

Annual Clinical Update

Abstract

Cook is pleased to provide you with this clinical update on the Zenith® TX2® TAA Endovascular Graft, which was commercially approved by FDA on May 21, 2008.

Section I provides an update on results from the multi-center clinical trial, focusing this year on the 48-month follow-up, which is now nearly complete, reflecting data received through March 18, 2011. Briefly, the study was designed to compare thoracic aneurysm/ulcer treatment with the Zenith® TX2® TAA Endovascular Graft in 160 patients to open surgical repair in 70 control patients. Patient follow-up remains ongoing and will continue through 5 years. Survival from aneurysm-related mortality at 1460 days was 89.8% in the endovascular treatment group and 84.7% in the open surgical control group. To date, no death in the endovascular treatment group was found to be related to failure of a component of the device. The percent of patients with new endoleak at 48 months was 5.0%, and the percent of patients with an increase in aneurysm/ulcer size was 4.6%, as compared with 61.5% who showed a decrease in size. New device integrity observations at 48 months included 1 patient with stent fracture and 5 patients with single barb separation, one of whom is the only patient also with clinically significant migration (requiring placement of a proximal extension and distal extension), though no endoleak was reported at any time and the aneurysm size at 48 months was unchanged compared to baseline – the core lab noted an inverted funnel-shaped proximal neck and funnel-shaped distal neck on pre-procedure imaging, and device oversizing at the proximal end appeared insufficient relative to the location of actual graft placement. The percent of patients requiring at least one reintervention subsequent to the initial aneurysm/ulcer repair procedure is 6.9% for the endovascular treatment group and 8.6% for the open surgical control group. There have been no ruptures or conversions to open surgical repair in the endovascular treatment group.

Section II summarizes worldwide commercial experience. A total of 26,198 components have been sold worldwide (including 13,802 sold in the US) since May 21, 2008. There have been 24 procedural and follow-up complaints reported during this time. **Section III** summarizes the findings from explant analysis. To date, four explants have undergone analysis. **Section IV** 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. **Section V** provides a brief summary of the indications, warnings, and precautions from the IFU.

Device Description

The Zenith[®] TX2[®] TAA Endovascular Graft is a two-piece cylindrical endovascular graft consisting of proximal and distal components. The proximal component can be either non-tapered or tapered and may be used alone or in combination with a distal component. The stent-grafts are constructed of woven polyester fabric sewn to self-expanding stainless steel Cook-Z stents with braided polyester and monofilament polypropylene sutures. The covered stent at the proximal end of the proximal component contains barbs, which protrude through the graft material. In addition, the bare stent at the distal end of the distal component contains barbs. Ancillary endovascular components (proximal and distal body extensions) are also available. Please refer to the IFU for a more detailed description of the components and the delivery system, as well as the indications, warnings, and precautions (also summarized in Section V).

Introduction

One of the conditions of approval of the Zenith[®] TX2[®] TAA Endovascular Graft was to provide a clinical update to physician users annually. This update has been formatted in accordance with a template that was agreed upon by FDA, industry, and clinicians during a meeting at FDA in October 2008. Accordingly, the clinical update is comprised of the following sections: Clinical Study Experience (Section I); Worldwide Commercial Experience (Section II); Explant Analysis (Section III); Notes to Clinicians (Section IV); and Brief Summary of Indications, Warnings, and Precautions from IFU (Section V). Of note with respect to Section I, although the data for all available time points are presented, the primary focus of any discussion in this year's annual clinical update will be the 48-month results, as this follow-up time point is now nearly complete, whereas at the time of previous reporting there was only partial data – the subsequent annual clinical update will accordingly focus on the 60-month follow-up data.

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Section I – Clinical Study Experience

Description of Study and Study Arms

The STARZ-TX2 Clinical Trial is a non-randomized, controlled, multi-center, multi-national study that was conducted to evaluate safety and effectiveness of the Zenith® TX2® TAA Endovascular Graft in the elective treatment of patients with descending thoracic aortic aneurysms or ulcers, as compared with open surgical repair. The study consisted of an endovascular treatment group and an open surgical control group. The open surgical control group was comprised of both prospectively enrolled and retrospectively enrolled patients. The same inclusion/exclusion criteria applied to both the endovascular treatment group and the open surgical control group, except that patients in the open surgical control group were not required to have anatomy amenable to endovascular repair with the Zenith® TX2® TAA Endovascular Graft.

The clinical study device is the same as the device that is commercially available, with the only exception pertaining to the delivery system – all patients enrolled in the clinical study were treated using the H&L-B One-Shot™ Introduction System, which has been replaced with the now commercially-approved Pro-Form™ and Z-Trak™ Plus Introduction System.

Forty-two (42) institutions enrolled a total of 160 endovascular treatment patients and 70 open surgical control patients. The study follow-up schedule for patients enrolled in the endovascular treatment group consisted of radiographic (CT scan and X-ray) and clinical assessments at pre-discharge, 30 days, 6 months, 12 months, and yearly thereafter through 5 years. The study follow-up schedule for patients enrolled in the open surgical control group consisted of radiographic (CT scan) and clinical assessments at pre-discharge (or 30 days) and 12 months, with an interim telephone contact at 6 months, and additional optional follow-up at yearly intervals through 5 years.

The study was designed to assess two primary and two secondary hypotheses regarding the endovascular treatment group as compared with the open surgical control group. The primary hypothesis for safety was non-inferior 30-day survival, and the primary hypothesis for effectiveness was non-inferior 30-day rupture-free survival (i.e., freedom from rupture). The secondary hypotheses were superior clinical utility in the endovascular treatment group and non-inferior 30-day morbidity, expressed as a composite morbidity score including 57 pre-specified events. All study hypotheses were met. In addition, the study assessed survival, morbidity, and device performance through

12 months, and will continue these assessments at yearly intervals through 5 years. This update reflects data received as of March 18, 2011.

Patient Availability

Patient availability for study follow-up is summarized in Table 1.

