Cook – Zenith Flex® AAA Endovascular Graft

Annual Clinical Update – 2024

I. Overview:

This annual clinical update provides a review of ongoing experience with the Zenith Flex AAA Endovascular Graft and ancillary components used in the treatment of abdominal aortic and aortoiliac aneurysms. In this update, 5 years of IDE and post-approval study data as well as 19 years of worldwide commercial experience are presented. The post-approval study requirements for this device consist of ongoing follow-up (through 5 years) of the pivotal patients enrolled in the IDE for the original size range (22-32 mm diameter main body components), sponsor-investigator IDE and Australian study patients treated with larger diameter main body components (36 mm), and patients enrolled in a post-market registry for the Zenith® Renu® AAA Ancillary Components.

The device was originally approved in 2003 (referred to at the time as the Zenith® AAA Endovascular Graft with H&L-B™ One-Shot Introduction System). Links to the original approval order and Summary of Safety and Effectiveness Data can be accessed here:

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P020018

The device has undergone several evolutionary modifications and line extensions since initial approval, as follows. In 2004, there was an increase in barb wire diameter and spacing between the most proximal stents in the bifurcated main body component as well as an update to the introduction system sheath and hemostatic valve, resulting in a tradename change to Zenith Flex AAA Endovascular Graft. In 2005, the Zenith Renu AAA Ancillary Components (for use in the treatment of failed preexisting AAA grafts) were added to the product line. Larger diameter (36 mm) Flex AAA Endovascular Graft main body components and Renu AAA Ancillary Components were added to the product line in 2006 and 2007, respectively. In 2008, there were modifications to the iliac leg graft (to increase spacing between the external stents; referred to as the Zenith Flex Iliac Leg Graft) and ergonomics of the main body component introduction systems (referred to as the Z-Trak™ Introduction System). In 2011, there were further modifications to the iliac leg graft (to increase the graft diameter in the overlap region and also incorporate a continuous nitinol spiral external stent in place of the individual stainless steel external stents; referred to as the Zenith® Spiral-Z® Iliac Leg Graft) as well as incorporation of the Z-Trak Introduction System for ancillary components.

The IFU for the Zenith Flex AAA Endovascular Graft can be accessed here:

https://ifu.cookmedical.com/data/IFU_PDF/T_ZAAAF_REV5.PDF

The IFU for the Zenith Spiral-Z Iliac Leg Graft can be accessed here:

https://ifu.cookmedical.com/data/IFU_PDF/T_ZAAASZ_REV4.PDF

The IFU for the Zenith Renu AAA Ancillary Components can be accessed here:

https://ifu.cookmedical.com/data/IFU_PDF/T_RAAAZ_REV3.PDF

II. Worldwide Device Distribution:

There have been approximately 675,000 devices distributed worldwide as part of the IDE (>700 main body components, >1,400 leg/ancillary components), post-approval studies (>40 main body components, >200 leg/ancillary components) and commercially (>150,000 main body components and >523,000 leg/ancillary components).

III. Clinical Evaluations:

A description of the completed multicenter IDE for the 22-32 mm diameter main body components and results through 24 months can be found in the summary of clinical studies section of the IFU (available at https://ifu.cookmedical.com/data/IFU_PDF/T_ZAAAF_REV5.PDF), with longer-term follow-up results from 3-5 years provided below.

A description of the completed post-approval registry for the Zenith Renu AAA Ancillary Components and results can be found in the corresponding section of the IFU (available at https://ifu.cookmedical.com/data/IFU_PDF/T_RAAAZ_REV3.PDF).

