%)	Migration Analysis n (%)	Fracture Analysis n (%)	Open Surgical Conversion	All Cause Death	Lost To Follow-up
Pre-discharge												
Standard Risk	199	192 (96.5)	187 (94)	176 (88.4)	192 (96.5)	N/A[4]	153 (76.9)	N/A	176 (88.4)	0	1	0
Roll-In[2]	52	48 (92.3)	43 (82.7)	39 (75)	48 (92.3)	N/A	27 (51.9)	N/A	39 (75)	0	1	0
High Risk	100	97 (97)	91 (91)	87 (87)	97 (97)	N/A	77 (77)	N/A	87 (87)	0	2	0
30-day												
Standard Risk	198	196 (99)	191 (96.5)	179 (90.4)	198 (100)	181 (91.4)	162 (81.8)	N/A	179 (90.4)	1	3	0
Roll-In[2]	51	50 (98)	47 (92.2)	43 (84.3)	50 (98)	40 (78.4)	33 (64.7)	N/A	43 (84.3)	0	2	1
High Risk	98	96 (98)	94 (95.9)	86 (87.8)	97 (99)	84 (85.7)	75 (76.5)	N/A	86 (87.8)	0	7	0
6-month												
Standard Risk	194	189 (97.4)	185 (95.4)	168 (86.6)	191 (98.5)	173 (89.2)	172 (88.7)	N/A	168 (86.6)	1	3	0
Roll-In[2]	48	45 (93.8)	41 (85.4)	35 (72.9)	45 (93.8)	37 (77.1)	35 (72.9)	N/A	35 (72.9)	0	3	1
High Risk	91	85 (93.4)	83 (91.2)	79 (86.8)	87 (95.6)	74 (81.3)	70 (76.9)	N/A	79 (86.8)	1	0	0
1-year												
Standard Risk	190	188 (98.9)	182 (95.8)	168 (88.4)	189 (99.5)	168 (88.4)	163 (85.8)	166 (87.4)	168 (88.4)	1	11[6]	6
Roll-In[2]	44	40 (90.9)	38 (86.4)	33 (75)	41 (93.2)	34 (77.3)	33 (75)	31 (70.5)	33 (75)	0	3	1
High Risk	90	85 (94.4)	79 (87.8)	72 (80)	86 (95.6)	68 (75.6)	62 (68.9)	66 (73.3)	72 (80)	1	13[7]	6
2-year												
Standard Risk	173	162 (93.6)	160 (92.5)	152 (87.9)	165 (95.4)	152 (87.9)	150 (86.7)	150 (86.7)	152 (87.9)	0	7	58
Roll-In[2]	40	38 (95)	38 (95)	27 (67.5)	39 (97.5)	32 (80)	30 (75)	29 (72.5)	27 (67.5)	0	6	14
High Risk	71	64 (90.1)	61 (85.9)	60 (84.5)	66 (93)	52 (73.2)	44 (62.0)	49 (69.0)	60 (84.5)	0	6	35
3-year[5]												
Standard Risk	108	83 (76.9)	76 (70.4)	65 (60.2)	86 (79.6)	65 (60.2)	62 (57.4)	71 (65.7)	65 (60.2)	0	1	2
Roll-In[2]	20	15 (75)	11 (55)	9 (45)	15 (75)	11 (55)	10 (50)	10 (50)	9 (45)	0	0	0
High Risk	30	24 (80)	16 (53.3)	13 (43.3)	24 (80)	14 (46.7)	12 (40)	11 (36.7)	13 (43.3)	0	0	0
4-year												
Standard Risk	105	95 (90.5)	78 (74.3)	80 (76.2)	96 (91.4)	76 (72.4)	62 (59)	75 (71.4)	80 (76.2)	1	3	8
Roll-In[2]	20	17 (85)	14 (70)	14 (70)	18 (90)	14 (70)	11 (55)	13 (65)	14 (70)	0	0	1
High Risk	30	26 (86.7)	22 (73.3)	22 (73.3)	27 (90)	20 (66.7)	16 (53.3)	18 (60)	22 (73.3)	0	4	1

Time of Visit	Eligible for Visit	Clinical Exam n (%)	Imaging		Clinical, CT, or KUB n (%)	Patients with Adequate Imaging to Assess				Patients Lost to Future Follow-up[5]		
			CT n (%)	KUB n (%)		Size Change n (%)	Endoleak Analysis[3] n (%)	Migration Analysis n (%)	Fracture Analysis n (%)	Open Surgical Conversion	All Cause Death	Lost To Follow-up
5-year												
Standard Risk	93	92 (98.9)	76 (81.7)	73 (78.5)	92 (98.9)	70 (75.3)	67 (72.0)	71 (76.3)	73 (78.5)	N/A	N/A	N/A
Roll-In[2]	19	19 (100)	15 (78.9)	14 (73.7)	19 (100)	14 (73.7)	12 (63.2)	14 (73.7)	14 (73.7)	N/A	N/A	N/A
High Risk	25	25 (100)	18 (72)	18 (72)	25 (100)	16 (64)	14 (56)	14 (56)	18 (72)	N/A	N/A	N/A

[1] Data analysis sample size varies for each of the time points and in the tables that follow. This variability is due to patient availability for follow-up, as well as quantity and quality of images available from specific time points for evaluation. For example, the number and quality of images available for evaluation of endoleak at 1 year is different than the number and quality of images available at 2 years 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.
[2] Roll-in includes some patients meeting standard risk criteria and some patients meeting high risk criteria.
[3] Renal considerations precluded contrast enhancement, which was necessary for analysis in some patients.
[4] N/A means not applicable.
[5] Of the 259 eligible patients for the long-term study, 158 patients consented to participate and 101 were then considered lost to follow-up due primarily to a lengthy approval process for the long-term follow-up study, which exceeded the interval between expiration of pivotal study consent and the first long-term follow-up study time point.
[6] One standard risk patient died 30 days post-conversion to open repair; thus, the same patient is included in both columns, but counted once.
[7] One high risk patient died 30 days post-conversion to open repair; thus, the same patient is included in both columns, but counted once.

Aneurysm-Related Mortality

For this conservative analysis, an aneurysm-related death is defined as 1) any death regardless of cause occurring within 30 days of the procedure, a secondary intervention, or a conversion to open repair, 2) any death after 30 days due to aneurysm rupture, and 3) in addition to other common definitions, any death in which the procedure, aneurysm disease progression, or a sequence of events beginning within 30 days of the procedure may have contributed to the eventual death. This definition may include more patient deaths as AAA-related than other common definitions for AAA-related death.

There were no deaths related to rupture of the treated aneurysm. Devices were intact and functional in all patients at the time of last follow-up prior to explant or death. The Kaplan-Meier analysis below demonstrates that standard risk, roll-in, and high risk patients have five-year freedom from aneurysm-related death rates of 98.9%, 94.2%, and 93.8%, respectively (see Figure 1 and Table 2). As expected, high risk patients have higher five-year AAA-related mortality compared to standard risk patients ($P = 0.01$).

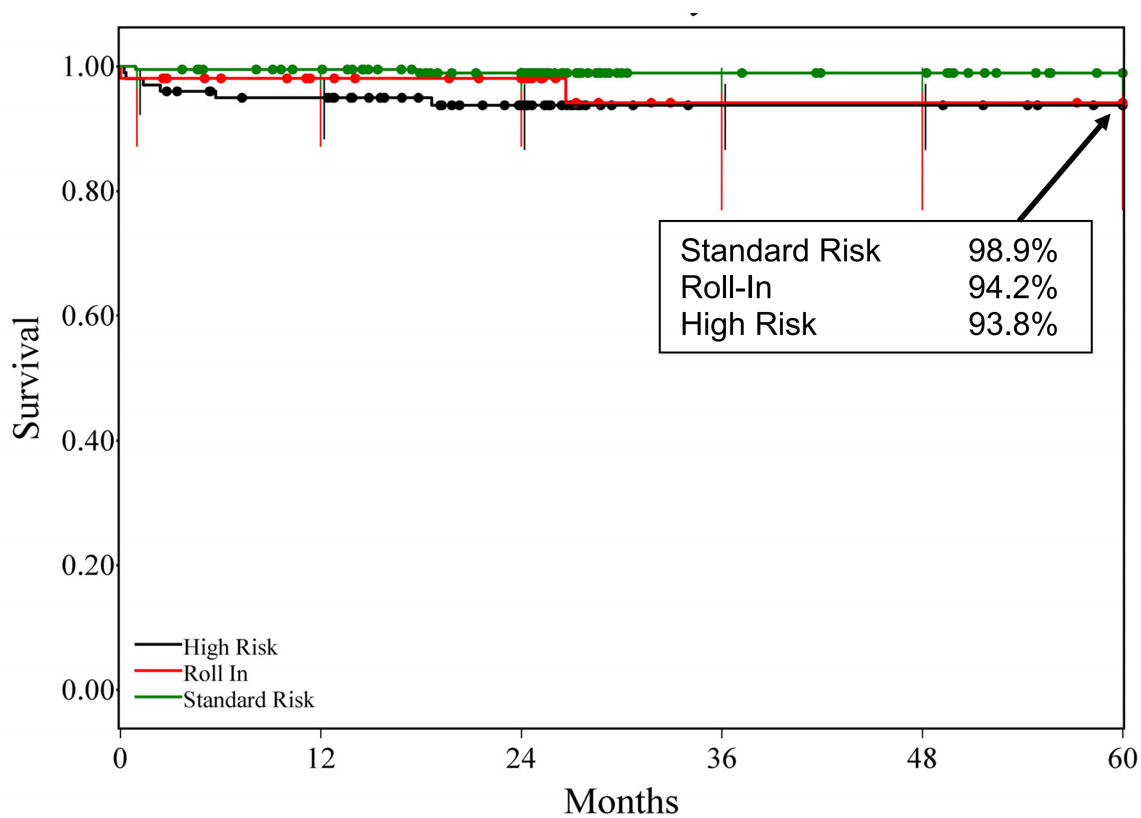

Figure 1. Freedom from AAA-related Mortality (Inclusive of Intra-operative, Peri-operative, Post-operative, and Late)

Table 2. Summary of Kaplan-Meier Curves (Freedom from AAA-related Mortality[1])

Study Arm	Parameter	Treatment to 30 days	30 days to 1 year	1 year to 2 years	2 years to 3 years	3 years to 4 years	4 years to 5 years
Standard Risk	# at risk[2]	199	198	190	173	108	105
	# of events	1	0	1	0	0	0
	# censored[3]	0	8	16	65	3	33
	Cumulative censored[4]	0	8	24	89	92	125
	Kaplan-Meier estimate[5]	0.995	0.995	0.989	0.989	0.989	0.989
	Standard error	0.005	0.005	0.007	0.007	0.007	0.007
Roll-In	# at risk[2]	52	51	44	40	20	20
	# of events	1	0	0	1	0	0
	# censored[3]	0	7	4	19	0	7
	Cumulative censored[4]	0	7	11	30	30	37
	Kaplan-Meier estimate[5]	0.981	0.981	0.981	0.942	0.942	0.942
	Standard error	0.019	0.019	0.019	0.043	0.043	0.043
High Risk	# at risk[2]	100	98	90	71	30	30
	# of events	2	3	1	0	0	0
	# censored[3]	0	5	18	41	0	10
	Cumulative censored[4]	0	5	23	64	64	74
	Kaplan-Meier estimate[5]	0.980	0.950	0.938	0.938	0.938	0.938
	Standard error	0.014	0.022	0.025	0.025	0.025	0.025

[1] All deaths within 30 days of the implant procedure, secondary intervention, or conversion to open repair were by definition included as AAA-related regardless of cause. Patients in whom the procedure, aneurysm disease progression, or a sequence of events beginning within 30 days of the procedure may have contributed to the eventual death were conservatively included in AAA-related death. This definition may include more patient deaths as AAA-related than other common definitions for AAA-related death. Devices were intact and functional in all patients at time of last follow-up prior to explant or death. There were no deaths related to rupture of the treated aneurysm.
[2] Number of patients at risk at the beginning of the interval.
[3] Patients are censored because their last follow-up was not reached due to lost to follow-up or death.
[4] The total censored for all time intervals up to and including that specific time interval.
[5] Estimate made at end of time interval

Table 3 presents the potential cause for each case of aneurysm-related mortality.

Table 3. Cause of AAA-related Mortality

Study arm	**Days after procedure**	**Age at death**	Cause
Roll-in	1	80	Arrhythmia or MI, otherwise unknown.[1]
High Risk	7	66	Respiratory failure.[1]
High Risk	11	87	MI/pulmonary embolism.[1]
Standard Risk	28	71	Atherosclerotic heart disease.[1]
High Risk	42	80	CHF, COPD, leading to multi-system organ failure, thrombotic thrombocytopenic purpura.[2]
High Risk	73	71	Pancreatitis, renal failure, sepsis.[2]
High Risk	174	84	Left retroperitoneal hemorrhage from ruptured visceral aorta due to severe atherosclerosis. Treated AAA was not ruptured.[2]
Standard Risk	543	81	Heart failure, sepsis, aortic graft infection.[3]
Standard Risk	567	65	Unknown, within 30 days of conversion to open repair.[3,4]
Roll-in	811	77	Ruptured cerebral aneurysm.[5]
Roll-in	1855	88	Colon ischemia.[5,6]

[1] Death occurred within 30 days of the procedure, but was not due to rupture or compromise in device integrity.
[2] Although death was beyond 30 days of initial procedure, the CEC determined that an event at the time of the procedure, aneurysm disease progression, or a sequence of events beginning within 30 days of the procedure may have contributed to the eventual death.
[3] Patient died within 30 days of conversion to open repair.
[4] Patient death not previously reported in IFU; reported subsequent to analysis date.
[5] Patient death was adjudicated by the CEC as not AAA-related, but death occurred within 30 days of a secondary intervention.
[6] Death was beyond 5 years post-implant, not shown on the KM curve or table.

Deaths were considered aneurysm-related in 3.1% of patients using the conservative definition described above. Deaths within 30 days of the initial treatment occurred in 1.1% of patients, but were not related to rupture of the treated aneurysm or failure of the graft. Death beyond 30 days of the initial procedure occurred in 2.0% of patients. In 0.6% of these patients, the CEC determined that the patient failed to thrive after the procedure due to a sequence of events that began within 30 days of the initial procedure. In 0.3% of patients, death was considered aneurysm-related because a second visceral aneurysm (not the treated aneurysm) in an atherosclerotic aorta hemorrhaged and death occurred within 30 days of that event. Two aneurysm-related deaths between one and two years were less than 30 days after conversion to open repair (0.6%) for graft infection. Two other deaths beyond 2 years occurred within 30 days of a secondary intervention, but were adjudicated by the CEC as not AAA-related.