Table 1: Follow-up Availability

Time point	Number eligible for follow-up*	Subjects with submitted data			Adequate imaging to assess parameter by core lab†				Events occurring before next visit			
		Clinical % (n)	CT % (n)	X-ray % (n)	Size increase % (n)	Endoleak % (n)	Migration % (n)	Fracture % (n)	Death (n)	Conversion (n)	LTF (n)	Not due for next visit (n)
Endovascular												
Pre-discharge	158 ^a (0)	100% (158)	100% (158)	99% (157)	n/a	85% (135)	n/a	96% (152)	3	0	0	0
30-day	155 (0)	95% (147)	95% (148)	95% (148)	78% (121)	81% (126)	72% (112)	88% (136)	5	0	4	0
6-month	146 (0)	89% (130)	94% (137)	93% (136)	80% (117)	78% (114)	77% (112)	87% (127)	5	0	5	0
12-month	136 (0)	95% (129)	95% (129)	93% (126)	84% (114)	77% (105)	80% (109)	91% (124)	14	0	5	0
24-month	117 (0)	89% (104)	90% (105)	88% (103)	77% (90)	77% (90)	77% (90)	85% (100)	8	0	6	0
36-month	103 (0)	88% (91)	92% (95)	88% (91)	81% (83)	81% (83)	85% (88)	87% (90)	7	0	8	0
48-month	88 (1)	85% (75)	91% (80)	82% (72)	74% (65)	68% (60)	81% (71)	84% (74)	9	0	3	4
60-month	72 (5)	85% (61)	86% (62)	78% (56)	65% (47)	65% (47)	79% (57)	82% (59)	n/a	n/a	n/a	n/a
Open Surgical												
Pre-discharge/ 30-day	70 (0)	100% (70)	n/a	n/a	n/a	n/a	n/a	n/a	8	n/a	0	0
6-month	62 (0)	60% (37)	n/a	n/a	n/a	n/a	n/a	n/a	2	n/a	0	0
12-month	60 (0)	72% (43)	n/a	n/a	n/a	n/a	n/a	n/a	1	n/a	3	24 ^b
24-month	32 (0)	59% (19)	n/a	n/a	n/a	n/a	n/a	n/a	1	n/a	0	0
36-month	31 (0)	58% (18)	n/a	n/a	n/a	n/a	n/a	n/a	1	n/a	0	0
48-month	30 (2)	60% (18)	n/a	n/a	n/a	n/a	n/a	n/a	5	n/a	0	2
60-month	23 (1)	43% (10)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

n/a – not applicable; *The number in parentheses indicates the number of patients without submitted data that are still considered eligible for follow-up.

^a Device insertion was not achieved in two patients. †Includes only adequate imaging with completed analysis, not received imaging awaiting analysis.

^b IRB/EC-approved follow-up was limited to 12 months at 11 sites that enrolled open surgical control patients (n=24).

Aneurysm-Related Mortality

Aneurysm-related mortality was defined as death occurring within 30 days of the initial implant procedure or a secondary intervention, or any death adjudicated to be aneurysm-related by the independent clinical events committee (CEC). For consistency with previous reports, any death in which the CEC was unable to determine whether the cause was related to the treated aneurysm was also counted as aneurysm-related.

The following data summarize survival from aneurysm-related mortality in the endovascular treatment and open surgical control groups. As illustrated in Figure 1 and presented in Table 2, survival from aneurysm-related mortality at 1460 days was 89.8% in the endovascular treatment group and 84.7% in the open surgical control group. To date, no death in the endovascular treatment group was found to be related to failure of a component of the device.

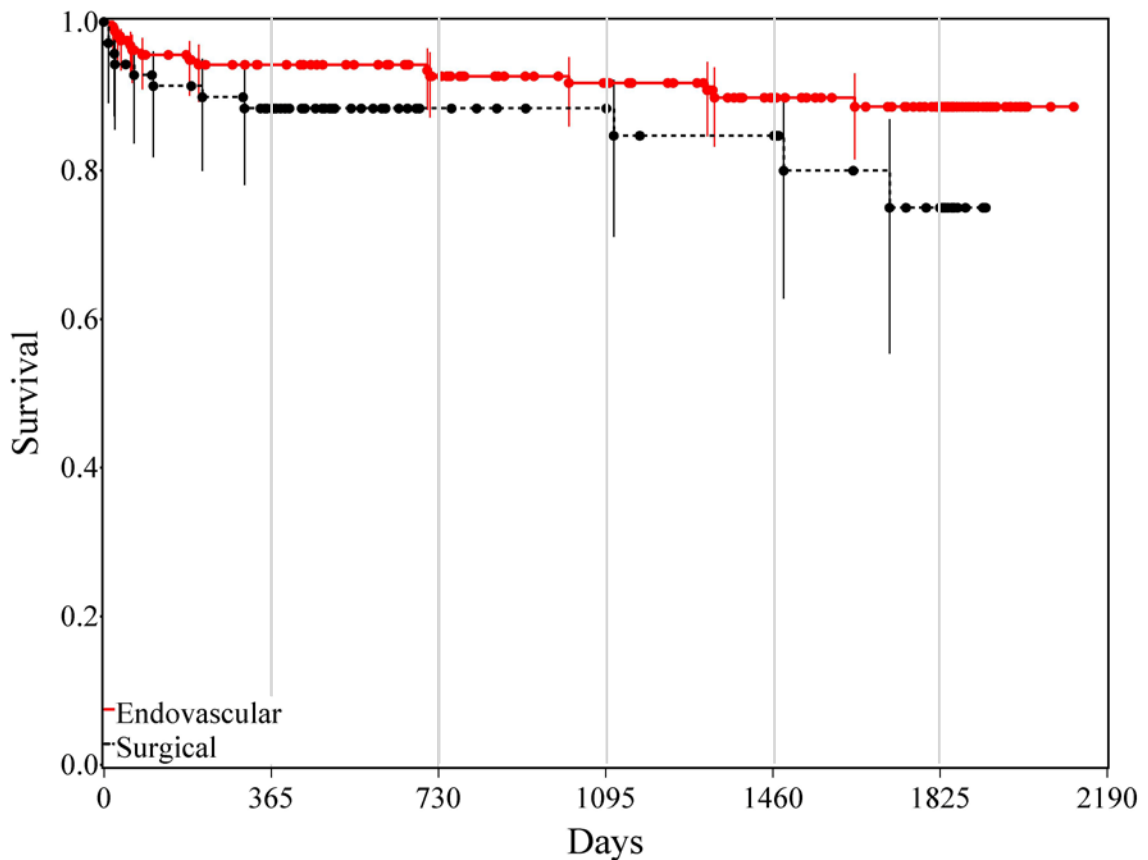


Figure 1: Survival from Aneurysm-Related Mortality

Table 2: Kaplan-Meier Aneurysm-Related Mortality Survival Estimates

Arm	Days	Kaplan-Meier Estimate	Standard Error	Cumulative Events	Cumulative Censored	Patients remaining
Endovascular	0	1.000	0.0000	0	0	160
	30	0.981	0.0107	3	1	156
	365	0.942	0.0187	9 ^a	15	136
	730	0.927	0.0214	11 ^b	32	117
	1095	0.918	0.0229	12 ^c	46	102
	1460	0.898	0.0264	14 ^f	66	80
	1825	0.886	0.0288	15 ^h	89	56
Surgical	0	1.000	0.0000	0	0	70
	30	0.943	0.0277	4	0	66
	365	0.883	0.0388	8 ^d	7	55
	730	0.883	0.0388	8	33	29
	1095	0.883	0.0388	8	37	25
	1460	0.847	0.0518	9 ^e	39	22
	1825	0.750	0.0792	11 ^g	47	12

^a Reported cause for aneurysm-related deaths occurring between 30 and 365 days as follows: septicemia and respiratory failure (procedure-related); multi-system organ failure (procedure-related); unable to be determined (therefore counted as aneurysm-related); respiratory failure (procedure-related); multi-system organ failure (procedure-related); cardiopulmonary arrest secondary to pneumonia (procedure-related).