A description of and the results from the completed post-approval study for the 36 mm diameter main body component are provided below.

a. Description of IDE and PAS:

Please refer to the link provided above for a description of the IDE for 22-32 mm diameter components, which enrolled 352 endovascular treatment patients between January 2000 and July 2001, including 52 roll-in, 200 standard risk, and 100 high risk. The post-approval study for the 22-32 mm size range consisted of continued follow-up of the roll-in, standard risk, and high-risk IDE patients through 5 years in order to evaluate longer-term performance, including evaluation of adverse events, endoleaks, change in aneurysm size, and rupture. While the IDE patients initially consented only for 24-month follow-up, 158 of 259 eligible patients subsequently consented for long-term follow-up through 5 years. A total of 136 patients (of 137 eligible) completed 5-year clinical follow-up (109 with imaging follow-up).

The post-approval study for the 36 mm diameter components consisted of long-term follow-up of patients enrolled in either a single sponsor-investigator IDE or a multicenter clinical trial in Australia to evaluate serious adverse events (death, rupture, conversion), measures of device performance (endoleak, change in aneurysm size, migration, integrity, patency), and the incidence of secondary interventions. These were prospective, nonrandomized studies enrolling 41 patients (26 from the IDE study, 15 from the Australian study) with abdominal aortic or aortoiliac aneurysms requiring a 36 mm diameter graft between March 2003 and December 2005. While patients were initially consented only for 24-month follow-up, 17 patients subsequently consented for longer-term follow-up through 5 years. A total of 5 patients (of 10 eligible) completed 5-year clinical follow-up (6 had imaging follow-up).

b. Results:

IDE Study

Longer-term site-reported data (3-5 years) from the IDE study for 22-32 mm grafts reveal the following (note: follow-up results from 0-2 years are provided for reference):

Event	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
All-cause mortality	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
AAA-related mortality[5]	Standard Risk	# at risk[1]	199	198	190	173	108	105
		# of events	1	0	1	0	0	0
		# censored[2]	0	8	16	65	3	33
		Cumulative censored[3]	0	8	24	89	92	125
		Kaplan-Meier Estimate[4]	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[1]	52	51	44	40	20	20
		# of events	1	0	0	1	0	0
		# censored[2]	0	7	4	19	0	7
		Cumulative censored[3]	0	7	11	30	30	37
		Kaplan-Meier estimate[4]	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[1]	100	98	90	71	30	30
		# of events	2	3	1	0	0	0
		# censored[2]	0	5	18	41	0	10
		Cumulative censored[3]	0	5	23	64	64	74
		Kaplan-Meier Estimate[4]	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

Event	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
Rupture[6]	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 risk1	100	98	90	71	30	30
		# of events	0	1	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
Conversion[7]	Standard Risk	# at risk[1]	199	198	190	173	108	105
		# of events	0	2	1	0	0	1
		# censored[2]	1	6	16	65	3	32
		Cumulative censored[3]	1	7	23	88	91	123
		Kaplan-Meier Estimate[4]	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[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	NA	NA	NA	NA	NA	NA
	High Risk	# at risk[1]	100	98	90	71	30	30
		# of events	0	1	1	0	0	0
		# censored[2]	2	7	18	41	0	10
		Cumulative censored[3]	2	9	27	68	68	78
		Kaplan-Meier Estimate[4]	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] 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 being 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] 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.
[6] 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.
[7] 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 (1 patient); hemorrhage from visceral aneurysm (not the treated AAA) (1 patient); and rupture (1 patient).

Longer-term core laboratory data (3-5 years) from the IDE study for 22-32 mm grafts reveal the following (note: follow-up results from 1-2 years are provided for reference):