None of the deaths were related to device integrity, maldeployment, rupture of the treated aneurysm, device migration, or aneurysm growth. Deaths were consistent with causes of death experienced after open surgical repair. Five-year freedom from aneurysm-related death rates was estimated at 98.9% for standard risk and 93.8% for high risk patients.

All-Cause Mortality

The Kaplan-Meier analysis below demonstrates that standard risk, roll-in, and high risk patients have a five-year freedom from all-cause mortality of 83.1%, 66.4%, and 57.8%, respectively (see Figure 2 and Table 4).

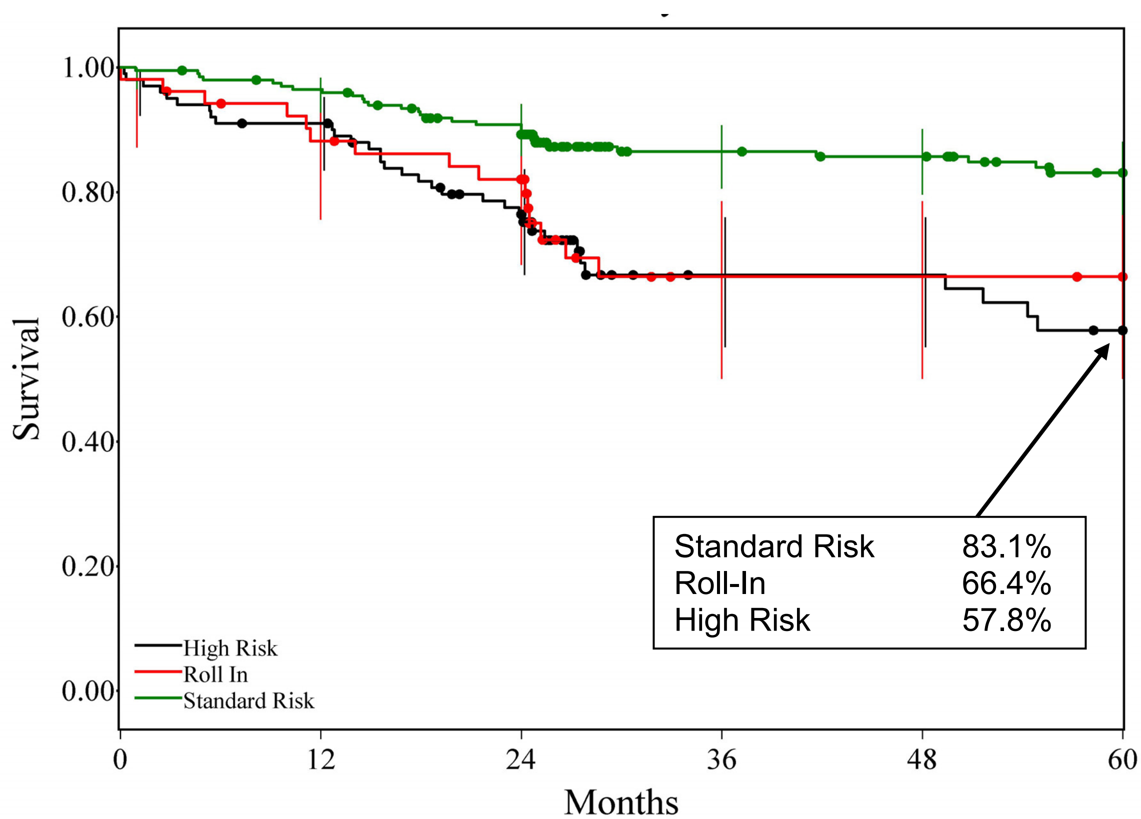

Figure 2. Freedom from All-cause Mortality (Inclusive of Intra-operative, Peri-operative, Post-operative and Late)

Table 4. Summary of Kaplan-Meier Curves (Freedom from All-cause Mortality)

Study Arm	Parameter	Treatment to 30 days	30 days to 1 year	1 year to 2 years	2 years to 3 years	3 years to 4 years	4 years to 5 years
Standard Risk	# at risk[1]	199	198	190	173	108	105
	# of events	1	6	11	7	1	3
	# censored[2]	0	2	6	58	2	30
	Cumulative censored[3]	0	2	8	66	68	98
	Kaplan-Meier estimate[4]	0.995	0.965	0.908	0.865	0.857	0.831
	Standard error	0.005	0.013	0.021	0.026	0.027	0.030
Roll-In	# at risk[1]	52	51	44	40	20	20
	# of events	1	5	3	6	0	0
	# censored[2]	0	2	1	14	0	7
	Cumulative censored[3]	0	2	3	17	17	24
	Kaplan-Meier estimate[4]	0.981	0.882	0.820	0.664	0.664	0.664
	Standard error	0.019	0.045	0.054	0.073	0.073	0.073
High Risk	# at risk[1]	100	98	90	71	30	30
	# of events	2	7	14	6	0	4
	# censored[2]	0	1	5	35	0	6
	Cumulative censored[3]	0	1	6	41	41	47
	Kaplan-Meier estimate[4]	0.980	0.910	0.764	0.667	0.667	0.578
	Standard error	0.014	0.029	0.043	0.053	0.053	0.062

[1] Number of patients at risk at the beginning of the interval.
[2] Patients are censored because their last follow-up was not reached due to lost to follow-up or death.
[3] The total censored for all time intervals up to and including that specific time interval.
[4] Estimate made at end of time interval.

Table 5 presents the potential causes of all-cause mortality by organ system.

Table 5. Potential Causes for All-cause Mortality by Organ System

Organ System	Standard Risk	Roll-in	High Risk
Cancer	3.5% (7/199)	5.8% (3/52)	6.0% (6/100)
Cardiac	3.5% (7/199)	1.9% (1/52)	10% (10/100)
Cerebral	0.5% (1/199)	3.8% (2/52)	2.0% (2/100)
GI	1.0% (2/199)	1.9% (1/52)	4.0% (4/100)
Hepatic	0.5% (1/199)	0.0% (0/52)	0.0% (0/100)
Pulmonary	1.5% (3/199)	5.8% (3/52)	3.0% (3/100)
Renal	0.0% (0/199)	0.0% (0/52)	1.0% (1/100)
Other	0.5% (1/199)	3.8% (2/52)	4.0% (4/100)

Consistent with the causes of death, patients had numerous co-morbid conditions prior to treatment with an endovascular graft. The five-year freedom from all-cause mortality was 83.1% for standard risk patients and 57.1% for high risk patients. As expected, standard risk patient survival was significantly better than high risk patient survival ($P = 0.001$).

Endoleak

Endoleaks were reported based upon core lab determination. The core lab used paired CT films with and without contrast at each follow-up interval to identify endoleaks. In the absence of a contrast and non-contrast film series, the core lab reported the imaging follow-up as non-assessable for endoleaks. Freedom from endoleaks at five years was 71.9% (see Figure 3 and Table 6). Most endoleaks were early and resolved spontaneously; the incidence of new late endoleaks was low. Most new endoleaks at the five-year follow-up were type II. Secondary interventions for treating endoleaks are discussed below.

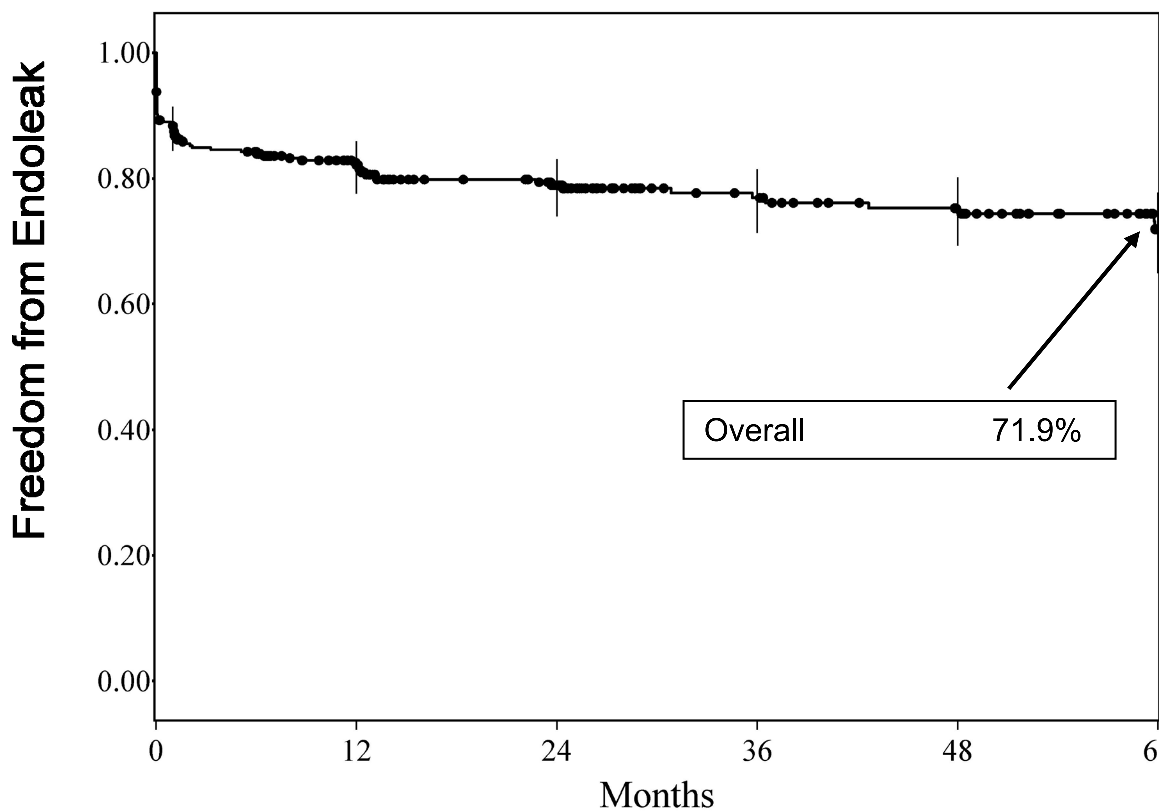

Figure 3. Freedom from Endoleak

Table 6. Summary of Kaplan-Meier Curve (Freedom from Endoleak)

	Parameter	Treatment to 30 days	30 days to 1 year	1 year to 2 years	2 years to 3 years	3 years to 4 years	4 years to 5 years
Overall	# at risk[1]	337	291	218	164	100	85
	# of events	39	19	8	3	2	3
	# censored[2]	7	54	46	61	13	31
	Cumulative censored[3]	7	61	107	168	181	212
	Kaplan-Meier estimate[4]	0.883	0.822	0.789	0.769	0.752	0.719
	Standard error	0.018	0.021	0.023	0.026	0.028	0.033

[1] Number of patients at risk at the beginning of the interval. Values at "Treatment to 30 days" represent total number of patients assessed for endoleak at any time period up to 30 days.
[2] Patients are censored because CT was not evaluable for endoleak, CT was not performed at later time periods, patient was lost to follow-up, or patient died.
[3] The total censored for all time intervals up to and including that specific time interval.
[4] Estimate made at end of time interval.

Table 7 presents endoleaks sub-classified by study group and type according to the definitions by White et al. (see Table 7 for reference); subtotals by study group and totals are also presented. The majority of all observed endoleaks were type II endoleaks.

Table 7. Evaluation of Endoleaks by Type[1] (Persistent and New) by the Core Lab

	Type I Proximal	Type I Distal	Type II	Type III	Type IV	Type Unknown	Multiple	All Types
	(%) (n/N)	(%) (n/N)	(%) (n/N)	(%) (n/N)	(%) (n/N)	(%) (n/N)	(%) (n/N)	(%) (n/N)
Post-procedure								
Standard Risk	2.0% (3/153)	0% (0/153)	9.2% (14/153)	1.3% (2/153)		1.3% (2/153)	0.7% (1/153)	14.4% (22/153)
Roll In	0% (0/27)	3.7% (1/27)	7.4% (2/27)	0% (0/27)		3.7% (1/27)	0% (0/27)	14.8% (4/27)
High Risk	0% (0/77)	0% (0/77)	10.4% (8/77)	0% (0/77)		2.6% (2/77)	1.3% (1/77)	14.3% (11/77)
Total	**1.2% (3/257)**	**0.4% (1/257)**	**9.3% (24/257)**	**0.8% (2/257)**		**2.0% (5/257)**	**0.8% (2/257)**	**14.4% (37/257)**
30-day								
Standard Risk	0.6% (1/162)	0.6% (1/162)	7.4% (12/162)	0.6% (1/162)		0.6% (1/162)	0% (0/162)	9.9% (16/162)
Roll In	0% (0/33)	3.0% (1/33)	6.1% (2/33)	0% (0/33)		0% (0/33)	0.6% (1/33)	12.1% (4/33)
High Risk	0% (0/75)	1.3% (1/75)	7.4% (7/75)	0% (0/75)		0% (0/75)	0% (0/75)	12% (9/75)
Total	**0.4% (1/270)**	**1.1% (3/270)**	**7.8% (21/270)**	**0.4% (1/270)**		**0.4% (1/270)**	**0.4% (1/270)**	**10.7% (29/270)**
6-month								
Standard Risk	0.6% (1/172)	0.6% (1/172)	7.6% (13/172)	0% (0/172)		0% (0/172)		8.7% (15/172)
Roll In	0% (0/35)	0% (0/35)	8.6% (3/35)	0% (0/35)		0% (0/35)		8.6% (3/35)
High Risk	0% (0/70)	0% (0/70)	7.1% (5/70)	0.6% (1/70)		2.9% (2/70)		11% (8/70)
Total	**0.4% (1/277)**	**0.4% (1/277)**	**7.6% (21/277)**	**0.4% (1/277)**		**0.7% (2/277)**		**9.4% (26/277)**
12-month								
Standard Risk		0.6% (1/163)	4.9% (8/163)	0.6% (0/163)		1.2% (2/163)		6.7% (11/163)
Roll In		0% (0/33)	6.1% (2/33)	0% (0/33)		0% (0/33)		6.1% (2/33)
High Risk		0% (0/62)	6.5% (4/62)	0% (1/62)		1.6% (1/62)		9.7% (6/62)
Total		**0.4% (1/258)**	**5.4% (14/258)**	**0.4% (1/258)**	**No Type IV Endoleaks**	**1.2% (3/258)**	**No Multiple Endoleaks**	**7.4% (19/258)**
24-month								
Standard Risk	**No Type I Proximal Endoleaks**	**No Type I Distal Endoleaks**	4.7% (7/150)			2.0% (3/150)		6.7% (10/150)
Roll In			0% (0/30)			0% (0/30)		0% (0/30)
High Risk			9.1% (4/44)			2.3% (1/44)		11.4% (5/44)
Total			**4.9% (11/224)**	**No Type III Endoleaks**		**1.8% (4/224)**		**6.7% (15/224)**
36-month								
Standard Risk		1.6% (1/62)	1.6% (1/62)			1.6% (1/62)		4.8% (3/62)
Roll In		0% (0/10)	0% (0/10)			0% (0/10)		0% (0/10)
High Risk		8.3% (1/12)	16.7% (2/12)			0% (0/12)		25.0% (3/12)
Total		**2.4% (2/84)**	**3.6% (3/84)**			**1.2% (1/84)**		**7.1% (6/84)**