^b Reported cause for aneurysm-related deaths occurring between 365 and 730 days as follows: removal of ventilator support following stroke after secondary intervention (procedure-related); unable to be determined (therefore counted as aneurysm-related).

^c Reported cause for aneurysm-related death occurring between 730 and 1095 days as follows: unable to be determined (therefore counted as aneurysm-related).

^d Reported cause for aneurysm-related deaths occurring between 30 and 365 days as follows: asystole (procedure-related); cardiopulmonary arrest (procedure-related); unknown (procedure-related); respiratory failure (procedure-related).

^e Reported cause for aneurysm-related death occurring between 1095 and 1460 days as follows: unable to be determined (therefore counted as aneurysm-related).

^f Reported causes for aneurysm-related deaths occurring between 1095 and 1460 days as follows: both unable to be determined (therefore counted as aneurysm-related).

^g Reported causes for aneurysm-related deaths occurring between 1460 and 1825 days as follows: sudden cardiac arrest (unable to determine if procedure- or aneurysm-related, therefore counted as aneurysm-related mortality); sudden shock (suspected leaking/rupture of AAA or TAA, but unable to determine which, therefore counted as aneurysm-related mortality).

^h Reported cause for aneurysm-related death occurring between 1460 and 1825 days as follows: unable to be determined (therefore counted as aneurysm-related)

All-Cause Mortality

The following data summarize survival from all-cause mortality in the endovascular treatment and open surgical control groups. As illustrated by Figure 2 and presented in Table 3, survival from all-cause mortality at 1460 days was 70.5% in the endovascular treatment group and 76.5% in the open surgical control group.

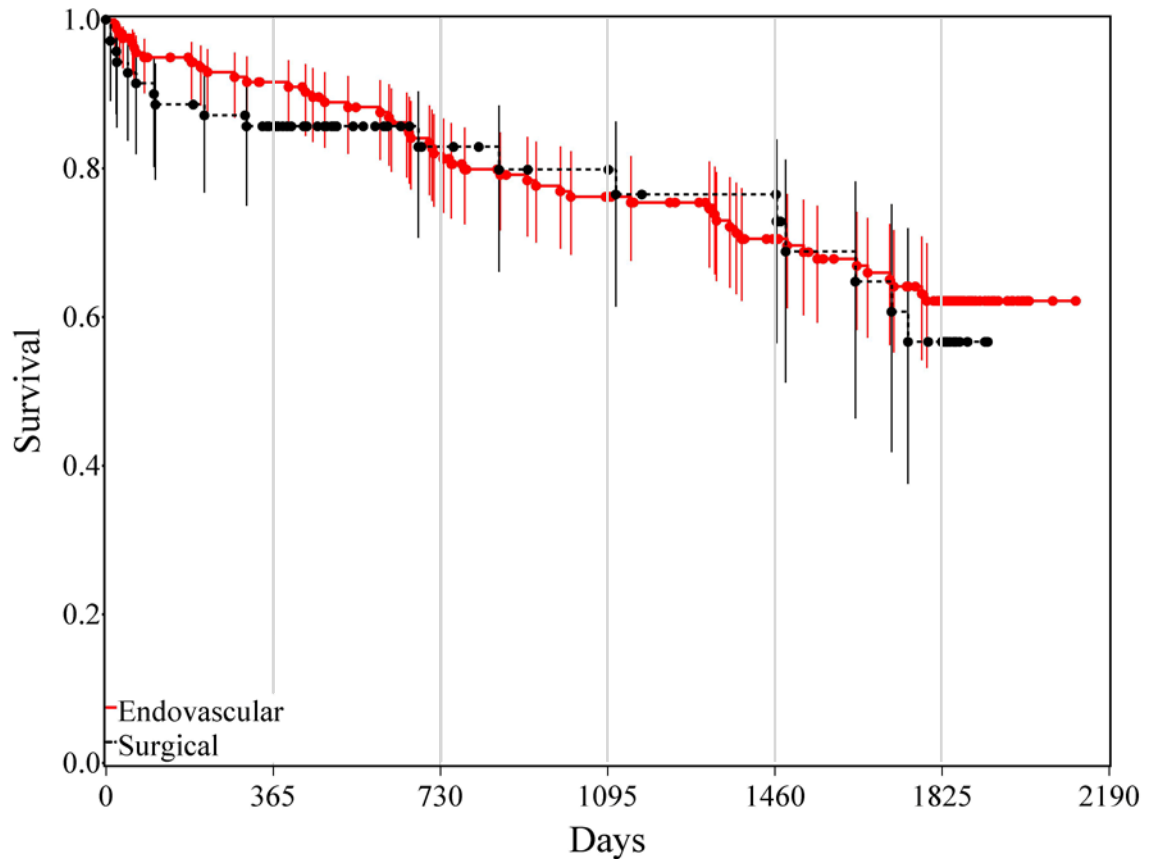


Figure 2: Survival from All-Cause Mortality

Table 3: Kaplan-Meier All-Cause Mortality Survival Estimates

Arm	Days	Kaplan-Meier Estimate	Standard Error	Cumulative Events	Cumulative Censored	Patients remaining
Endovascular	0	1.000	0.0000	0	0	160
	30	0.981	0.0107	3	1	156
	365	0.916	0.0223	13	11	136
	730	0.820	0.0315	27	16	117
	1095	0.762	0.0353	35	23	102
	1460	0.705	0.0387	42	38	80
	1825	0.622	0.0430	51	53	56
Surgical	0	1.000	0.0000	0	0	70
	30	0.943	0.0277	4	0	66
	365	0.856	0.0420	10	5	55
	730	0.829	0.0489	11	30	29
	1095	0.798	0.0559	12	33	25
	1460	0.765	0.0627	13	35	22
	1825	0.567	0.0895	18	40	12

Endoleak

Table 4 reports the percent of patients with endoleak (by type) at each follow-up time point based on the results from core lab analysis. Patients who underwent a secondary intervention for endoleak or who had associated aneurysm size increase are indicated by footnotes. The percent of patients with new endoleak at 48 months was 6.7%, which includes a proximal Type I, a distal Type I, a Type IIa, and a Type III endoleak.