Event	Arm[1]	12-month	24-month	36-month	48-month	60-month
Type I endoleak						
Type Ia endoleak	SR	0	0	0	1.6% (1/62)	0
	RI	0	0	0	0	0
	HR	0	0	0	0	0
Type Ib endoleak	SR	0.6% (1/163)	0	1.6% (1/62)	0	0
	RI	0)	0	0	0	0
	HR	0	0	8.3% (1/12)	0	7.1% (1/14)
Type III endoleak[2]	SR	0.6% (0/163)	0	0	1.6% (1/62)	0
	RI	0	0	0	0	0
	HR	0	0	0	6.3% (1/16)	0
Aneurysm enlargement >5 mm	SR	1.2% (2/168)	2.6% (4/152)	1.5% (1/65)	5.3% (4/76)	4.3% (3/70)
	RI	0	3.1% (1/32)	9.1% (1/11)	7.1% (1/14)	7.1% (1/14)
	HR	1.5% (1/68)	1.9% (1/52)	28.6% (4/14)	25.0% (5/20)	31.3% (5/16)
Migration >10 mm	SR	0	0	0	0	0
	RI	0	0	0	0	0
	HR	0	0	0	0	0
Occlusion	SR	1.2% (2/170)	1.3% (2/155)	2.9% (2/70)	1.4% (1/69)	1.4% (1/71)
	RI	0	0	0	0	0
	HR	0	0	0	0	0
Barb separation[3]	SR	2.4% (4/168)	2.0% (3/152)	4.6% (3/65)	2.5% (2/80)	1.4% (1/73)
	RI	0	0	0	0	0
	HR	1.4% (1/72)	1.7% (1/60)	0	4.5% (1/22)	0
Stent-to-graft separation[4]	SR	0.6% (1/168)	0	1.5% (1/65)	0	0
	RI	0	0	0	0	0
	HR	0	0	0	0	0
Stent fracture	SR	0.6% (1/168)	0.7% (1/152)	0	3.8% (3/80)	0
	RI	0	0	0	0	0
	HR	0	0	0	0	5.6% (1/18)
Component separation	SR	0	0.7% (1/152)	1.5% (1/65)	0	0
	RI	0	3.7% (1/27)	0	0	0
	HR	0	0	0	0	0

[1] SR = standard risk; RI = roll-in; HR = high risk.

[2] Type III endoleaks were not further subdivided into IIIa and IIIb at the time of core laboratory analysis.
[3] Original barb design (i.e., 0.0093" wire diameter, not the current 0.011" wire diameter).
[4] Original stent-to-graft attachment design (i.e., single suturing, not the current double suturing).

The most common secondary intervention was embolization for treatment of Type II endoleak (n=30). Proximal Type I endoleaks were treated with embolization (n=2), main body extensions (n=3), and stent placement (n=1). Distal Type I endoleaks were treated with embolization (n=2), iliac leg extensions (n=5), and angioplasty (n=2). Reinterventions for Type III endoleak involved stent placement (n=1) and angioplasty (n=1). Treatment for unknown/multiple endoleak types involved embolization (n=2), iliac leg extensions (n=2), stent placement (n=2), and angioplasty (n=1). Reinterventions for limb occlusion involved femoral-femoral bypass (n=4) and endarterectomy in combination with femoral-femoral bypass (n=1). Reintervention for component separation involved placement of additional leg components (n=3). Also reported was placement of a custom proximal extension for treatment of top-stent separation from the graft (n=1) and angioplasty in combination with placement of a stent and an iliac leg extension for treatment of aneurysm growth, limb migration, and kink (n=1).

PAS

Data from the PAS for 36 mm grafts at 12 months through 5 years reveal the following:

Event	Cohort[1]	12 months	24 months	36 months	48 months	60 months
Mortality (all cause)	AUS	0	8.3% (1/12)	27.3% (3/11)	14.3% (1/7)	0
	PSIDE	7.7% (2/26)	4.2% (1/24)	10.0% (2/20)	16.7% (3/18)	12.5% (2/16)
Aneurysm rupture	AUS	6.7% (1/15)	0	0	0	0
	PSIDE	0	0	0	0	0
Conversions	AUS	0	0	0	0	0
	PSIDE	0	0	0	0	0
Type I or III endoleak	AUS	0	0	0	0	0
	PSIDE	0	0	0	0	0
Aneurysm enlargement	AUS	16.7% (2/12)	12.5% (1/8)	0	50.0% (1/2)	66.7% (2/3)
	PSIDE	5.3% (1/19)	13.3% (2/15)	0	16.7% (1/6)	0
Prosthesis migration	AUS	0	0	n/a	n/a	n/a
	PSIDE	0	0	0	0	0
Occlusions	AUS	0	0	0	0	0
	PSIDE	0	0	0	0	50% (1/2)
Loss of device integrity	AUS	0	0	0	n/a	0
	PSIDE	25% (4/16)	33.3% (4/12)	37.5% (3/8)	25% (1/4)	66.7% (2/3)