	Type I Proximal	**Type I Distal**	**Type II**	**Type III**	**Type IV**	**Type Unknown**	**Multiple**	**All Types**
	(%) (n/N)	**(%) (n/N)**	**(%) (n/N)**	**(%) (n/N)**	**(%) (n/N)**	**(%) (n/N)**	**(%) (n/N)**	**(%) (n/N)**
48-month								
Standard Risk	1.6% (1/62)	**No Type I Distal Endoleaks**	1.6% (1/62)	1.6% (1/62)		1.6% (1/62)	0% (0/62)	6.5% (4/62)
Roll In	0% (0/11)		0% (0/11)	0% (0/11)		0% (0/11)	0% (0/11)	0% (0/11)
High Risk	0% (0/16)		6.3% (1/16)	6.3% (1/16)		0% (0/16)	6.3% (1/16)	18.8% (3/16)
Total	**1.1% (1/89)**		**2.3% (2/89)**	**2.3% (2/89)**		**1.1% (1/89)**	**1.1% (1/89)**	**7.9% (7/89)**
60-month								
Standard Risk	**No Type I Proximal Endoleaks**	0% (0/67)	3.0% (2/67)	**No Type III Endoleaks**		1.5% (1/67)	0% (0/67)	4.5% (3/67)
Roll In		0% (0/12)	8.3% (1/12)			0% (0/12)	0% (0/12)	8.3% (1/12)
High Risk		7.1% (1/14)	7.1% (1/14)			0% (0/14)	7.1% (1/14)	21.4% (3/14)
Total		**1.1% (1/93)**	**4.3% (4/93)**			**1.1% (1/93)**	**1.1% (1/93)**	**7.5% (7/93)**

[1] Type sub-classified as by White GH, et al. J. Endo. Surg. 1998; 5:305-309.

Core lab results demonstrate a low rate of endoleak for patients treated with the Zenith® AAA Endovascular Graft. The rates of type I and type III endoleaks were quite low for all arms through five years. None of the endoleaks were attributed to graft material defects or porosity. Thus, all of the (few) type III endoleaks were at the junction between the main body and the iliac leg component. One patient with proximal neck dilatation and endoleak required conversion to open repair between 4 and 5 years. The majority of endoleaks were type II endoleaks. While treatment of type I and type III endoleaks was mandated by the study protocol, treatment of type II endoleaks was left to the discretion of the physician. Many type II endoleaks seal spontaneously over time; therefore, type II endoleaks were often not treated unless associated with aneurysm growth or persistence. Secondary interventions to treat endoleaks are listed in Table 8.

Table 8. Secondary Interventions for Endoleaks Through 5 Years[1]

Endoleak Type	**Embolization**	**Zenith® AAA Endovascular Graft Leg Extension**	**Zenith® AAA Endovascular Graft Main Body Extension**	**Stent**	**Angioplasty**
Type I					
Proximal	2	0	3	1	0
Distal	2	5	0	0	2
Type II	30	2	0	0	1
Type III	0	5	0	1	1
Type IV	0	0	0	0	0
Unknown	1	2	0	1	0
Multiple	1	0	0	1	1

[1] Patients may have required more than one secondary intervention or more than one treatment during a single secondary intervention.

The most common secondary intervention was embolization for treatment of type II endoleak. Angioplasty, stents, extensions, and embolization were used for treatment of type I endoleaks. Angioplasty, stents, and extensions were used for treatment of type III endoleaks.

In summary, at five years, there were no type I (proximal), type III, or type IV endoleaks. There were 3 endoleaks first appreciated at five years. Some persistent endoleaks, primarily type II, were associated with lack of aneurysm shrinkage, suggesting the need for continued imaging follow-up and possible intervention.

Aneurysm Enlargement

Aneurysm shrinkage, stabilization, and growth were determined for each patient. Aneurysm size was determined by the core lab using the major axis diameter of the aneurysm from CT images. Aneurysm shrinkage or growth was defined as a greater than 5 mm change compared to the baseline measurement (taken at pre-discharge). Table 9 presents the percent of patients with aneurysm shrinkage, stabilization, or growth by study group at each time period. Patients with no growth included all patients with aneurysm shrinkage as well as those patients with no significant change in aneurysm diameter. By five years, 91% of the patients treated with the Zenith® AAA Endovascular Graft had no aneurysm growth, with 72% of the patients having aneurysm shrinkage (> 5 mm decrease). There were no new cases of aneurysm growth identified at 5 years.

Table 9. Patients with Aneurysm Shrinkage, Stabilization, or Growth[1]

	1 month	6 month	1 year	2 years	3 years	4 years	5 years
Standard Risk							
Shrinkage	1.7% (3/181)	37.0% (64/173)	64.9% (109/168)	73.0% (111/152)	70.8% (46/65)	71.1% (54/76)	75.7% (53/70)
Stabilized	97.2% (176/181)	62.4% (108/173)	33.9% (57/168)	24.3% (37/152)	27.7% (18/65)	23.7% (18/76)	20.0% (14/70)
No Growth	98.9% (179/181)	99.4% (172/173)	98.8% (166/168)	97.4% (148/152)	98.5% (64/65)	94.7% (72/76)	95.7% (67/70)
Growth	1.1% (2/181)	0.6% (1/173)	1.2% (2/168)	2.6% (4/152)[2]	1.5% (1/65)	5.3% (4/76)	4.3% (3/70)
Roll-In							
Shrinkage	0.0% (0/40)	48.6% (18/37)	67.6% (23/34)	65.6% (21/32)	54.5% (6/11)	78.6% (11/14)	78.6% (11/14)
Stabilized	97.5% (39/40)	51.4% (19/37)	32.4% (11/34)	31.3% (10/32)	36.4% (4/11)	14.3% (2/14)	14.3% (2/14)
No Growth	97.5%(39/40)	100%(37/37)	100% (34/34)	96.9% (31/32)	90.9% (10/11)	92.9% (13/14)	92.9% (13/14)
Growth	2.5%(1/40)	0.0%(0/37)	0.0% (0/34)	3.1% (1/32)	9.1% (1/11)	7.1% (1/14)	7.1% (1/14)
High Risk							
Shrinkage	4.8% (4/84)	40.5% (30/74)	61.8% (42/68)	63.5% (33/52)	50.0% (7/14)	55.0% (11/20)	50.0% (8/16)
Stabilized	94.0% (79/84)	59.5% (44/74)	36.8% (25/68)	34.6% (18/52)	21.4% (3/14)	20.0% (4/20)	18.7% (3/16)
No Growth	98.8% (83/84)	100% (74/74)	98.5% (67/68)	98.1% (51/52)	71.4% (10/14)	75.0% (15/20)	68.8% (11/16)
Growth	1.2% (1/84)	0.0% (0/74)	1.5% (1/68)	1.9% (1/52)	28.6% (4/14)	25.0% (5/20)	31.3% (5/16)

[1] Patients are not unique and may have been assessed with aneurysm growth at more than one time period.
[2] One additional patient without assessable baseline (pre-discharge) had growth compared to 30-day values.

Through five years of follow-up there were no unexplained cases of aneurysm growth. Between one and two years, two patients with graft infection had aneurysm growth with subsequent graft explantation. Other than those cases of graft infection, aneurysm growth was observed in the presence of persistent endoleak (primarily type II endoleak) or secondary interventions for treatment of type II endoleaks. The growing aneurysm in one patient was suspected to be associated with a persistent endoleak per the implanting physician; however, a conclusive endoleak was unable to be demonstrated via ultrasound in this obese patient with renal insufficiency which precluded the use of non-ionic contrast injection during CT evaluation. One patient with type II leak also had a suspected graft infection. One patient with proximal neck dilatation and endoleak required graft explantation between 4 and 5 years.

Evaluation of patients with aneurysm growth at any point in time revealed that the pattern of growth varied. Of 5 patients with early growth > 5 mm (at 30 days or 6 months), two patients subsequently experienced shrinkage > 5 mm below baseline, two patients subsequently returned to within 5 mm of baseline, while one remained > 5 mm above baseline but was stable through five years. Of 14 patients with late growth, none had a pattern of continuous shrinkage before growth; all exhibited at least a trend toward growth before the threshold of > 5mm above baseline was reached. Eleven showed a trend toward growth immediately prior to reaching > 5 mm above baseline, and three had a trend toward growth earlier and were essentially stable immediately prior to the growth reaching significance. One additional patient was not assessable at baseline but had a continuous trend toward growth with respect to 30-day follow-up.

Hence, periodic imaging was adequate to identify patients having the potential for aneurysm growth. Moreover, periodic imaging provided observation of endoleaks, especially late type II endoleaks, which were associated with aneurysm growth. Evidence of continued aneurysm growth in the presence of type II endoleak is suggestive of the need for intervention.

Aneurysms exhibited shrinkage (> 5 mm decrease) in 72% of patients and stabilization in 19%, that is, a total of 91% of aneurysms were not growing at five years. Periodic imaging was adequate to identify patients with aneurysm growth. Growing aneurysms were associated with graft infection or endoleak (primarily type II). There were no cases of aneurysm growth due to device migration or leakage through the graft material. To date, there have been no unexplained cases of aneurysm growth associated with the Zenith® AAA Endovascular Graft. Additionally, there were no new cases of aneurysm growth at 5 years.

Rupture

The Kaplan-Meier curves below demonstrate patients in the standard risk and roll-in groups have a five-year freedom from rupture of 100%, while this rate for patients in the high risk group is 98.9% (one patient with an insufficient iliac landing zone length of only 6 mm). Overall, patients treated with the Zenith® AAA Endovascular Graft have a five-year freedom from rupture of 99.7% (see Figure 4 and Table 10). There were no deaths related to rupture of the treated aneurysm.

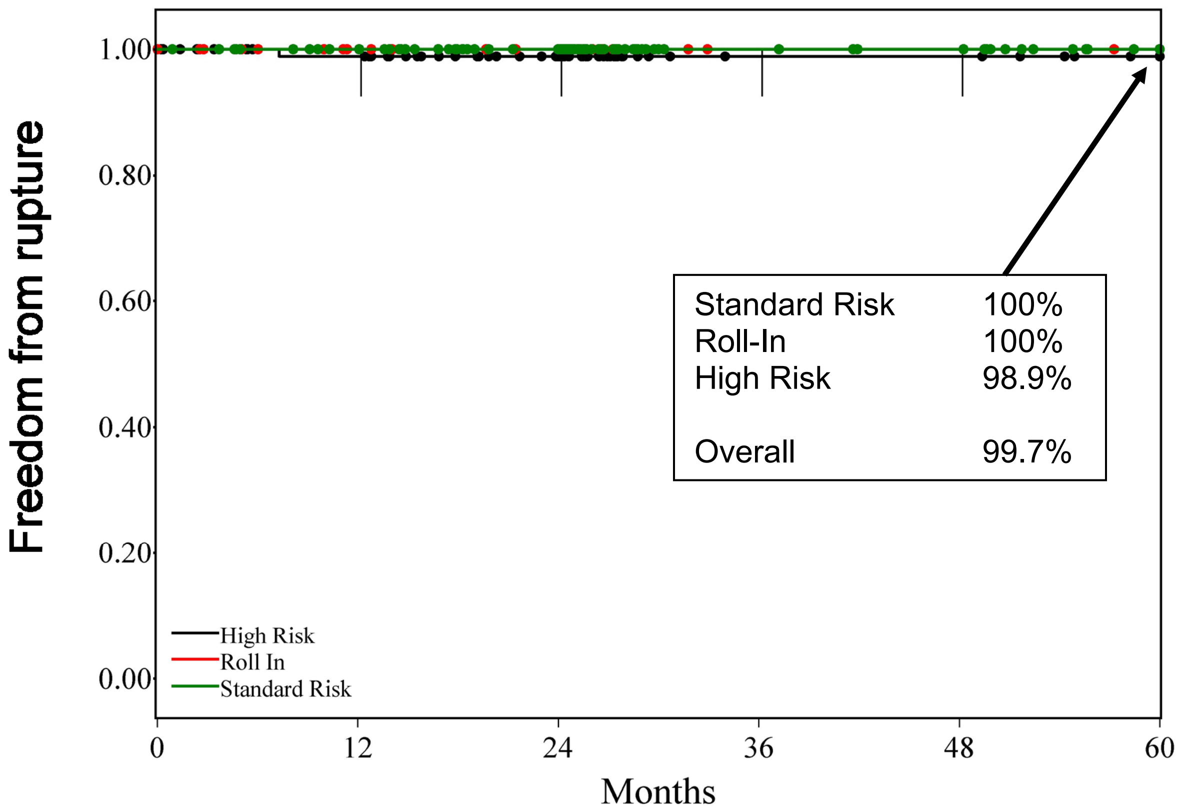

Figure 4. Freedom from Rupture (Inclusive of Intra-operative, Peri-operative, Post-operative, and Late)

Table 10. Summary of Kaplan-Meier Curves (Freedom from Rupture)

Study Arm	Parameter	Treatment to 30 days	30 days to 1 year	1 year to 2 years	2 years to 3 years	3 years to 4 years	4 years to 5 years
Standard Risk	# at risk[1]	199	198	190	173	108	105
	# of events	0	0	0	0	0	0
	# censored[2]	1	8	17	65	3	33
	Cumulative censored[3]	1	9	26	91	94	127
	Kaplan-Meier estimate[4]	1.000	1.000	1.000	1.000	1.000	1.000
	Standard error	N/A	N/A	N/A	N/A	N/A	N/A
Roll-In	# at risk[1]	52	51	44	40	20	20
	# of events	0	0	0	0	0	0
	# censored[2]	1	7	4	20	0	7
	Cumulative censored[3]	1	8	12	32	32	39
	Kaplan-Meier estimate[4]	1.000	1.000	1.000	1.000	1.000	1.000
	Standard error	N/A	N/A	N/A	N/A	N/A	N/A
High Risk	# at risk[1]	100	98	90	71	30	30
	# of events	0	1[5]	0	0	0	0
	# censored[2]	2	7	19	41	0	10
	Cumulative censored[3]	2	9	28	69	69	79
	Kaplan-Meier estimate[4]	1.000	0.989	0.989	0.989	0.989	0.989
	Standard error	NA	0.011	0.011	0.011	0.011	0.011

[1] Number of patients at risk at the beginning of the interval.
[2] Patients are censored when their last follow-up was not reached due to lost to follow-up or death.
[3] The total censored for all time intervals up to and including that specific time interval.
[4] Estimate made at end of time interval.
[5] The only aneurysm rupture in this study occurred in a patient with an insufficient iliac landing zone length of 6 mm; a short iliac limb retracted into the sac. The patient survived partial conversion.