Table 4: Percent of Endovascular Treatment Patients with Endoleak Based on Core Lab Analysis

Type	Time point							
	Pre-discharge	30 days	6 months	12 months	24 months	36 months	48 months	60 months
Any (new only)	14.1% (19/135)	1.6% (2/126)	0% (0/114)	0% (0/105)	1.1% (1/90)	1.2% (1/83)	6.7% (4/60)	0% (0/47)
Any (new and persistent)	14.1% (19/135)	4.8% (6/126)	2.6% (3/114)	3.8% (4/105)	2.2% (2/90)	2.4% (2/83)	8.3% (5/60)	4.3% (2/47)
Multiple	0.7% (1/135) ^a	0.8% (1/126) ^a	0.9% (1/114) ^a	0% (0/105)	0% (0/90)	0% (0/83)	0% (0/60)	0% (0/47)
Proximal Type I	0% (0/135)	0% (0/126)	0% (0/114)	0% (0/105)	1.1% (1/90)	0% (0/83)	1.7% (1/60)	2.1% (1/47)
Distal Type I	0.7% (1/135) ^a	0.8% (1/126) ^a	0.9% (1/114) ^a	0% (0/105)	1.1% (1/90) ^b	1.2% (1/83) ^b	1.7% (1/60)	2.1% (1/47)
Type IIa	1.5% (2/135)	0.8% (1/126)	0% (0/114)	0% (0/105)	0% (0/90)	0% (0/83)	1.7% (1/60)	0% (0/47)
Type IIb	7.4% (10/135) ^{a,c}	3.2% (4/126) ^a	2.6% (3/114) ^a	1.9% (2/105)	1.1% (1/90)	0% (0/83)	0% (0/60)	0% (0/47)
Type III	1.5% (2/135)	0.8% (1/126)	0% (0/114)	1.0% (1/105)	0% (0/90)	0% (0/83)	1.7% (1/60) ^c	0% (0/47)
Type IV	1.5% (2/135)	0% (0/126)	0% (0/114)	0% (0/105)	0% (0/90)	0% (0/83)	0% (0/60)	0% (0/47)
Unknown	2.2% (3/135) ^{d,e}	0% (0/126)	0% (0/114)	1.0% (1/105)	0% (0/90)	1.2% (1/83)	1.7% (1/60) ^b	0% (0/47)

^a (2612011) Site reported distal Type I endoleak requiring two secondary interventions (one after the 1-month exam, and one after the 6-month exam); patient also with aneurysm increase by core lab first noted at 12-month exam, but with decrease in size between 12-month and 48-month exams.

^b (0412014) Site reported distal Type I endoleak requiring secondary intervention following 36-month exam. Unknown endoleak type by core lab analysis of 48-month follow-up exam, not confirmed by site, and with no increase in aneurysm diameter.

^c (0412018) Site reported distal Type I endoleak requiring secondary intervention (placement of two distal extensions) following pre-discharge exam. Additional secondary intervention (placement of additional main body component) reported by site following 48-month exam for treatment of Type III endoleak (between separated main body component and previously placed extensions) in setting of aortic elongation. No associated increase in aneurysm diameter noted at any timepoint.

^d (0412016) Site reported proximal Type I endoleak requiring secondary intervention prior to pre-discharge exam.

^e (2512001) Secondary intervention (angiogram) performed to rule out endoleak following pre-discharge exam – no endoleak detected.

Change in Size

Table 5 reports the percent of patients with an increase (> 5 mm), decrease (> 5 mm), or no change (≤ 5 mm) in aneurysm diameter (or ulcer depth) by core lab analysis at each

follow-up time point subsequent to pre-discharge, which represented baseline. The percent of patients with an increase in size at 48 months was 4.6%, as compared with 61.5% who showed a decrease in size. In total, 14 patients (12 aneurysm, 2 ulcer) have experienced an increase in size at one or more time points: 5 with detectable endoleak at one or more time points (2 requiring secondary intervention and 3 which resolved without reintervention); 3 with no detectable endoleak (or evidence of infection), but who underwent secondary intervention for a decrease in overlap between components for 1, migration for 1, and suspected endotension for 1; 4 without detectable endoleak (or evidence of infection), but with a decrease or stabilization in size at subsequent follow-up without reintervention; 1 with no detectable endoleak (or evidence of infection), no reintervention, and no subsequent follow-up as of yet; and 1 with no detectable endoleak (or evidence of infection), no reintervention, and has reached the final follow-up timepoint. Any patient with size increase and associated endoleak and/or requiring a secondary intervention is indicated by a footnote in Table 5. There have been no reports of rupture or conversion to open surgical repair in the endovascular treatment group.

Table 5: Percent of Endovascular Treatment Patients with an Increase, Decrease, or No Change in Aneurysm/Ulcer Size Based on Core Lab Analysis

Time point	Combined % (n)	Aneurysm % (n)	Ulcer % (n)
30-day			
Increase (> 5 mm)	0.8% (1/121)	0.9% (1/106)	0% (0/15)
Decrease (> 5 mm)	5.8% (7/121)	5.7% (6/106)	6.7% (1/15)
No change (≤ 5 mm)	93.4% (113/121)	93.4% (99/106)	93.3% (14/15)
6-month			
Increase (> 5 mm)	3.4% (4/117)	3.0% (3/99) ^a	5.6% (1/18) ^e
Decrease (> 5 mm)	32.5% (38/117)	33.3% (33/99)	27.8% (5/18)
No change (≤ 5 mm)	64.1% (75/117)	63.6% (63/99)	66.7% (12/18)
12-month			
Increase (> 5 mm)	7.0% (8/114)	7.1% (7/99) ^{a,b,c,d}	6.7% (1/15)
Decrease (> 5 mm)	47.4% (54/114)	50.5% (50/99)	26.7% (4/15)
No change (≤ 5 mm)	45.6% (52/114)	42.4% (42/99)	66.7% (10/15) ^e
24-month			
Increase (> 5 mm)	3.3% (3/90)	2.6% (2/78) ^{c,f}	8.3% (1/12)
Decrease (> 5 mm)	52.2% (47/90)	55.1% (43/78)	33.3% (4/12)
No change (≤ 5 mm)	44.4% (40/90)	42.3% (33/78) ^{b,d}	58.3% (7/12) ^e
36-month			
Increase (> 5 mm)	4.8% (4/83)	5.6% (4/71) ^{b,f,g}	0% (0/12)
Decrease (> 5 mm)	59.0% (49/83)	63.4% (45/71)	33.3% (4/12) ^e
No change (≤ 5 mm)	36.1% (30/83)	31.0% (22/71) ^{c,d}	66.7% (8/12)
48-month			
Increase (> 5 mm)	4.6% (3/65)	5.5% (3/55) ^{b,c,h}	0% (0/10)
Decrease (> 5 mm)	61.5% (40/65)	65.5% (36/55) ^d	40.0% (4/10)
No change (≤ 5 mm)	33.8% (22/65)	29.1% (16/55) ^f	60.0% (6/10)

60-month			
Increase (> 5 mm)	6.4% (3/47)	7.7% (3/39) ^{b,h}	0% (0/8)
Decrease (> 5 mm)	59.6% (28/47)	64.1% (25/39)	37.5% (3/8)
No change (≤ 5 mm)	34.0% (16/47)	28.2% (11/39) ^f	62.5% (5/8)

^a (0912003) Patient underwent two secondary interventions after the 12-month exam for continued increase without detectable endoleak or evidence of graft infection and expired within 30 days of the latter secondary intervention (after removal of ventilator support following a stroke), prior to the 24-month exam.