[1] AUS= Australian clinical study; PSIDE= U.S. physician-sponsored IDE study

Six patients underwent reintervention for the following reasons: rupture (n=1), Type II endoleak (n=2), suspected proximal Type I endoleak (n=1), suspected distal Type I endoleak (n=1), and iliac artery occlusion (n=1).

IV. Worldwide Recalls, Safety Communications, and Field Safety Notices:

There have been two class II recalls (no class I recalls), both of which occurred in 2004. The first was due to observations during production of introducer sheaths having lines of unmixed material within the sheath wall, prompting changes in manufacturing and quality control. The second recall was due to complaints of difficulty removing the top cap or suprarenal stent from the top cap during the implant procedure, prompting changes in manufacturing, quality control, and labeling as well as establishing a new design input requirement.

V. Worldwide Commercial Experience:

There have been no reported adverse reactions, side effects, or injuries attributable to the device that are not addressed in the labeling for the device or that occurred with unexpected frequency.

VI. Explant Analysis:

Forty-eight explants from worldwide commercial experience have been received and analyzed (45 involving main body components, 3 involving Renu ancillary components). The reasons for explant were unknown (n=18), endoleak (n=13), migration (n=2), infection (n=3), rupture (n=3), off-label use (n=1), aneurysm growth (n=5), graft damage (n=1), and maldeployment (n=2). The number of days implanted was unknown in 9 of 48 – the mean implant duration in 39 explants was approximately 1179 days (range 1-4500 days). Twenty-two explants were found to have damaged or broken stents. Nine explants were found to have barb separations. Thirty-three explants were found to have cut or broken sutures (green). Six explants were found to have cut or broken sutures (blue). One explant was found to have suture hole elongations. Five 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.

VII. Literature Review:

In total, 215 publications involving use of Zenith AAA Endovascular Grafts for any reason have been identified since 2003. There were no notable publications during this reporting period. Adverse events reported in publications are treated as complaints by the manufacturer and may similarly result in filing of a Medical Device Report (MDR) to FDA, if applicable. As noted in Section V, there have been no reported adverse reactions, side effects, or injuries attributable to the device that are not addressed in the labeling for the device or that occurred with unexpected frequency.

VIII. Conclusion:

Based on available clinical study data and world-wide clinical experience to date, endovascular therapy with the Zenith Flex AAA Endovascular Graft and ancillary components continues to be a viable treatment option for patients with abdominal aortic or aortoiliac aneurysms.

Adverse Event Reporting:

Accurate and timely reporting of adverse events to Cook and FDA is critical for monitoring device performance and detection of potential device-related safety issues. Adverse events should be reported to Cook via email to CustomerRelationsNA@CookMedical.com or via phone at 1-800-457-4500,

ext. 152146 (7:30 am-5:00 pm EST) and to FDA via MedWatch FDA Form 3500, a copy of which is available at: https://www.fda.gov/media/135528/download.

Patient Follow-up and Selection:

Regular follow-up of all patients treated with the Zenith Flex AAA Endovascular Graft and ancillary components is required. Physicians should tailor patient follow-up to the needs and circumstances of each individual patient. Please refer to the IFU for additional information regarding recommended follow-up.

Please refer also to FDA's Letter to Health Care Providers that summarizes the Circulatory System Devices Advisory Panel recommendations on lifelong surveillance and long-term postmarket data collection for patients with AAA endovascular aortic repair, a copy of which is available at:

https://www.fda.gov/medical-devices/letters-health-care-providers/fda-advisory-panel-recommendations-lifelong-surveillance-and-long-term-postmarket-data-collection