The single aneurysm rupture in this study occurred prior to the one-year follow-up in a high risk patient with an insufficient iliac landing zone length of only 6 mm. The minimum landing zone for the study was 10 mm, with 20 mm being preferred. The chosen iliac graft component was too short and retracted into the sac as the sac remodeled. The patient survived partial conversion. The lessons learned from this case were the importance of adequate landing zone length (preferably greater than 20 mm), proper device sizing (appropriate lengths and diameters), and monitoring of distal limb fixation in at risk patients (patients with suboptimal placements).

In this study, there were no unexplained ruptures and no deaths due to rupture of the treated aneurysm through five years of follow-up. There were no reported ruptures in this study cohort between one and five years. With only one aneurysm rupture (related to insufficient iliac landing zone length), the estimated five-year freedom from rupture was 99.7%.

Device Patency

CT films were examined by the core lab to assess whether a graft was patent at follow-up based upon visual observations of contrast within the endovascular graft components. There were 6 cases of limb occlusion through the 1-year follow-up. There were no additional cases of limb occlusion detected between one and five years. One case observed at 1-year follow-up remained untreated and asymptomatic and lack of patency observed by the 1-year follow-up was addressed with bypass in 1.4% of patients.
Table 11 presents the radiographic evaluation of patency at each exam period by study arm.

Table 11. Patency by Study Arm (New and Persistent Events)

	Post-procedure	1-month	6-month	1-year	2-year	3-year	4-year	5-year
Standard Risk	99.4% (180/181)	100.0% (187/187)	99.5% (183/184)	98.8% (168/170)	98.7% (153/155)	97.1% (68/70)	98.6% (68/69)	98.6% (70/71)
Roll-In	100.0% (43/43)	100.0% (47/47)	100.0% (39/39)	100.0% (34/34)	100.0% (34/34)	100.0% (10/10)	100.0% (12/12)	100.0% (13/13)
High Risk	100.0% (85/85)	97.7% (84/86)	100.0% (74/74)	100.0% (67/67)	100.0% (50/50)	100.0% (12/12)	100.0% (18/18)	100.0% (14/14)

Table 12 presents the individual cases with loss of limb patency and the contributing factors. Additionally, the lack of patency could be associated with difficult arterial anatomy, placement of an excessively oversized leg extension, or progression of pre-existing arterial disease.

Table 12. Contributing Factors to Loss of Patency

Study arm	Exam first identified	Contributing Factors	Treatment
Standard Risk	Pre-discharge	Excessively oversized extension into the left external iliac artery.	Right to left fem-fem bypass at 53 days.
High Risk	1-month	Leg extension placed procedurally to the external iliac. Angioplasty of stenosis resulted in dissection and stent placement.	Left to right fem-fem bypass at 55 days.
High Risk	1-month	Right limb kink and subsequent thrombosis were felt to be due to a narrow, tortuous iliac artery.	Common femoral endarterectomy and fem-fem bypass at 48 days.
Standard Risk	6-month	Progression of distal femoral disease.	Right to left fem-fem bypass at 189 days.
Standard Risk	12-month	Left limb occlusion due to tortuous proximal common iliac compression causing claudication.	Right external iliac to left fem bypass at 406 days.
Standard Risk	12-month	Leg extension placed procedurally to right external iliac, right graft limb thrombosis.	No intervention; patient denied claudication or significant symptoms.

Across the three study arms, there were no additional cases of limb occlusion detected between one and five years. Further, lack of patency observed by the 1-year follow-up was addressed with bypass in 1.4% of patients and one case observed at 1-year follow-up remained asymptomatic and untreated.

Device Integrity

To date, there have been infrequent device integrity observations identified by radiographic assessment in the U.S. clinical study patients. Table 13 presents the rates of barb separation, stent-to-graft separation, stent fracture, and graft material rupture.

Table 13. Device Integrity (Date of First Occurrence)

	Post-procedure	1-month	6-month	1-year	2-year	3-year	4-year	5-year
Standard Risk	No events	No events						
Barb separation			0.6% (1/168)[1]	2.4% (4/168)[1]	2.0% (3/152)[1]	4.6% (3/65)[1]	2.5% (2/80)[1]	1.4% (1/73)
Stent to graft separation			0.0% (0/168)	0.6% (1/168)[2]	0.0% (0/152)	1.5% (1/65)[2]	0.0% (0/80)	0.0% (0/73)
Stent fracture			0.0% (0/168)	0.6% (1/168)	0.7% (1/152)	0.0% (0/65)	3.8% (3/80)	0.0% (0/73)
Graft material rupture			0.0% (0/168)	0.0% (0/168)	0.0% (0/152)	0.0% (0/65)	0.0% (0/80)	0.0% (0/73)
Graft limb separation			0.0% (0/168)	0.0% (0/168)	0.7% (1/152)	1.5% (1/65)	0.0% (0/80)	0.0% (0/73)
Roll-In	No events	No events	No events	No events		No events	No events	No events
Barb separation					0.0% (0/27)			
Stent to graft separation					0.0% (0/27)			
Stent fracture					0.0% (0/27)			
Graft material rupture					0.0% (0/27)			
Graft limb separation					3.7% (1/27)			
High Risk	No events	No events				No events		
Barb separation			2.5% (2/79)[1]	1.4% (1/72)[1]	1.7% (1/60)[1]		4.5% (1/22)[1]	0.0% (0/18)
Stent to graft separation			0.0% (0/79)	0.0% (0/72)	0.0% (0/60)		0.0% (0/22)	0.0% (0/18)
Stent fracture			0.0% (0/79)	0.0% (0/72)	0.0% (0/60)		0.0% (0/22)	5.6% (1/18)
Graft material rupture			0.0% (0/79)	0.0% (0/72)	0.0% (0/60)		0.0% (0/22)	0.0% (0/18)
Graft limb separation			0.0% (0/79)	0.0% (0/72)	0.0% (0/60)		0.0% (0/22)	0.0% (0/18)

[1] Original barb design.
[2] Stent to graft attachment design prior to commercial distribution.

There was no radiographic evidence of graft material rupture in this study. To date, 19 patients were noted with confirmed barb separation in this study; one was identified with two separated barbs, and the others each had a single separated barb. No clinical events have been associated with either the single or double separated barbs. The Zenith® AAA Endovascular Graft includes 10 barbs located around the circumference of the suprarenal stent (12 barbs for larger diameter grafts) to aid in device fixation and to minimize the likelihood of caudal migration of the proximal end of the graft. If the force between the barb and aorta is excessive, the barb will separate, protecting the integrity of the aortic wall. While 10 or 12 barbs are available for fixation, four are adequate to counter forces exerted under normal clinical conditions as determined through bench testing. Therefore, the separation of one or two barbs is not considered clinically significant. This conclusion is confirmed by the absence of clinical sequelae in the few instances where barb separations were observed.

Two patients had a confirmed separation of the proximal uncovered stent from the graft material in a design used prior to the currently enhanced suprarenal stent attachment. In one case, the physician opted not to treat the partial separation of the proximal top stent since it had not completely separated and the patient had a long proximal aortic neck. The other case was most likely associated with repeated repositioning of the partially deployed graft cephalad and then caudad during attempts to cannulate the contralateral graft limb on the main body. The patient remained asymptomatic; however, imaging revealed top-stent separation of 2.4 mm at 1 year and 5 mm at 2 years. This patient was successfully treated with a custom-made proximal extension that included an uncovered stent with barbs.

A single stent fracture was confirmed in six patients. No clinical sequelae (conversion, rupture, or AAA-related death) or aorto-enteric fistulas have been associated with stent fracture for any of these six patients. Four of these six patients had a shrinking aneurysm (> 10 mm in 3 patients and > 5 mm in 1 patient), and one of these six patients had a stable aneurysm. One patient was identified with a growing aneurysm (> 5 mm) associated with a distal type I endoleak at 3 years. The location of the stent with the fracture was not related to the endoleak as the stent was in a location well removed from the distal end of the main body graft. The patient was successfully treated for growing aneurysm, limb migration and kink with angioplasty, and placement of a stent and a Zenith® AAA Endovascular Graft ancillary leg component. No multiple stent fractures were observed in any patient. The observations of single stent fracture do not change the risk/benefit of the device and do not at this time pose a known clinical concern.

Through five years of follow-up, component separation was observed in three patients as follows. In one patient, leg and extension separation was noted after five secondary procedures to treat a persistent type II endoleak. It is unknown whether re-instrumentation of the graft was a contributing factor in this separation. Two limb extensions were deployed to successfully address the separation. This patient later died of a ruptured cerebral aneurysm within 30 days of the secondary procedure to repair the component separation. A second patient had separation of the iliac leg component that was successfully addressed by the deployment of two Zenith® AAA Endovascular Graft iliac leg components. Component separation for a third patient was observed and was successfully treated with a stent and a leg extension. None of the patients have experienced aneurysm rupture or conversion to open surgical repair, and all three patients were successfully treated for the limb separation.

No radiographic evidence of graft material failure was noted in the study. Barb separation was noted in 19 patients, but was not clinically important. A custom-made device was placed to treat one separation between the top stent and the main body after excessive graft manipulation during challenging contralateral limb cannulation. Single stent fracture was identified in six patients and extensions were successfully placed for three separations between the leg and main body. Annual imaging follow-up is recommended to detect progression of disease, aneurysm growth, endoleak, loss of patency, and compromises in device integrity.

Migration

Migration was assessed radiographically from CT images at the 1-, 2-, 3-, 4-, and 5-year follow-ups in comparison to the baseline CT scan. Changes are reported as > 5 mm and > 10 mm movement in graft position (Table 14). KUBs were not used for assessing migration due to the potential for parallax error inherent to the imaging modality.

Table 14. Migration (Date of First Occurrence)

	1-year	2-year	3-year	4-year	5-year
Standard Risk > 10 mm > 5 mm	 0% (0/166) 2.4% (4/166)[1]	 0% (0/150) 2.7% (4/150)[1]	 0% (0/71) 0% (0/71)	 0% (0/75) 1.3% (1/75)[1]	 0% (0/71) 2.8% (2/71)[1]
Roll-In > 10 mm > 5 mm	 0% (0/31) 0% (0/31)	 0% (0/29) 0% (0/29)	 0% (0/10) 0% (0/10)	 0% (0/13) 0% (0/13)	 0% (0/14) 7.1% (1/14)[1]
High Risk > 10 mm > 5 mm	 0% (0/66) 3.0% (2/66)[1]	 0% (0/49) 0% (0/49)	 0% (0/11) 0% (0/11)	 0% (0/18) 0% (0/18)	 0% (0/14) 0% (0/14)

[1] No patient with radiographic evidence of migration > 5 mm but ≤ 10 mm had clinical sequelae or secondary intervention for migration.

At five years, no patients (0%) have been identified with device migration > 10 mm. Moreover, there were no clinically significant device migrations of any length of movement, and there were no proximal type I endoleaks, clinical sequelae, or secondary interventions related to device migration. Radiographic migration > 5 mm but ≤ 10 mm was observed in 4.9% of patients overall with evaluable imaging through five years. With the exception of one patient, there were no associated adverse clinical sequelae, no related secondary interventions, no type I endoleaks, and at five-year follow-up, the aneurysm size was stable or decreased. In these 14 patients with > 5 mm but ≤ 10 mm migration, the aneurysm size had decreased more than 10 mm in 64.3%, decreased more than 5 mm in an additional 21.4% (total shrinkage > 85%), and was stabilized in 7.1% of these patients. One patient had aneurysm growth > 5 mm associated with a distal type I endoleak that was subsequently treated with a Zenith® AAA Endovascular Graft iliac leg component.

Conversion

The Kaplan-Meier analysis below demonstrates that standard risk, roll-in, and high risk patients have 5-year freedom from conversion rates of 97.5%, 100%, and 97.7%, respectively (see Figure 5 and Table 15). Overall, patients treated with the Zenith® AAA Endovascular Graft have a 5-year freedom from conversion of 97.8%. In total, there were 6 reports of conversion to open surgical repair, including 5 within the original study follow-up period of 2 years, and 1 during the extended study follow-up period of 2 to 5 years, for which not all patients participated.