^b (2612011) Patient underwent two secondary interventions (one after the 1-month exam, and one after the 6-month exam) for distal type I endoleak; there was no change in size between the 12-month and 60-month exams.

^c (3612012) Patient presented with flank pain and underwent secondary intervention between the 12-month and 24-month exams because of decreasing overlap between components from device alignment with greater curve over time (without associated junctional Type III endoleak).

^d (4112010) Patient presented with flank pain and underwent secondary intervention between the 12-month and 24-month exams to treat symptoms due to junctional Type III endoleak from component separation – retrospective review of procedural imaging suggests the length of overlap achieved between components at the time of initial deployment was less than the minimum recommended amount.

^e (3212011) Patient was noted to have a Type IIa endoleak at pre-discharge, but not on subsequent follow-up and was without secondary intervention.

^f (3612006) Patient underwent secondary intervention between 48- and 60-months for CEC-confirmed migration. No endoleak has been noted at any follow-up timepoint. No change in aneurysm size at last follow-up.

^g (4112001) Patient was noted to have endoleak of unknown type at pre-discharge, but not on subsequent follow-up and was without secondary intervention.

^h (0412013) Patient was noted to have a Type IIb endoleak at pre-discharge, but not on subsequent follow-up and was without secondary intervention.

Rupture

As shown in Table 6, there have been no ruptures in either the endovascular treatment group or open surgical control group.

Table 6: Kaplan-Meier for Freedom from Rupture

Arm	Days	Kaplan-Meier Estimate	Standard Error	Cumulative Events	Cumulative Censored	Patients remaining
Endovascular	0	1.000	0.0000	0	0	160

Arm	Days	Kaplan-Meier Estimate	Standard Error	Cumulative Events	Cumulative Censored	Patients remaining
	30	1.000	0.0000	0	4	156
	365	1.000	0.0000	0	24	136
	730	1.000	0.0000	0	43	117
	1095	1.000	0.0000	0	58	102
	1460	1.000	0.0000	0	80	80
	1825	1.000	0.0000	0	104	56
Surgical	0	1.000	0.0000	0	0	70
	30	1.000	0.0000	0	4	66
	365	1.000	0.0000	0	15	55
	730	1.000	0.0000	0	41	29
	1095	1.000	0.0000	0	45	25
	1460	1.000	0.0000	0	48	22
	1825	1.000	0.0000	0	58	12

Device Integrity

The percent of patients with device integrity findings at each follow-up time point based on the results from core lab analysis are presented in Table 7. New device integrity findings at 48 months included 1 patient with stent fracture and 5 patients with single barb separation, one of whom is the only patient with migration requiring secondary intervention. As indicated in the footnotes to the table, isolated observations of device integrity findings have been noted at other time points, where the need for associated reintervention was infrequent.

Table 7: Percent of Patients with Device Integrity Findings Based on Core Lab Analysis (Date of First Occurrence)

Finding	Time point
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	Pre-discharge	30 days	6 Months	12 months	24 months	36 months	48 months	60 months
Stent fracture	0% (0/152)	0% (0/136)	0% (0/127)	0% (0/124)	1.0% (1/100) ^c	1.1% (1/90) ^b	1.4% (1/74) ^h	1.7% (1/59) ^p
Barb separation	0% (0/152)	0% (0/136)	0% (0/127)	0.8% (1/124) ⁱ	4.0% (4/100) ^g _{j,s,t}	4.4% (4/90) ^{d,e,k,q}	6.8% (5/74) ^{f,h,l,m,n}	5.1% (3/59) ^{o,p,r}
Stent-to-graft separation	0% (0/152)	0% (0/136)	0% (0/127)	0% (0/124)	0% (0/100)	0% (0/90)	0% (0/74)	0% (0/59)
Component separation	0% (0/152)	0% (0/136)	0% (0/127)	0% (0/124)	0% (0/100)	1.1% (1/90) ^d	0% (0/74)	0% (0/59)
Other	0.7% (1/152) ^a	0% (0/136)	0% (0/127)	0% (0/124)	0% (0/100)	0% (0/90)	0% (0/74)	0% (0/59)

^a (7012004) Entanglement of neighboring struts of distal bare stent; finding not associated with migration, endoleak, increase in aneurysm size, or the need for secondary intervention.

^b (0611001) Single stent fracture on proximal component not associated with endoleak, migration, or need for secondary intervention – increase in size noted at 6-month and 12-month follow-up, but with no change in size at the 24-, 36-, 48-, and 60-month follow-up, as compared with baseline.

^c (7012007) Single stent fracture on distal component not associated with endoleak, increase in size, or need for secondary intervention – caudal migration noted at 24-month follow-up, but of the proximal component; no migration of the distal component.

^d (0412018) Single barb separation on proximal component not associated with endoleak, increase in size, or requiring secondary intervention. Radiographic migration of proximal component noted at 24-month follow-up. Separation between proximal component and distal main body extension in the setting of aortic elongation, resulting in Type III endoleak requiring secondary intervention (additional main body component placement) following 48-month exam; separation first noted by core lab on 36-month exam.

^e (2511001) Single barb separation on proximal component not associated with migration, increase in size, or secondary intervention – Type I endoleak noted on subsequent follow-up, but at distal seal site, not the proximal seal site.

^f (7012001) Single barb separation on distal component not associated with endoleak, migration, increase in size, or need for secondary intervention.

^g (2612011) Single barb separation on proximal component not associated with migration – patient previously underwent two secondary interventions for distal Type I endoleak and was also noted to have an increase in size at 12 months but the diameter at 48 months had decreased compared with 12 months.

^h (3612009) Single barb separation on proximal component and 2 fractures of distal stent on distal component not associated with increase in size or need for secondary intervention – caudal migration of the proximal component had been noted at 12-month follow-up and a proximal Type I endoleak was noted at 48-month follow-up (the core lab noted an inverted funnel-shaped proximal neck on pre-procedure imaging, and device oversizing appeared insufficient relative to the location of actual graft placement).

ⁱ (0912009) Single barb separation on proximal component not associated with endoleak, increase in size, or the need for secondary intervention- caudal migration of the proximal component and cranial migration of the distal component noted at 24-month follow-up (the core lab noted an inverted funnel-shaped proximal neck with circumferential thrombus and a funnel-shaped distal neck with circumferential thrombus on pre-procedure imaging).

^j (0412013) Single barb separation on distal component not associated with endoleak (Type IIb endoleak noted at pre-discharge, but not on subsequent follow-up), migration, or need for secondary intervention - increase in aneurysm size was noted at 48-month follow-up, with no further follow-up as of yet.

^k (2612009) Single barb separation on proximal component not associated with endoleak, migration, increase in size, or need for secondary intervention.

^l (3612006) Single barb separation on proximal component not associated with endoleak or increase in size (aneurysm size increase was noted at 24- and 36-month follow-up, but no change from baseline size at 48-month follow-up, and a decrease in size compared to 24-months) – caudal migration of proximal end and cranial migration of distal end noted at 48-month follow-up and a secondary intervention (placement of proximal and distal graft extensions) was performed between 48 and 60 months (the core lab noted an inverted funnel-shaped proximal neck and funnel-shaped distal neck on pre-procedure imaging, and device oversizing at the proximal end appeared insufficient relative to the location of actual graft placement).

^m (0412016) Single barb separation from proximal component not associated with endoleak, migration, increase in size, or need for secondary intervention.

ⁿ (0912001) Single barb separation on distal component not associated with endoleak, migration, increase in size, or need for secondary intervention.

^o (0111001) Multiple (two) barb separation on proximal component not associated with endoleak, migration, increase in size, or need for secondary intervention.

^p (0912005) Multiple (three) barb separation and one stent fracture on distal component not associated with endoleak, migration, increase in size, or need for secondary intervention.

^q (4112010) Single barb separation on proximal component not associated with endoleak, migration, increase in size (aneurysm size increase was noted at 12-month follow-up, but no change from baseline size at 36-month follow-up and decreased on baseline size at 48-month follow-up), or need for secondary intervention (intervention was performed between 12 and 24 months to treat component separation that was not verified by core lab and persistent endoleak).

^r (2312001) Single barb separation on proximal component not associated with endoleak, migration, increase in size, or need for secondary intervention.

^s (3112014) Single barb separation on proximal component not associated with endoleak, migration, increase in size, or need for secondary intervention.

^t (2612012) Single barb separation on proximal component not associated with endoleak, increase in size, or secondary intervention – caudal migration of the proximal component was noted at 24 months.

Migration

Migration (radiographic) was defined as core laboratory determination, with CEC confirmation, of antegrade or retrograde movement of the proximal or distal components of the endoprosthesis > 10 mm relative to anatomical landmarks identified on the first post-operative CT scan, with clinically significant migration defined as migration resulting in the need for secondary intervention.

While the definitions have not changed, the methods by which to systematically evaluate migration have continued to be refined and improved throughout the course of the study so as to better account for apparent movement due to seating of barbs, as well as to assess relative movement in the context of conformational changes in the aorta over time (e.g., lengthening of anatomy). Accordingly, cases previously thought to be migration may continue to be reassessed in light of these considerations so as to provide a better understanding of device performance.

Table 8 reports the percent of patients with clinically significant migration (date of first occurrence). Also reported in Table 8 is the percent of patients with radiographic migration. Inadequate aortic neck anatomy and/or insufficient device oversizing relative to the location of actual graft placement was often identified as a potential contributing factor to migration.

Table 8: Percent of Patients with CEC-Confirmed Migration (Date of First Occurrence)

Item	30-day	6-month	12-month	24-month	36-month	48-month	60-month
Clinically	0%	0%	0%	0%	0%	1.4%	0%

significant migration	(0/112)	(0/112)	(0/109)	(0/90)	(0/88)	(1/71) ^a	(0/57)
Radiographic migration	0% (0/112)	0% (0/112)	1.8% (2/109)	5.6% (5/90)	1.1% (1/88)	1.4% (1/71)	1.8% (1/57)

^a (3612006) Caudal migration of proximal end and cranial migration of distal end not associated with endoleak or increase in size (aneurysm size increase was previously noted at 24- and 36-month follow-up, but no change from baseline size at 48-month follow-up, and size had decreased compared with 24-months) – secondary intervention was performed (placement of proximal and distal main body extensions).

Secondary Interventions

Eleven (6.9%) endovascular treatment patients (10 aneurysm, 1 ulcer) and 6 (8.6%) open surgical control patients (4 aneurysm, 2 ulcer) underwent at least one re-intervention subsequent to the initial aneurysm/ulcer repair procedure. The site-reported reasons for reintervention are provided in Table 9. There have been no cases of conversion to open surgical repair in the endovascular treatment group.

Table 9: Site-reported Reasons for Secondary Interventions

Reason (per site)	Endovascular						Open Surgical					
	0-30 days	31-365 days	366-730 days	731-1095 days	1096-1460 days	1461-1825 days	0-30 days	31-365 days	366-730 days	731-1095 days	1096-1460 days	1461-1825 days
Aneurysm rupture	0	0	0	0	0	0	0	0	0	0	0	0
Component separation	0	0	2 ^{a,b}	0	0	1 ^o	n/a	n/a	n/a	n/a	n/a	n/a
Symptoms	0	0	1 ^b	0	0	0	1 ^j	1 ^k	0	0	0	0
Occlusion	0	0	0	0	0	0	0	0	0	0	0	0
Device stenosis	0	0	0	0	0	0	n/a	n/a	n/a	n/a	n/a	n/a
Device kink	0	0	0	0	0	0	n/a	n/a	n/a	n/a	n/a	n/a
Device migration	0	0	0	0	0	1 ^p	n/a	n/a	n/a	n/a	n/a	n/a
Infection	0	0	0	0	0	0	0	0	0	0	0	0
Endoleak	3	2 ^c	1 ^b	0	1 ⁱ	1 ^o						
Proximal Type I	1 ^d	0	0	0	0	0						
Distal Type I	1 ^e	2 ^c	0	0	1 ⁱ	0						
Type IIa	0	0	0	0	0	0	n/a	n/a	n/a	n/a	n/a	n/a
Type IIb	0	0	0	0	0	0						
Type III	1 ^f	0	1 ^b	0	0	1 ^o						
Type IV	0	0	0	0	0	0						
Unknown	0	0	0	0	0	0						
Other	0	3 ^g	1 ^h	0	0	0	3 ^{j,l}	2 ^{k,m}	0	0	1 ⁿ	0

n/a – not applicable

^a (3612012) Aneurysm patient treated with placement of an additional proximal component for decreasing component overlap from device alignment with greater curve.

^b (4112010) Aneurysm patient with symptoms from Type III endoleak due to component separation treated with placement of additional main body components; retrospective review of procedural imaging suggests length of overlap achieved between components at time of initial deployment was less than minimum recommended amount.