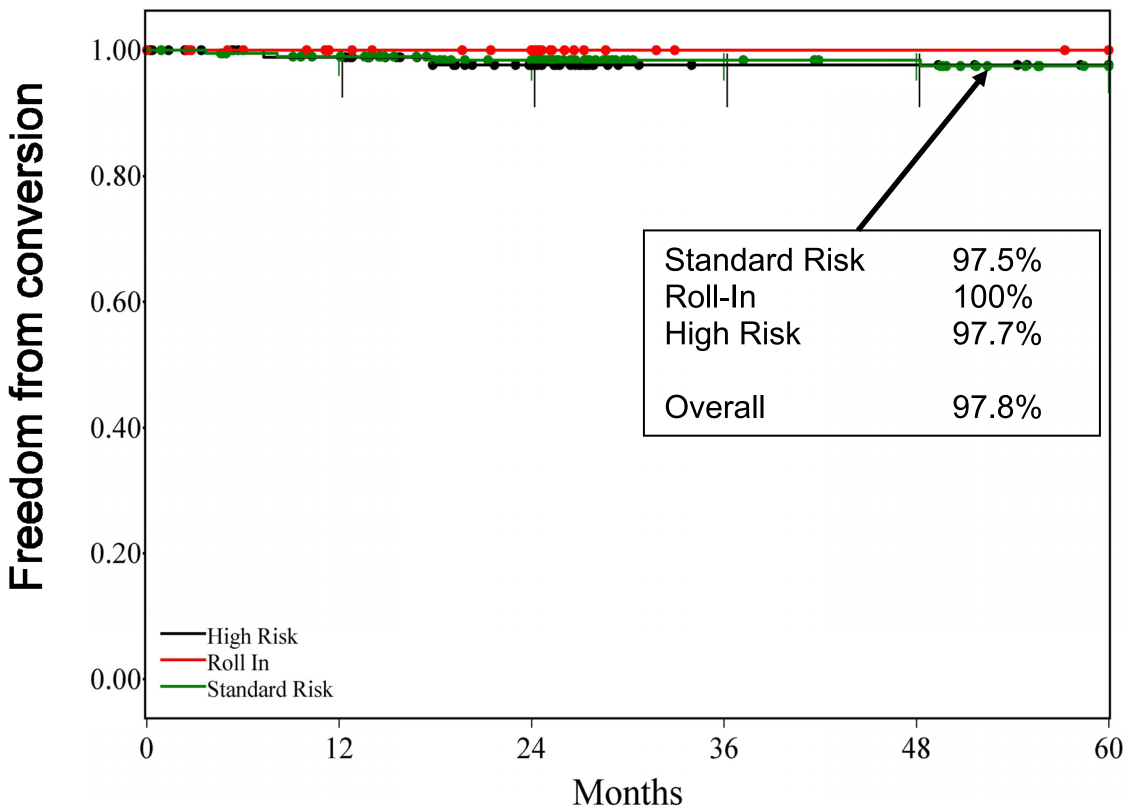

Figure 5. Freedom from Conversion to Open Surgical Repair (Inclusive of Intra-operative, Peri-operative, Post-operative, and Late)

A summary of the Kaplan Meier Curves is presented in Table 15.

Table 15. Summary of Kaplan-Meier Curves (Freedom from Conversion[1])

Study Arm	Parameter	Treatment to 30 days	30 days to 1 year	1 year to 2 years	2 years to 3 years	3 years to 4 years	4 years to 5 years
Standard Risk	# at risk[2]	199	198	190	173	108	105
	# of events	0	2	1	0	0	1
	# censored[3]	1	6	16	65	3	32
	Cumulative censored[4]	1	7	23	88	91	123
	Kaplan-Meier estimate[5]	1.000	0.990	0.984	0.984	0.984	0.975
	Standard error	NA	0.007	0.009	0.009	0.009	0.013
Roll-In	# at risk[2]	52	51	44	40	20	20
	# of events	0	0	0	0	0	0
	# censored[3]	1	7	4	20	0	7
	Cumulative censored[4]	1	8	12	32	32	39
	Kaplan-Meier estimate[5]	1.000	1.000	1.000	1.000	1.000	1.000
	Standard error	NA	NA	NA	NA	NA	NA
High Risk	# at risk[2]	100	98	90	71	30	30
	# of events	0	1	1	0	0	0
	# censored[3]	2	7	18	41	0	10
	Cumulative censored[4]	2	9	27	68	68	78
	Kaplan-Meier estimate[5]	1.000	0.989	0.977	0.977	0.977	0.977
	Standard error	NA	0.011	0.016	0.016	0.016	0.016

[1] There were no intra-operative or peri-operative conversions to open repair. Five patients required conversion to open repair beyond 30 days due to graft infection (2 patients); persistent type I endoleak due to undersized proximal graft diameter; hemorrhage from visceral aneurysm (not the treated AAA); and rupture, as discussed above.
[2] Number of patients at risk at the beginning of the interval.
[3] Patients are censored because their last follow-up was not reached due to lost to follow-up or death.
[4] The total censored for all time intervals up to and including that specific time interval.
[5] Estimate made at end of time interval.

Table 16 outlines the primary causes of conversion to open repair.

Table 16. Primary Causes of Conversion

Study arm	Days after procedure	Cause of conversion
Standard Risk	112	Visceral aortic aneurysm (not the Zenith® AAA Endovascular Graft-treated AAA).
Standard Risk	248	Persistent, proximal, type I endoleak due to undersized proximal graft diameter.
High Risk	222	Rupture[1] due to insufficient length of iliac landing zone.
High Risk	543	Graft infection[2]
Standard Risk	543	Graft infection[2]
Standard Risk	1468	Aortic neck dilatation with proximal type I endoleak and subsequent aneurysm growth.

[1] This is the same patient discussed previously (see Aneurysm Rupture section), where there was an insufficient landing zone length.
[2] Patients with graft infection died within 30 days of conversion (see Mortality section); all other patients survived conversion by at least 30 days.

No conversions to open repair were required intra-operatively or peri-operatively, and they were infrequent post-operatively. Prior to one year, conversions to open repair were related to rupture due to insufficient length of iliac landing zone (0.3%), persistent proximal type I endoleak due to an undersized proximal graft (0.3%), and secondary visceral aortic aneurysm (0.3%), all resulting in at least 30-day survival. The lessons learned from these cases were the importance of careful planning and sizing to obtain adequate diameters and lengths of components for the patient anatomy, and selection of patients with good proximal anatomy. Between one and five years, conversions to open repair were related only to graft infection (0.6%) and one instance of neck dilatation with endoleak (proximal type I), resulting in a 5-year freedom from conversion of 97.8%.

Study Summary

The U.S. clinical study of 351 patients who received the Zenith® AAA Endovascular Graft provided a prospective evaluation of clinical and radiographic performance related to safety and effectiveness. The study examined freedom from mortality, rupture, and open surgical conversion. In addition, the study examined aneurysm size change, device migration, endoleak, patency, and device integrity. The long-term results from those patients who agreed to participate continue to support the safety and effectiveness of the device and the need for annual clinical and imaging follow-up for detection of progression of disease, aneurysm growth, endoleak, loss of patency and device integrity.

36 mm diameter Zenith Flex® AAA Endovascular Graft

Approval to add the 36 mm diameter Zenith Flex® AAA Endovascular Graft to the existing Zenith Flex® AAA Endovascular Graft product line was granted by the FDA on September 7, 2006. The product line was expanded to include 36 mm diameter sizes for use in treatment of patients with AAA that have larger infrarenal neck diameters of up to 32 mm. A requirement of approval was that follow-up data from patients implanted with the 36 mm diameter device from the Australian clinical study and U.S. physician-sponsored IDE study at the Cleveland Clinic Foundation be collected and submitted annually. This summary provides updated follow-up data received through August 29, 2011, for the Australian clinical study and the U.S. physician-sponsored IDE clinical study (total of 41 patients).

The results presented in this report reiterate that the outcomes associated with clinical use of the 36 mm diameter Zenith Flex® AAA Endovascular Graft appear comparable to those of the US clinical trial for the 22 to 32 mm diameter Zenith AAA Endovascular Graft. There were no deaths within 12 months that were AAA-related (as adjudicated by the CEC). There were thirteen deaths beyond 12 months, and ten of these deaths were judged by the treating physician to be related to pre-existing conditions or not device- or procedure-related. The causes of the final three deaths are unknown at present. There continues to be only one reported rupture, but of a common iliac artery (presumably due to excessive over-sizing of the iliac leg component), and no reports of conversion to open repair (reference Table 17).

Table 17: Adverse events in the Australian Clinical Study and U.S. Physician Sponsored IDE Study

		Percent of patients					
		0-1 month	0-12 months	12-24 months	24-36 months	36-48 months	48-60 months
Australian clinical study	Serious adverse events Death Conversion Rupture	 0% (0/15) 0% (0/15) 0% (0/15)	 0% (0/15) 0% (0/15) 6.7% (1/15)	 8.3% (1/12) 0% (0/12) 0% (0/12)	 27.3% (3/11) 0% (0/9) 0% (0/9)	 14.3% (1/7[1]) 0% (0/5) 0% (0/5)	 0%(0/6[1]) 0%(0/4) 0%(0/4)
	At least one adverse event in any category[2]	13.3% (2/15)	53.3% (8/15)	41.7% (5/12)	22.2% (2/9)	20.0% (1/5)	0% (0/4)
U.S. physician-sponsored IDE study	Serious adverse events Death Conversion Rupture	 0% (0/26) 0% (0/26) 0% (0/26)	 7.7% (2/26) 0% (0/26) 0% (0/26)	 4.2% (1/24) 0% (0/24) 0% (0/24)	 10.0% (2/20[1]) 0% (0/12) 0% (0/12)	 16.7% (3/18[1]) 0% (0/11) 0% (0/11)	 12.5%(2/16[1]) 0%(0/9) 0%(0/9)
	At least one adverse event in any category[2]	38.5% (10/26)	53.8% (14/26)	26.0% (6/23)	25.0% (3/12)	27.3% (3/11)	33.3% (3/9)

[1] Deaths are considered public knowledge and may be reported without patient consent
[2] Adverse event categories are as follows: cardiovascular, pulmonary, renal, bowel, neurologic, vascular, and other.

Given the comorbidities of the patient population, the incidence of adverse events was not unexpected. No Type I endoleaks were noted during follow-up. Additionally, no type III or IV endoleaks were noted during follow-up. The few cases of aneurysm growth were mostly associated with Type II endoleak, were stable when compared to aneurysm size at 1-month rather than pre-procedure size, or had stabilized upon additional follow-up. One case of aneurysm growth showed no detectable endoleak, but possible growth due to endotension resulting from unsuitable proximal neck characteristics. There were no reports of device migration (> 10 mm), confirming both the barbs and stent-to-graft attachment are adequate to withstand migration forces acting on the 36 mm diameter device. . No new safety or effectiveness concerns were identified with this limited experience with the 36 mm diameter Zenith Flex® AAA Endovascular Graft (reference Table 18).

Table 18. Endoleak, Aneurysm Change from Baseline, Migration, Graft Patency, and Secondary Interventions at Each Follow-up Exam Period

		Percent of patients							
		Pre-discharge	1-month	6-month	12-month	24-month	36-month	48-month	60-month
Australian clinical study	Endoleak (all types)	50% (1/2[1])	13.3% (2/15)	20% (2/10)	0% (0/11)	0% (0/8)	0% (0/2)	50.0% (1/2)	50.0% (1/2)
	Aneurysm Change								
	Shrinkage	N/A (0/0)	20.0% (3/15)	33.3% (4/12)	41.7% (5/12)	37.5% (3/8)	0% (0/1)	0% (0/2)	33.3% (1/3)
	No change	N/A (0/0)	53.3% (8/15)	58.3% (7/12)	41.7% (5/12)	50.0% (4/8)	100% (1/1)	50.0% (1/2)	0% (0/3)
	Growth[2,3]	N/A (0/0)	26.7% (4/15)	8.3% (1/12)	16.7% (2/12)	12.5% (1/8)	0% (0/1)	50.0% (1/2)	66.7% (2/3)
	Migration	0% (0/2)	0% (0/15)	0% (0/12)	0% (0/12)	0% (0/4)	N/A (0/0)	N/A (0/0)	N/A (0/0)
	Intact devices	N/A (0/0)	100% (12/12)	100% (10/10)	100% (10/10)	100% (4/4)	100% (1/1)	N/A (0/0)	100% (1/1)
	Graft patency	100% (2/2)	100% (15/15)	100% (12/12)	100% (12/12)	100% (8/8)	100% (2/2)	100% (2/2)	100% (2/2)
	Any secondary intervention	6.7 % (1/15)							
U.S. physician-sponsored IDE study	Endoleak (all types)	22.7% (5/22)	8.3% (2/24)	10.5% (2/19)	6.3% (1/16)	6.7% (1/15)	0% (0/6)	0% (0/6)	0% (0/2)
	Aneurysm Change[3]								
	Shrinkage	N/A (0/0)	4.2% (1/24)	47.6% (10/21)	57.9% (11/19)	66.7% (10/15)	85.7% (6/7)	83.3% (5/6)	100% (3/3)
	No change	N/A (0/0)	95.8% (23/24)	42.9% (9/21)	36.8% (7/19)	20.0% (3/15)	14.3% (1/7)	0% (0/6)	0% (0/3)
	Growth[2]	N/A (0/0)	0% (0/24)	9.5% (2/21)	5.3% (1/19)	13.3% (2/15)	0% (0/7)	16.7% (1/6)	0% (0/3)
	Migration	N/A[4]	0% (0/22)	0% (0/17)	0% (0/15)	0% (0/12)	0% (0/8)	0% (0/4)	0% (0/3)
	Intact devices	96.0% (24/25)	91.7% (22/24)	88.2% (15/17)	75.0% (12/16)	66.7% (8/12)	62.5% (5/8)	75.0% (3/4)	33.3% (1/3)
	Graft patency	100% (24/24)	100% (25/25)	100% (19/19)	100% (18/18)	100% (15/15)	100% (6/6)	100% (6/6)	50% (1/2)
	Any secondary intervention	19.2% (5/26)							

[1] Only two patients had a pre-discharge CT exam in the Australian study.
[2] All cases in which continued aneurysm enlargement was observed had identifiable causative factors such as endoleak or inadequate proximal neck.
[3] The use of pre-procedure image values for baseline values may have caused false positive findings of aneurysm growth, because any aneurysm growth that occurred between pre-procedure imaging and treatment would contribute to the overall measured change.
[4] Device migration was not assessed at this time point.

Section II - Worldwide Commercial Experience

Zenith® AAA Endovascular Graft

The Zenith® AAA Endovascular Graft (including the Zenith Flex® AAA Endovascular Graft) has been in commercial distribution in the U.S. since market release in June 2003. A total of 275,895 components comprising 71,372 Zenith® AAA Endovascular Grafts have been sold in the U.S. through March 31, 2012.

As of March 31, 2012, a total of 159,200 bifurcated Zenith® AAA endovascular grafts have been distributed worldwide. Cook evaluates product performance from this commercial experience based on adverse event reporting systems throughout the world. Table 19 presents a summary of reports received from commercial experience with the Zenith® AAA Endovascular Graft through March 31, 2012.