^c (2612011) One aneurysm patient had two interventions for a distal Type I endoleak – bare stent placement and stent placement/coil embolization/distal extension placement.

^d (0412016) Aneurysm patient treated with proximal main body extension placement.

^e (0412018) Aneurysm patient treated with molding balloon angioplasty and distal extension placement.

^f (2512001) Aneurysm patient underwent angiogram to rule out endoleak; no endoleak was detected and the endovascular graft was intact.

^g Includes one ulcer patient with iliac artery occlusion, treated with femoral-femoral bypass (0612001); one aneurysm patient with size increase was treated with distal extension placement in overlap and distal end of graft (0912003); and one aneurysm patient who developed a pseudoaneurysm at follow-up, treated with proximal extension placement (1512004).

^h (0912003) One aneurysm patient with size increase, treated with placement of additional endovascular graft components, who also underwent secondary intervention for increase at 31-365 days, as discussed in note ‘g’.

ⁱ (0412014) Aneurysm patient treated with distal main body extension placement.

^j (1114001) One ulcer patient with multiple reasons (symptoms and other [continued bleeding]), treated with re-exploration and hemostatic sealing agents.

^k (3314002) Aneurysm patient who developed symptoms due to tracheal stroma bleeding was treated with sternotomy and patch repair.

^l Includes one aneurysm patient with intrapleural hematoma, treated with exploratory thoracotomy and evacuation (0913009); one ulcer patient with bleeding and tamponade, treated with intercostal vessel ligation (1413001)

^m (1513001) One aneurysm patient who developed an aorto-esophageal fistula at follow-up, treated with custom endograft placement.

ⁿ (0914002) Aneurysm patient developed juxtarenal AAA and upstream thoracoabdominal aortic aneurysm and was treated with endograft placement extending from the prior proximal repair.

^o (0412018) Aneurysm patient with Type III endoleak in setting of aortic elongation, treated with placement of an additional proximal component to bridge the gap between the initial proximal component and a distal main body extension that had been placed in a previous secondary intervention at 0-30 days, as discussed in note 'e'.

^p (3612006) Aneurysm patient who experienced caudal migration of proximal end and cranial migration of distal end, not associated with endoleak or increase in size (aneurysm size increase was noted at 24- and 36-month follow-up, but no change from baseline size at 48-month follow-up, and size had decreased compared with 24 months) was treated with placement of proximal and distal main body extensions.

Conversion

As shown in Table 10, there have been no conversions to open surgical repair in the endovascular treatment group.

Table 10: Kaplan-Meier for Freedom from Conversion

Arm	Days	Kaplan-Meier Estimate	Standard Error	Cumulative Events	Cumulative Censored	Patients remaining
Endovascular	0	1.000	0.0000	0	0	160
	30	1.000	0.0000	0	4	156
	365	1.000	0.0000	0	24	136
	730	1.000	0.0000	0	43	117
	1095	1.000	0.0000	0	58	102
	1460	1.000	0.0000	0	80	80
	1825	1.000	0.0000	0	104	56

Summary

Patient follow-up in the multi-center pivotal clinical study remains on-going and will continue through 5 years. As of March 18, 2011, survival from aneurysm-related mortality at 1460 days was 89.8% in the endovascular treatment group and 84.7% in the open surgical control group. To date, no death in the endovascular treatment group was found to be related to failure of a component of the device. The percent of patients with new endoleak at 48 months was 5.0%, and the percent of patients with an increase in aneurysm/ulcer size was 4.6%, as compared with 61.5% who showed a decrease in size. New device integrity observations at 48 months included 1 patient with stent fracture and 5 patients with barb separation, one of which occurred in the only patient with migration requiring reintervention (due likely to inadequate aortic neck anatomy and/or insufficient device oversizing relative to the location of actual graft placement but without report of endoleak at any time). The percent of patients requiring at least one reintervention subsequent to the initial aneurysm/ulcer repair procedure is 6.9% in the endovascular treatment group and 8.6% for the open surgical control group. There have been no ruptures or conversions to open surgical repair in the endovascular treatment group. These data continue to support the safety and effectiveness of the Zenith® TX2® TAA Endovascular Graft.

Section II – Worldwide Commercial Experience

The Zenith® TX2® TAA Endovascular Graft was commercially available in the US soon after marketing clearance was granted by FDA on May 21, 2008, and has been in commercial use throughout the rest of world since 2004 (Canada in 2009; Japan 2011). While the device is indicated in the US to treat only patients with aneurysms or ulcers of the descending thoracic aorta, the approved indications outside the US (except Canada and Japan) include treatment of patients with atherosclerotic or enlarging aneurysms, symptomatic acute or chronic dissections, or contained ruptures.

As shown in Table 11, a total of 26,198 components (including 13,802 components in the US) have been distributed worldwide between May 21, 2008 and March 31, 2011.

Table 11: Total Number of Zenith® TX2® TAA Endovascular Graft Components Sold Worldwide (between May 21, 2008 and March 31, 2011)

Component	Global Number Sold	US Number Sold
ZTEG-2P (proximal component)	12,798	6,927
ZTEG-2PT (proximal tapered component)	5,545	2,515
ZTEG-2D (distal component)	4,294	2,194
ESBE-T (distal body extension)	914	569
TBE (proximal body extension)	2,647	1,597
Total	26,198	13,802

Cook evaluates product performance from this commercial experience based on complaint reporting systems throughout the world. Table 12 summarizes the procedural and follow-up complaints received during commercial experience with the Zenith® TX2® TAA Endovascular Graft between May 21, 2008 and March 31, 2011. All complaints received related to the Zenith® TX2® TAA Endovascular Graft are processed through the Customer Relations Department of the William Cook Europe Quality System. Complaints relating to user error, procedural complication, or device malfunction undergo a clinical review by Cook medical personnel. Based on this review, additional information may be requested from the user facility at which the event occurred. Cook medical staff along with the Quality Engineering group make a final determination of root cause, and the findings are evaluated for any necessary corrective action.

Table 12: Complaints from Commercial Experience with the Zenith® TX2® TAA Endovascular Graft between May 21, 2008 and March 31, 2010

Complaint	n
Death	
Early (≤ 30 days)	9 ^{a,b,c,d,e,f,l,m,n}
Late (> 30 days)	0
Serious injury	
Not device related	1 ^g
Proximal dissection	2 ^{h,o}
Separation of delivery system	1 ^p
Infolding/incomplete expansion	2 ^{q,r}
Endoleak	
Type unknown or not reported	1 ⁱ
Required additional intervention	
During procedure	1 ^j
Other	
Difficult to remove trigger wire	2
Difficult trackability due to difficult anatomy	1
Sheath buckling	2
Valve too tight	1
Proximal stent portion failed to open	1 ^k
Total	24

^aDeath due to DIC.