Table 19. Reported Serious Adverse Events from Commercial Experience with the Zenith® (Flex) AAA Endovascular Graft (includes 36 mm diameter graft)

Adverse Event	U.S. (June 3, 2003 through March 31, 2012)	Outside U.S. (through March 31, 2012)
Death (≤ 30 days)	63	38
Aneurysm rupture (post-procedure)	13	10
Conversion to Open Surgical Repair	109	39
Total	**185**	**87**

In the U.S., there were 13 post-procedural aneurysm ruptures reported through the company's complaint system. Eleven of the thirteen patients had known outcomes and were successfully treated; one with surgical ligation of an unresolved type II endoleak, one with endovascular placement of a leg component for a distal type I endoleak, one with endovascular placement of another manufacturer's graft for a distal type I endoleak, two with endovascular placement of a leg component to bridge a leg disjunction, one with placement of a Renu device and a main body extension, one with placement of a Renu converter, one with placement of a modified thoracic stent-graft, and three with conversion to open repair. The remaining two patients' outcomes are unknown as it was not provided by the reporter. There were 63 deaths within 30 days and 109 open surgical conversions reported in the US.

Outside the U.S., there were 10 post-procedural aneurysm ruptures reported. One of these cases was associated with partial detachment of a suprarenal stent (manufactured prior to the strengthened suprarenal stent attachment implemented for U.S. commercialization) and the patient expired. Nine of these cases were successfully treated; one with axillo-bilateral femoral bypass surgery, one with placement of another manufacturer's endoprostheses and stent to treat a proximal type I endoleak, one with placement of another manufacturer's endoprostheses to treat a proximal type I endoleak, one with an unspecified treatment, one with open surgical repair, one with endovascular placement of another manufacturer's endoprostheses to treat a distal type I endoleak, and three with endovascular placement of a leg component for a distal type I endoleak. There were 38 deaths within 30 days and 39 open surgical conversions reported outside the US.

The Company's established post-market surveillance activities outside the U.S. have confirmed factors included in the IFU that can mitigate the risk of limb thrombosis. These factors include: recognizing prospectively when patient anatomy is not consistent with the IFU; properly planning graft components to avoid undersizing (causing migration and kinking), or oversizing (causing obliteration of the lumen with graft material); removing any stiff wire guide before recording a final angiogram, thus allowing the physician to appreciate and treat tortuosity and kinking, if necessary, at the time of the procedure; and considering adjunctive procedures as described in the Zenith® training program and literature[1] when unexpected severe iliac tortuosity causes kinking of the graft.

While not observed in the U.S. study, worldwide commercial use has shown rare cases of patients without periodic imaging having undetected progressive vascular disease involving dilation of the visceral aorta, with the proximal seal site aortic diameter eventually exceeding the endograft diameter leading to proximal leakage, multiple barb separations and attendant clinical consequences. Annual clinical and radiographic follow-up is recommended to assess progressive disease and aortic neck dilation.

<u>Zenith Renu® AAA Ancillary Graft</u>

The Zenith Renu® AAA Ancillary Graft (Renu) is a modification of the Zenith® AAA Endovascular Graft. Prior to availability of this device, treatment for inadequate proximal fixation or seal was limited (i.e., medical management, open surgical conversion, or cuff implantation). Cook recognized the limitations of the available treatment options for many patients and, with input from the medical community, designed the Zenith Renu® AAA Ancillary Graft as an alternative treatment option.

[1] Sivamurthy N, Schneider DB, Reily LM, Rapp JH, Skovobogaty H, and Chuter TAM. Adjunctive primary stenting of Zenith endograft limbs during endovascular abdominal aortic aneurysm repair: Implications for limb patency. *J Vasc Surg* 2006;43:662-70.

Although the Zenith Renu® AAA Ancillary Graft is a very specialized device intended to have limited use only during secondary interventions, Cook believed that patients with failed pre-existing grafts deserved to have a viable alternative to the available treatment options.

The Zenith Renu® AAA Ancillary Graft uses the same materials and has the same proximal fixation characteristics (a bare, suprarenal stent with caudally-oriented barbs and an internal stainless steel sealing z-stent) as the clinically-proven Zenith Flex® AAA Endovascular Graft. The Zenith Renu® AAA Ancillary Graft is intended to be used as a bailout device for situations in which a previously implanted AAA stent graft does not provide adequate proximal fixation or seal. It is available in two configurations: 1) a converter configuration to treat short-bodied pre-existing grafts and 2) a main body configuration to treat longer-bodied pre-existing grafts.

The Zenith Renu® AAA Ancillary Graft has been in commercial distribution in the U.S. since market release in June 2005. A total of 7,784 Zenith Renu® AAA Ancillary Grafts have been sold in the U.S. through March 31, 2012.

As of March 31, 2012, a total of 10,865 Zenith Renu® AAA Ancillary Grafts have been distributed worldwide. As is the case for the Zenith® AAA Endovascular Graft, Cook evaluates product performance from this commercial experience based on adverse event reporting systems throughout the world. Table 20 presents a summary of reports received from commercial experience with the Zenith Renu® AAA Ancillary Graft through March 31, 2012.

Table 20. Reported Serious Adverse Events from Commercial Experience with the Zenith Renu® AAA Ancillary Graft

Adverse Event	U.S. (May 2005 through March 31, 2012)	Outside U.S. (through March 31, 2012)
Death (≤ 30 days)	11	5
Aneurysm rupture (post-procedure)	2	0
Conversion to Open Surgical Repair	21	3
Total	**34**	**8**

Worldwide, 2 post-procedural aneurysm ruptures, 16 deaths within 30 days, and 24 open surgical conversions have been reported. The conversions to open repair were due to rupture of the aortic wall proximal to the Zenith Renu® AAA Ancillary Graft (4), proximal type I endoleak (3), misplacement of the device due to extremely tortuous anatomy (3), migration due to deployment errors (6), infection (3), difficulty removing the top cap (5), incorrect sizing relative to patient anatomy (1), and inadvertent covering of the renal arteries (2). In one case, the patient presented to the hospital with a ruptured aneurysm, and the physicians decided to treat the patient with a Renu converter because they thought it would be faster than placing a bifurcated device. After placement, the trauma surgeon opened the patient's abdomen to prevent compartment syndrome, observed that blood flow continued to leak into the patient's abdomen, and decided to convert to open repair. This patient was successfully treated. The remaining four patients with aortic rupture included three patients where difficulty removing the top cap was encountered, and one patient with inadvertent covering of the renal arteries that did not survive the conversion.

Zenith Renu® AAA Ancillary Graft Post-Market Surveillance Registry

On June 9, 2005 the Zenith Renu® AAA Ancillary Graft received FDA approval. One condition of the approval by FDA was the collection of physician experience with the Zenith Renu® AAA Ancillary Graft. Cook has established a registry to capture this post-market surveillance information. For each implanted graft, the implanting physician was requested to minimally provide clinical and imaging information at the following time points: registration, implant procedure, short-term follow-up (within 30 days and at 12 months), and long-term follow-up (annually thereafter for a period of 5 years after enrollment begins). All requested follow-ups were already recommended in the approved labeling; therefore, no additional information beyond what was considered standard of care was required as part of the registry.

An independent Clinical Events Committee (CEC) was established (Harvard Clinical Research Institute, Boston, MA) to examine any reports of death, aneurysm rupture, conversion to open surgical repair, or other adverse events to determine association with the endovascular repair. The registry was overseen by a Data Safety Monitoring Board (DSMB), which regularly reviewed adverse events to assure acceptable patient safety. An independent core lab analyzed de-identified pre-operative, intra-operative, and follow-up imaging to assess aneurysm size, presence of endoleak, graft patency, and device integrity.

Between September 9, 2005 and February 15, 2007, 151 cases of physician experience with the Zenith Renu® AAA Ancillary Graft were registered in the post-market surveillance registry. These 151 cases reflect use of 89 converters and 62 main body extensions, implanted at 95 institutions. A summary of the U.S. Zenith Renu® AAA

Ancillary Graft post-market surveillance registry results, as provided by the implanting physicians as of February 8, 2011, is presented in this report. Follow-up for these cases is now complete.

Failure Mode(s) of Pre-existing Grafts Treated with Renu

Each Zenith Renu® AAA Ancillary Graft was used to treat a pre-existing graft with inadequate proximal fixation or seal. The failure modes of the pre-existing grafts as reported by each site through the on-line registry are provided in Table 21.

Table 21. Failure modes of pre-existing grafts treated with the Zenith Renu® AAA Ancillary Graft[1]

		Pre-existing Graft									
		All	AneuRx®	Ancure®	Excluder®	Fortron™	Lifepath™	Talent™	Vanguard™	Zenith®	Other [2]
Devices Treated		**151**	**126**	**9**	**6**	**1**	**1**	**3**	**2**	**1**	**2**
Reported Failure Modes [3]	Endoleak	**108**	**89**	**6**	**4**	**1**	**1**	**2**	**2**	**1**	**2**
	Proximal Type I	**86**	**74**	**4**	**2**	**1**	**1**	**1**	**1**	**1**	**1**
	Migration	**136**	**120**	**6**	**2**	**1**	**1**	**3**	**2**	0	**1**
	Stent Fracture/ Breakage	**3**	**3**	0	0	0	0	0	0	0	0
	Graft Tear	**3**	**2**	**1**	0	0	0	0	0	0	0
	Component Separation	**2**	**1**	0	0	0	0	0	**1**	0	0
	Occlusion	**2**	**1**	**1**	0	0	0	0	0	0	0
	Kink	**7**	**5**	**1**	0	0	0	0	0	0	**1**
	Other[4]	**2**	**1**	0	**1**	0	0	0	0	0	0

[1] Failure modes of pre-existing grafts are based on site-reported data.
[2] Hand-made grafts (1 aorto-uni-iliac and 1 bifurcated).
[3] Ninety-nine pre-existing grafts were reported as having multiple failure modes. Failure mode(s) of one AneuRx® graft was not provided by one implanting institution. Per Cook representative present at the procedure, the pre-existing graft had both migrated and had a proximal type I endoleak. These failure modes were confirmed by evaluation of pre-operative imaging and have been included in this analysis.
[4] One AneuRx® was noted as having a loss of graft integrity discovered during the Renu procedure. One Excluder® was noted as having aneurysm sac growth due to the material.

The most commonly reported failure modes of pre-existing grafts were proximal type I endoleak (86 cases) and migration (136 cases). Other failure modes included additional endoleak, stent fracture, graft tear or leakage, component separation, kink, and occlusion. More than one failure mode was reported in 99 cases.

Aneurysm Rupture

Four aneurysm ruptures following Renu implantation were identified. Three of the patients were converted to open surgical repair following aneurysm rupture. One subsequently recovered (see Table 22 for additional information) and the other two deceased intra-operatively or post-operatively (see Table 23 for additional information). The patient who did not undergo conversion to open surgical repair had previously declined surgery to treat a type II endoleak with subsequent aneurysm expansion and died following the aneurysm rupture (see Table 23 for additional information).

Conversion

Nine conversions to open repair were reported. All conversions underwent review by the CEC to allow adjudication as to whether conversion was related to the endovascular intervention. If the conversion was related to the endovascular intervention, the CEC determined if the event was procedure-related, technique-related, or device-related (Renu or pre-existing graft). The results from CEC adjudication of each conversion are listed in Table 22.

Table 22. Conversions

Months after procedure	Reason for conversion	CEC adjudication
0	Rupture of aortic wall proximal to aneurysm and Renu device	Procedure-related and technique-related
0	Leakage due to incomplete sealing/persistent blood flow into the aneurysm from patent vessels (proximal type I endoleak)	Procedure-related and Renu-related
3	Leakage due to incomplete sealing of the aneurysm (proximal type I endoleak)	Procedure-related, technique-related, and Renu-related
12	Leakage due to incomplete sealing of the aneurysm, inadequate sealing between the Renu main body extension and the AneuRx® graft (a Renu converter had been recommended but a Renu extension was used, with less than recommended overlap), and aneurysm rupture	Technique-related and Renu-related
12	Inadequate sealing between the Renu main body extension (a Renu converter had been recommended) and the AneuRx® graft, and aneurysm rupture	Renu-related
16	Leakage due to migration of pre-existing graft (AneuRx®) and aneurysm rupture	Renu-related
19	Infection of the pre-existing graft (AneuRx®)[1]	Not related
30	Leakage due to incomplete sealing of the aneurysm (proximal type I endoleak)	Renu-related
45	Rupture of external iliac artery during secondary intervention to treat distal type I endoleak (distal to Renu main body extension)	Pre-existing graft-related

[1] Core lab analysis of pre-Renu imaging noted stranded contrast that was potentially indicative of infection. An independent CEC adjudicated this case to be unrelated to the Renu endovascular repair.

Two intra-operative conversions and seven late (> 30-day) conversions were reported. The intra-operative conversions to open repair were due to rupture of the aortic wall proximal to the Renu device (1) and proximal type I endoleak (1). The patient with aortic wall rupture did not survive the conversion (see Table 23). The late conversions were related to a suspected graft infection (1), a persistent proximal type I endoleak initially identified during the procedure (2), inadequate sealing between the Renu main body extension and the AneuRx® graft leading to component separation and aneurysm rupture (3), and rupture of the external iliac artery during secondary intervention to treat distal type I endoleak (1). In two conversions (1 intra-operative and 1 late) due to proximal endoleak, the physician chose not to use additional components (e.g., Palmaz® stent, main body extension, etc.) during the Renu implantation procedure to resolve the proximal type I endoleak. Both patients were considered candidates for open surgical repair by their implanting physicians, thus additional components may not have been implanted to avoid complicating the eventual conversion to open repair. In the third conversion due to proximal type I endoleak, the physician had previously attempted to treat the endoleak using coil embolization (25 months) and additional stenting at the graft neck (29 months); however, the attempts to resolve the endoleak were unsuccessful. The patient successfully underwent conversion to open surgical repair. In all three late conversions due to inadequate sealing between the Renu main body extension and the AneuRx® graft with subsequent aneurysm rupture, physician peer review of pre-procedure imaging noted that a Renu converter would be a better treatment choice. Despite the physician's recommendation, one patient requested the main body extension because it required a less extensive intervention than the converter; however, the recommended overlap with the pre-existing graft was not achieved following Renu deployment. Subsequently, the pre-existing graft separated from the Renu (by 12 months), the patient declined an intervention to treat the separation, the aneurysm ruptured, and the patient was successfully converted to open surgical repair. The other two patients with aneurysm rupture died following the conversion (see Table 23). In the case of late conversion performed due to rupture of the external iliac artery during secondary intervention to treat a persistent distal type I endoleak, attempts to advance iliac limbs resulted in rupture of the iliac artery. The patient underwent conversion to open surgical repair, which required aortic cross-clamping that possibly resulted in dissection of the aorta treated with two thoracic endografts. The patient died two days following the secondary intervention due to cardiopulmonary arrest, respiratory failure, and renal failure. This event was considered related to the pre-existing graft by the CEC.

Mortality

Forty-five deaths were reported in the Zenith Renu® AAA Ancillary Graft post-market surveillance registry. All deaths underwent review by the CEC to allow adjudication as to whether mortality is related to the endovascular intervention. If the death was related to the endovascular intervention, the CEC further determined if the event was procedure-related, technique-related, or device-related (Renu or pre-existing graft). The results from CEC adjudication of each death are listed in Table 23.

Table 23. Deaths

Months after procedure	Age at registration	Cause of death	CEC adjudication
0	82	Intra-operative rupture of aorta proximal to aneurysm and Renu device[1]	Procedure-related and technique-related
1	78	Congestive heart failure 35 days post-procedure	Not related
2	79	Wegener's granulomatosis	Not related
1	90[2]	Low platelet count, hematological complications[3]	Procedure-related
10	73	Cardiorespiratory arrest secondary to hypotension and sepsis[4]	Procedure-related and technique-related
3	80	Cardiopulmonary failure[5]	Cause unable to be determined
7	90[2]	Failure to thrive/old age	Not related
12	80	Metastatic lung cancer	Not related
12	81	Multi-system organ failure following aortic aneurysm rupture and subsequent emergent conversion[6]	Renu-related
13	82	Cancer	Not related
4	83	Direct cause of death not available to reporting institution[7]	Not related
20	73	Congestive heart failure and respiratory failure secondary to congestive heart failure	Not related
17	77	Pulmonary emboli secondary to malignancy	Not related
20	79	Pulmonary	Not related
19	75	Ventricular fibrillation, ischemic cardiomyopathy, and GI bleed	Not related
12	77	Unknown, information unable to be obtained by reporting institution[8]	Not related
11	69	Recurrent cholangiocarcinoma	Not related
17	65	Cancer	Not related
23	85	Unknown, but believed by site to be unrelated to the Renu	Pending
16	76	Cardiac arrest following aneurysm rupture and emergent conversion to open repair[9]	Renu-related

Months after procedure	**Age at registration**	**Cause of death**	**CEC adjudication**
14	69	Pneumonia with fever and septic shock	Not related
27	75	Unrelated to aneurysm, patient died at home[10]	Cause unable to be determined
10	79	Myocardial infarction[11]	Cause unable to be determined
29	82	Cancer	Not related
33	84	Cardiopulmonary arrest	Not related
28	67	Cardiac issues related to CHF	Pending
21	81	Complications from pneumonia and organ failure	Not related
36	67	Cancer	Pending
37	82	Unknown – notification came from primary care physician	Pending
24	Not provided	Unknown[12]	Cause unable to be determined
21	76	Heart attack	Not related
Unknown	76	Unknown[13]	Cause unable to be determined
36	61	Unknown[14]	Cause unable to be determined
48	72	Urinary bacteremia, prostate cancer, MRSA	Not related
30	69	Lung cancer	Not related
40	79	Cardiogenic shock following hip repair of femoral neck fracture	Not related
18	80	Paralysis secondary to cervical fracture from fall; renal failure	Not related
36	71	CVA, respiratory failure, cancer 2008	Not related
36	74	Cardiac causes	Not related
40	90[2]	Respiratory failure	Not related
45	78	Cardiopulmonary arrest, respiratory failure, renal failure 2 days after secondary intervention[15]	Pre-existing graft-related[16]
30	78	Ruptured AAA after patient refused to return for repair of type II endoleak with aneurysm expansion	Pre-existing graft-related[17]
36	77	Respiratory/cardiac arrest	Not related
36	90[2]	Unknown[18]	Cause unable to be determined
48	87	Cancer	Not related

[1] The patient failed to recover from conversion to open surgical repair, which was performed to treat a rupture of the aorta proximal to the Renu device. The aorta was ruptured by a spicule of calcium after Renu deployment, either during deployment of a Palmaz stent or ballooning of a Renu device.

[2] To comply with HIPAA regulations, the age of any patient ≥ 90 years old was recorded and reported as 90 years.

[3] The patient was admitted with a low platelet count and an AneuRx® with a proximal type I endoleak. The patient's aneurysm ruptured prior to the scheduled Renu implantation date, but was able to be treated emergently with the Renu converter. The event was conservatively adjudicated as procedure-related because the CEC was unable to exclude the possibility that the death was related to the procedure even though the aneurysm had ruptured prior to the procedure.

[4] The site noted that the death was likely caused by an undiagnosed infection prior to Renu implantation; however, the CEC was unable to exclude the possibility that the death was related to the implant procedure. As a result, the death was conservatively adjudicated as procedure-related.

[5] Exact cause of death was unknown. The family described the death as related to cardiopulmonary failure; the patient had a documented 10-year history of severe cardiopulmonary disease.
[6] Rupture with emergent conversion was secondary to separation of the Renu main body extension from the pre-existing AneuRx® graft. Although a Renu converter had been recommended prior to the procedure (during physician peer review of the case), the implanting physician chose to implant a Renu main body extension.
[7] Patient was undergoing evaluation for neuromuscular degeneration. Per institution, there was no indication that death was related to the aneurysm or the endograft.
[8] Cause of death was unknown. Per the reporting institution, an autopsy was performed and the death was related to a pre-existing comorbidity. Based on the available information, the CEC determined the death to be unrelated to the endovascular repair.
[9] Rupture with emergent conversion was secondary to migration of the AneuRx® graft with subsequent type III endoleak. Although a Renu converter had been recommended prior to the procedure (during physician peer review of the case), the implanting physician chose to implant a Renu main body extension.
[10] The site noted this death to be unrelated to the aneurysm; however, the CEC was unable to adjudicate the death without confirmation that the site obtained the information from a death certificate or an autopsy was performed.
[11] The patient died after an MI; however, the CEC was unable to adjudicate the death because the patient passed away at home and an autopsy was not performed.
[12] Cause of death was unknown. Per the reporting institution, the death was reported to the physician by the family. The CEC was unable to adjudicate the death based on the information provided.
[13] Cause of death was unknown. Per the reporting institution, information was not available about cause of death or time of death with respect to Renu implantation. The last contact the site had with the patient was at the 1-month follow-up.
[14] Cause of death was unknown. Per the reporting institution, the death was related to a pre-existing comorbidity and the graft was fine 2 months prior to death.
[15] Secondary intervention was performed to treat distal type I endoleak. Iliac artery rupture during advancement of additional iliac limbs led to conversion to open surgical repair. Patient died two days following intervention/conversion.
[16] CEC adjudicated death as related to endovascular intervention, but related to the salvage procedure, which was for a distal type I endoleak of the pre-existing graft (distal to the Renu device).
[17] CEC adjudicated death as related to endovascular intervention, but related to the pre-existing graft, not the Renu.
[18] Cause of death was unknown. Per the reporting institution, a family member had called the office with the date of death, but the cause was unknown. The site noted that the patient was being treated for cancer.

One intra-operative, one early (≤ 30-day), and 43 late (> 30-day) deaths have been reported. One intra-operative, endovascular intervention-related death occurred after the patient failed to recover from conversion to open repair following rupture of the aorta proximal to the Renu™ device. One early death occurred approximately 2 weeks after the initial procedure, where the patient died from a low platelet count and hematological complications. Of note, the patient was treated emergently with the Renu after being admitted with a low platelet count and after aneurysm rupture. This event was determined to be procedure-related. Death beyond 30 days of the initial procedure occurred in 43 cases. Twenty-nine cases were determined to be unrelated to endovascular repair. Of the fourteen remaining cases, five have been adjudicated as related to endovascular repair (i.e., procedure, technique, pre-existing graft, and/or Renu-related), nine are unable to be adjudicated due to insufficient information from the site (no additional information is able to be collected). The first of the endovascular repair-related deaths occurred 10 months after implantation and the cause was reported to be cardiorespiratory arrest secondary to hypotension and sepsis (procedure-related and technique-related). The second of the endovascular repair-related deaths (Renu-related) occurred prior to the 12-month follow-up exam. Anatomical changes in the patient over time contributed to device separation of the pre-existing graft from the Renu main body extension, leading to an eventual aneurysm rupture. The patient was subsequently converted to open surgical repair, but died post-operatively due to multi-system organ failure. The third of the endovascular repair-related deaths (Renu-related and technique-related) occurred 16 months after implantation. Although the 12-month follow-up form was not completed, 12-month imaging was provided. Core lab analysis of the 12-month imaging indicated component separation of the right leg component; however, a definitive type III endoleak was unable to be confirmed since non-contrast imaging was not provided. At 16 months, the physician noted that AneuRx® migration led to type III endoleak and rupture. The patient was emergently converted to open surgical repair, but did not survive the conversion. The remaining two endovascular repair-related deaths were identified as related to the pre-existing graft, rather than the Renu graft. One death at 45 months occurred following an emergent conversion to open repair, which was required to treat an iliac artery that ruptured during a secondary intervention to implant additional iliac limbs to treat a distal type I endoleak (endoleak was unrelated to the implanted Renu main body extension). The other death occurred 30 months after implantation. Approximately 10 months prior to Renu implantation (19 months after implantation of the pre-existing graft), the patient had undergone coil embolization to treat a type II endoleak; however, based on either site or core lab analysis, the type II endoleak persisted through 12 months with aneurysm expansion at 12 months. The physician discussed the need for additional intervention with the patient; however, the patient declined the surgery and died from aneurysm rupture 30 months following Renu implantation. The death was considered related to the pre-existing graft and not the Renu graft.

None of the CEC-adjudicated deaths were related to deployment of the Zenith Renu® AAA Ancillary Graft or Renu integrity. None of the endovascular repair-related deaths were unanticipated since they were noted as possibilities in the Instructions for Use of this device.

Registry Summary

Between September 9, 2005 and February 15, 2007, 151 cases of physician experience have been registered in the Zenith Renu® AAA Ancillary Graft post-market surveillance registry. Registration of follow-up data was complete on February 8, 2011. The Zenith Renu® AAA Ancillary Graft has been used to treat many different types of endovascular grafts. These pre-existing grafts were primarily treated for proximal type I endoleak (86 cases) or migration (136 cases), although additional failure modes were also reported. Of the proximal type I endoleaks reported, 99% (95/96) resolved without further intervention following Renu implantation; one persisted through one-month follow-up and was converted to open surgical repair. Of the 151 registered cases of Renu implantation, 89.4% (135/151) have had no procedure-related or Renu-related adverse events, conversions, or deaths. These mid-term post-market registry data confirm that the Renu device may be used during secondary intervention to successfully treat proximal fixation failures.

It is imperative that implanting physicians carefully review the Zenith Renu® AAA Ancillary Graft Instructions for Use for guidelines on patient and device selection and carefully consider all options (e.g., endovascular treatment, open surgical repair) prior to choosing the best treatment for each patient. Regular clinical and imaging follow-up will be necessary for detecting progression of the disease, aneurysm growth, endoleak, loss of patency, and compromises in device integrity.

Summary of Device Improvements

From the widespread clinical use of the Zenith® AAA Endovascular Graft, information on the performance of the device has been received. Cook is committed to evolutionary improvements to the Zenith® AAA Endovascular Graft in response to this information as well as information from other sources such as *in vitro* testing and experience from other devices. The company has been proactive in making minor modifications to the device to further improve device performance and mitigate potential risks as much as possible.

Clinical evidence shows that strong proximal fixation including hooks or barbs for aortic wall attachments are important to avoid early and late migration. The low migration rate of the Zenith® AAA Endovascular Graft has been attributed to its suprarenal proximal fixation mechanism. As a result of observations of suprarenal stent separation and the knowledge that strong fixation is important, two enhancements were made to the proximal fixation mechanism. Before U.S. release of the Zenith® AAA Endovascular

Graft, the strength and durability of the attachment of the suprarenal stent to the rest of the endovascular graft were increased to improve the safety factor for patients in whom excessive force is exerted on the suprarenal fixation mechanism. Because clinical data suggest barbs in addition to radial force on the proximal stent are necessary to durably engage the aorta, stronger barbs were approved.

The low proximal type I endoleak rate after implantation of a Zenith® AAA Endovascular Graft has been attributed to the separate sealing stent at the proximal end of the graft. To improve the flexibility and apposition to the aortic wall in the sealing zone in marginal anatomy within the indications for use such as angulated necks, the spacing between stents in the proximal section of the graft was increased subsequent to U.S. approval (referred to as Zenith Flex®). Two improvements have been made since market release to better accommodate marginal anatomy of tortuous iliac arteries within the indications for use; spacing between stents in leg components was increased, followed by replacement of the individual external z-stent segments with a continuous spiral external z-stent (referred to as the Zenith® Spiral-Z AAA Iliac Leg).

The introduction system has been improved by incorporating Cook's approved Flexor® sheath technology with greater flexibility and a hydrophilic coating, and by incorporating Cook's approved Captor® valve technology for better hemostasis. In addition, improved user interfaces have been incorporated into the delivery system (referred to as the Z-Trak™ system), and a large diameter proximal trigger wire has been implemented to increase resistance to bending.

The company had received several requests from physicians for a viable alternative to open surgical conversion of patients whose primary endograft has inadequate proximal fixation or seal. In response, Cook developed and obtained approval for a set of modified Zenith® ancillary components called the Zenith Renu® AAA Ancillary Graft.

An estimated 10% of patients with AAA disease require use of a device that is larger in diameter than 32 mm. The Zenith Flex® AAA Endovascular Graft product line was expanded to include 36 mm diameter sizes for use in treatment of patients with AAA that have infrarenal neck diameters of up to 32 mm.

Section III - Explant Analysis

This section summarizes the findings from explant analysis of grafts from clinical study and worldwide commercial experience.

Clinical Study Experience

In addition to radiographic and clinical data, information was obtained from eight explanted devices that were submitted as a part of the U.S. multi-center clinical study (pivotal and continued access). Devices were explanted at the time of conversion to open repair or autopsy for a variety of reasons unrelated to compromises in device integrity.

Explants included complete grafts, partial grafts, and fragments of grafts. While damage from surgical instruments during explantation was sometimes obvious, it was not always possible to determine if observations occurred before explantation or if the explantation process contributed to, or caused, the observations. Explanted devices were assessed using high resolution X-ray, gross examination, histological microscopy, and scanning electron microscopy. The assessment was focused upon graft material wear, suture wear, and metal component fatigue.

Complete grafts, partial grafts, and fragments of grafts were available from eight cases with an average of 574 (range 1 – 1467) days of implantation. The reasons leading to explantation and observations are listed in Table 24. None of the devices were explanted because of failure of device integrity.

Table 24. Observations from complete grafts, partial grafts, and fragments of grafts explanted in the U.S. multi-center study

Reason for explant[1]	Days Implanted	Damaged or Broken Stents	Barb Separation	Graft Wear	Cut or Broken Sutures (green)[2]	Cut or Broken Sutures (blue)[3]	Suture Hole Elongation
Autopsy (MI)	1						
Autopsy (unrelated death)	165	1					1[4]
Conversion for persistent type I endoleak	248				1		
Autopsy (persistent bacteremia)	401	1	1		4		
Conversion for infection	543		1				
Conversion for infection	543					4	
Autopsy (unrelated death)	1221		1				
Conversion for persistent type I and type III endoleak	1467						

[1] None of the explantation procedures were due to failure in device integrity. Noted observations may have been due to damage caused during device removal.
[2] Sutures used to attach external stents; observation may have been due to damage caused during device explant.
[3] Sutures used to attach suprarenal stent; observation may have been due to damage caused during device explant.
[4] Noted observation may have been due to damage caused during device explant.

Sutures were evaluated on the complete grafts, partial grafts, and fragments of grafts. All sutures were intact on some devices, while on other devices isolated sutures were either cut by surgical instruments or broken on some grafts. The isolated suture breaks were not attributed to failure of the device.

There were no fatigue fractures of suprarenal or sealing stents. External stents were either damaged with a surgical instrument or fractured in two explanted grafts, without any observable untoward effect. There were no clinical adverse events or radiographic evidence of stent fracture, endoleak, migration, or component separation prior to their explantation.

The barbs on the proximal (suprarenal) fixation stent are designed to resist migration through attachment to the aorta. Because the device was designed with more barbs (10 to 12) than necessary for fixation (four), the separation of one or two barbs is not clinically significant. Barb separation was identified in explanted grafts in the U.S. multi-center clinical study. No migration, endoleak, or separation was observed in these patients by the investigative site or core lab prior to the explant; the barb separations were not associated with adverse clinical sequelae.

Three explants from other non-commercial experiences outside the multi-center study have been analyzed. The reason for explant is unknown, and the number of days implanted was unknown in two of three – one was implanted for 57 days. One explant was found to have damaged or broken stents. Two explants were found to have cut or broken sutures (blue). While damage from surgical instruments during explantation was sometimes obvious, it was not always possible to determine if observations occurred before explantation or if the explantation process contributed to, or caused, the observations.

Worldwide Commercial Experience

Twenty-eight explants from worldwide commercial experience have been received and analyzed. The reason for explant were unknown (19/28), leaking (4/28), migration (1/28), infection (2/28), rupture (1/28) and off-label use (1/28). The number of days implanted was unknown in four of twenty-eight – the mean implant duration in twenty-four explants was approximately 812 days (range of 1 to 1946 days). Eleven explants were found to have damaged or broken stents. Eight explants were found to have barb separations. Sixteen explants were found to have cut or broken sutures (green). Six explants were found to have cut or broken sutures (blue). Two explants were found to have suture hole elongations. Two explants were found to have holes of uncertain origin, and one explant was found to have holes near suture breaks. Importantly, the holes had shapes and locations that were inconsistent with z-stent abrasion of the graft material. Additionally, the holes were not observed in any overlapped regions. While damage from surgical instruments during explantation was sometimes obvious, it was not always possible to determine if observations occurred before explantation or if the explantation process contributed to, or caused, the observations.

Summary

Isolated cases of graft material wear were noted on the explanted grafts. Given the shape and location of the wear, these observations are consistent with the clinical and radiographic evidence that the graft material used in the Zenith® AAA Endovascular Graft is adequate for endograft applications.

Isolated suture breaks were observed on explants. These isolated observations are consistent with radiographic or clinical evidence suggesting that broken sutures have been rarely observed in clinical use. Of note, the suture attachment of the suprarenal stent was strengthened before release to the U.S. market. Nevertheless, periodic imaging should be examined for compromises in device integrity due to suture breaks (e.g., suprarenal stent separation).

Damaged or broken stents have also been observed on explant. *In vivo* radiographic evidence of only a single fractured stent (without clinical sequelae) has been observed in U.S. commercial use. Nevertheless, periodic imaging, and in particular KUB films, should be examined for stent fracture.

While not observed in the U.S. study, worldwide commercial use has shown rare cases of patients without periodic imaging having undetected progressive vascular disease involving dilation of the visceral aorta, with the proximal seal site aortic diameter eventually exceeding the endograft diameter leading to proximal leakage, multiple barb separations and attendant clinical consequences. Annual clinical and radiographic follow-up is recommended to assess progressive disease and aortic neck dilation.

Results of the explant analyses further support the device integrity of the Zenith® AAA Endovascular Graft.

<u>Section IV - Summary</u>

The 2-year results of the U.S. clinical study of the Zenith® AAA Endovascular Graft were positive, and the long-term results through five years for the patients who agreed to remain in the study support the earlier results. Importantly, the Zenith® AAA Endovascular Graft was not associated with any clinically significant migration and there have been few cases of aneurysm growth with none unexplained.

The only aneurysm rupture was non-fatal and occurred in a high risk patient with an insufficient iliac landing zone length of only 6 mm, resulting in an overall 5-year freedom from rupture of 99.7%. This is consistent with the lack of clinically significant migration due to the active proximal fixation, lack of late proximal type I endoleaks due to the stable proximal seal, lack of leakage due to the full thickness graft material, a high incidence of aneurysm shrinkage, and reasonable imaging follow-up.

Conversions to open repair were not required peri-operatively and were infrequent post-operatively, occurring from graft infection (2), a rupture due to insufficient length of iliac landing zone, a persistent proximal type I endoleak due to an undersized proximal graft diameter, a secondary visceral aortic aneurysm (not the treated aneurysm), and proximal neck dilation with endoleak resulting in a 5-year freedom from conversion of 97.8%.

Five-year freedom from AAA-related mortality (including all-cause mortality within 30 days of the procedure or of conversion) was 98.9% for standard risk patients. Five-year freedom from all-cause mortality was 81.3% for standard risk patients. As expected, mortality was higher in high risk patients, consistent with higher pre-procedure co-morbidity. Five-year freedom from AAA-related mortality (including all-cause mortality within 30 days of the procedure) was 93.8% for high risk patients. Five-year freedom from all-cause mortality was 57.8% for high risk patients. In no case was death related to device component failure.

Aneurysms exhibited shrinkage (> 5 mm decrease) in 72% of patients and stabilization in another 19%, that is, a total of 91% of aneurysms were not growing at five years. Periodic imaging was adequate to identify patients with aneurysm growth. Patients with a growing aneurysm were associated with graft infection or endoleak, primarily type II endoleak. One patient with aneurysm enlargement associated with proximal neck dilatation and endoleak required explantation between four and five years. There were no cases of aneurysm growth due to device migration or leakage through the graft material. To date, there have been no unexplained cases of aneurysm growth associated with the Zenith® AAA Endovascular Graft.

Endoleaks decreased over the follow-up period. At five years, there were no proximal type I, type III, or type IV endoleaks remaining after secondary interventions. The most common secondary intervention was embolization for treatment of type II endoleak. Other secondary interventions included angioplasty, stenting, placement of extensions, and embolization. There were three endoleaks first appreciated at five years and some persistent type II endoleaks were associated with lack of aneurysm shrinkage, suggesting the need for continued imaging follow-up and possibly intervention.

No patients have been identified with device migration > 10 mm. Moreover, there were no clinically significant device migrations of any length of movement, and there were no type I endoleaks, clinical sequelae or secondary interventions related to device migration. Radiographic migration > 5 mm, but ≤ 10 mm was observed in 4.9% of patients with evaluable imaging through 5 years. For these patients, there were no associated adverse clinical sequelae, no related secondary interventions, no proximal type I endoleaks, and at last follow-up aneurysm size was stable or decreased in 93% of these patients.

Across the three study arms, there were 6 cases of limb thrombosis through one year and no additional cases of limb occlusion detected between one and five years; lack of patency observed by one year was addressed with bypass in 1.4% of patients, and one case observed at 12-month follow-up remained asymptomatic and untreated.

No radiographic evidence of graft material failure was noted in the study. Radiographic evidence of a single stent fracture was noted in six study patients without sequelae. Barb separation was noted in 19 study patients, but was not clinically important. Extensions were placed for separations between the leg and main body and for one separation between the top stent and the main body after excessive graft manipulation during challenging contralateral limb cannulation. Annual imaging follow-up is still recommended to detect progression of disease, aneurysm growth, endoleak, loss of patency, and device integrity, and determine the need for reintervention, as was necessary in the US study for reasons such as endoleak (Type I, Type II, Type III), limb separation, top stent detachment, and limb thrombosis.

Explants included complete grafts, parts of grafts, and graft fragments that have been analyzed using high resolution X-ray, gross examination, light microscopy, and scanning electron microscopy. Isolated cases of graft material wear were noted on the explanted grafts. Isolated suture breaks were observed upon explant; however, these isolated observations are consistent with radiographic or clinical evidence suggesting that broken sutures have been rarely observed in clinical use. Radiographic evidence of a fractured stent without clinical sequelae has been observed in U.S. commercial use. Explants received and analyzed further support the device integrity of the Zenith® AAA Endovascular Graft.

Worldwide experience with the Zenith® AAA Endovascular Grafts includes over 159,198 bifurcated devices. Since FDA approval on May 23, 2003, 275,895 components comprising 71,372 Zenith® AAA Endovascular Grafts have been sold in the U.S. In this U.S. group, 63 deaths within 30 days, 13 post-procedural aneurysm ruptures and 109 open surgical conversions have been reported through the Company's complaint system. Post-market surveillance has confirmed factors in the IFU that mitigate the risk of limb thrombosis including recognizing patient anatomy that is not consistent with the IFU; properly planning and sizing graft components; removing any stiff wire guide before recording a final angiogram; and considering adjunctive procedures when unexpected severe iliac tortuosity causes kinking of the graft.

Approval to add the 36 mm diameter Zenith Flex® AAA Endovascular Graft to the existing Zenith Flex® AAA Endovascular Graft product line was granted by the FDA on September 7, 2006. The results presented in this report reiterate that the outcomes associated with clinical use of the 36 mm diameter Zenith Flex® AAA Endovascular Graft appear comparable to those of the US clinical trial for the 22 to 32 mm diameter Zenith AAA Endovascular Graft. No new safety or effectiveness concerns were identified with this limited experience with the 36 mm diameter Zenith Flex® AAA Endovascular Graft.

The Zenith Renu® AAA Ancillary Graft has been in commercial distribution in the U.S. since market release in June 2005. A total of 10,865 Zenith Renu® AAA Ancillary Grafts have been distributed worldwide. Initial results from physician experience in the U.S. with the Zenith Renu® AAA Ancillary Graft, which was collected through an on-line Post-Market Surveillance Registry, showed that the Renu device has been used primarily to treat pre-existing grafts with proximal type I endoleak or migration, although additional failure modes were also reported. The low incidence of mortality, conversion, and rupture continue to support the safety and effectiveness of the Zenith Renu® AAA Ancillary Graft. Annual imaging follow-up remains recommended to detect progression of the disease, and to ensure aneurysm stabilization and device integrity.

Improvements to the device have included strengthening suture attachments prior to market release. After market release, improvements included strengthening of the aortic attachment barbs that resist migration. To improve the flexibility and apposition to the sealing zone in marginal anatomy such as angulated necks within the indications for use, the spacing between stents in the proximal section of the graft was increased. To better accommodate marginal anatomy of tortuous iliac arteries within the indications for use, spacing between stents in leg components has been increased since market release, and the Zenith® Spiral-Z AAA Endovascular Graft has been added to the product line. New technology was also incorporated into the delivery system. These advances include more flexibility and a hydrophilic coating for easier introduction (referred to as the Flexor® sheath) as well as improved user interfaces (referred to as the Z-Trak™ system), and a large diameter proximal trigger wire has been implemented to increase resistance to bending. Further, new technology was incorporated into the hemostasis valve to reduce blood loss (referred to as the Captor® valve).

In response to physician requests for a viable alternative to open surgical conversion of patients whose primary endograft has inadequate proximal fixation or seal, Cook developed and obtained approval for a set of modified Zenith® ancillary components called the Zenith Renu® AAA Ancillary Graft. Finally, the product line has been expanded to include 36 mm diameter sizes for use in treatment of patients with AAA that have larger infrarenal neck diameters of up to 32 mm.

In conclusion, the 5-year results of the U.S. clinical study continue to support the safety and effectiveness of the Zenith® AAA Endovascular Graft. Commercial experience and explant analysis are consistent with clinical trial results, and Cook remains committed to continuing device improvements.

Section V - Notes to Clinicians

At this time, there are no additional notes or instructions to clinicians beyond what is already described in the IFU.

Section VI - Brief Summary of Indications, Warnings, and Precautions from the IFU

The Zenith® AAA Endovascular Graft is indicated for the endovascular treatment of patients with abdominal aortic or aortoiliac aneurysms having morphology suitable for endovascular repair. Additionally, the patient should have adequate iliac/femoral access compatible with the required introduction system. The Zenith® AAA Endovascular Graft is contraindicated in patients with known sensitivities or allergies to stainless steel, polyester, solder (tin, silver), polypropylene, nitinol, or gold and those with a systemic infection who may be at an increased risk of endovascular graft infection.

The Zenith® AAA Endovascular Graft should only be used by physicians and teams trained in vascular interventional techniques and in the use of this device. All patients should be advised that endovascular treatment requires life-long, regular follow-up to assess their health and the performance of their endograft. Additionally, patients with specific clinical findings (e.g., endoleaks, enlarging aneurysm) should receive enhanced follow-up. The Zenith® AAA Endovascular Graft is not recommended in patients unable to undergo, or who will not be compliant with, the necessary pre- and post-operative imaging and implantation studies outlined in the IFU.

A vascular surgery team should always be available during implantation or reintervention procedures in the event that conversion to open surgical repair is necessary. Intervention or conversion to standard open surgical repair should be considered for patients experiencing enlarging aneurysms, unacceptable decreases in fixation length, and/or endoleak. An increase in aneurysm size and/or persistent endoleak may lead to aneurysm rupture. Further, patients experiencing reduced blood flow through the graft limb and/or leaks may be required to undergo secondary interventions or surgical procedures.