^bDeath due to MI.

^cCause of death unknown.

^dDeath due to complications of procedure; spinal cord infarction and respiratory failure.

^eDeath due to presenting trauma at time of procedure.

^fDeath due to pre-existing condition.

^gHemothorax.

^hProximal extension of dissection in patient with pre-existing dissection.

ⁱResolved following extension placement within 30 days of initial procedure.

^jRepositioning of graft with ballooning for treatment of distal Type I endoleak.

^kLimited information suggests a pre-existing iliac stent may have been carried up with the device and constricted its complete expansion; no flow restriction was reported.

^lDeath due to proximal dissection within 30 days of secondary intervention to treat proximal Type I endoleak in patient with pre-existing dissection.

^mDeath due to ischemic gut.

ⁿDeath due to proximal dissection in patient with pre-existing dissection.

^oNoted following ballooning at proximal end.

^pDilator tip/cannula assembly separated from delivery system during removal in a patient with severe angulation – successful retrieval of assembly surgically.

^qNo additional procedures reported.

^rResolved with ballooning.

None of the complaints received resulted in corrective or preventative action. Overall, the nature and frequency of complaints during this time period are consistent with those observed during periods of commercial use prior to approval in the US.

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 one explanted device that was submitted as a part of the multi-center clinical study. The device was explanted at the time of autopsy following death unrelated to aneurysm repair or a failure in device integrity.

While damage from surgical instruments during explantation is sometimes obvious in explant analysis, it is not always possible to determine if observations occurred before explantation or if the explantation process contributed to, or caused, the observations. Explant analysis was performed 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.

The length of implant in the one explant was 222 days. The observations from explant analysis are listed in Table 13.

Table 13: Observations from Grafts Explanted during the Multi-center Clinical Study

Reason for explant	Days Implanted	Observations ¹					
		Damaged or Broken Stents	Barb Separation	Graft Wear	Cut or Broken Sutures (green) ²	Cut or Broken Sutures (blue) ³	Suture Hole Elongation
Autopsy (unrelated death)	222			1 ⁴	3		1

¹ Noted observations may have been due to damage caused during explantation.

² Sutures used to attach external stents.

³ Sutures used to attach internal stents and bare stent.

⁴ Not associated with endoleak.

Three explants from other non-commercial experiences outside the multi-center study have been analyzed. None of the explantation procedures were due to failure in device integrity, and the mean implantation time was 394 days (range of 20 to 711 days). None of the explants were found to have graft wear or damaged/broken stents. Two explants had barb separation; however the barb wire was smaller in diameter than what is currently available. Each explant had cut or broken sutures (green). One explant had cut

or broken sutures (blue), and one explant had suture hole elongation. 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

There have been no explants analyzed from worldwide commercial experience.

Summary

In total, there have been four explants analyzed. None of the explants analyzed were explanted due to failure in device integrity, and there were no reported adverse clinical sequelae associated with the post-explant observations, which may have been due to damage caused during explantation. Nonetheless, routine imaging follow-up remains important in detecting any potential compromises in device integrity that might require reintervention.

Section IV – Notes to Clinicians

At this time, there are no additional notes or instructions to clinicians beyond what is already described in the IFU – the key aspects are briefly summarized in Section V.

Section V – Brief Summary of Indications, Warnings, and Precautions from IFU

Indications

The Zenith[®] TX2[®] TAA Endovascular Graft is indicated for the endovascular treatment of patients with aneurysms or ulcers of the descending thoracic aorta having morphology suitable for endovascular repair, including:

- Adequate iliac/femoral access compatible with the required introduction systems,
- Non-aneurysmal aortic segments (fixation sites) proximal and distal to the aneurysm or ulcer:
 - With a length of at least 25 mm, and
 - With a diameter measured outer wall to outer wall of no greater than 38 mm and no less than 24 mm.

Warnings and Precautions

Patient Selection

- The Zenith[®] TX2[®] TAA Endovascular Graft is designed to treat aortic neck diameters no smaller than 24 mm and no larger than 38 mm. The Zenith[®] TX2[®] TAA Endovascular Graft is designed to treat proximal aortic necks (distal to either the left subclavian or left common carotid artery) of at least 25 mm in length. Additional proximal aortic neck length may be gained by covering the left subclavian artery (with or without discretionary transposition) when necessary to optimize device fixation and maximize aortic neck length. A distal aortic neck length of at least 25 mm proximal to the celiac axis is required. These sizing measurements are critical to the performance of the endovascular repair.
 - Key anatomic elements that may affect successful exclusion of the aneurysm or ulcer include a radius of curvature <35 mm; localized aortic neck angulation >45 degrees; short proximal or distal fixation sites (<25 mm); an inverted funnel shape at the proximal fixation site or a funnel shape at the distal fixation site (greater than 10% change in diameter over 25 mm of fixation site length); and circumferential thrombus and/or calcification at the arterial fixation sites. In the presence of anatomical limitations, a longer neck length may be required to obtain adequate sealing and fixation. Irregular calcification and/or plaque may compromise the attachment and
-

sealing at the fixation sites. Neck exhibiting these key anatomic elements may be more conducive to graft migration or endoleak.

Device Selection

- The recommended amount of overlap between devices is 3-4 stents. However, the proximal sealing stent of the proximal component or distal sealing stent of the distal component should not be overlapped, as doing so may cause malapposition to the vessel wall. The minimum required amount of overlap between devices is 2 stents (~50 mm) – less than 2 stents may result in endoleak (with or without component separation). Device lengths should be selected accordingly.
- Strict adherence to the Zenith[®] TX2[®] TAA Endovascular Graft IFU sizing guide is strongly recommended when selecting the appropriate device size. Appropriate device oversizing has been incorporated in the IFU sizing guide. Sizing outside of this range can result in endoleak, fracture, migration, device infolding, or compression.

Implant Procedure

- Do not bend or kink the delivery system. Doing so may cause damage to the delivery system and the Zenith[®] TX2[®] TAA Endovascular Graft.
- Do not continue advancing the wire guide or any portion of the delivery system if resistance is felt. Stop and assess the cause of resistance; vessel, catheter, or graft damage may occur. Exercise particular care in areas of stenosis, intravascular thrombosis, or calcified or tortuous vessels.
- Repositioning the stent graft distally after partial deployment of the covered proximal stent may result in damage to the stent graft and/or vessel injury.
- Landing the proximal and distal ends of the device in parallel aortic neck segments without acute angulation (>45 degrees) or circumferential thrombus/calcification is important to ensuring fixation and seal.
- Landing the proximal or distal ends of the device in an aortic neck segment with a diameter that differs from that to which the graft was sized initially may potentially result in inadequate sizing (<10% or >25%) and therefore migration, endoleak, aneurysm or ulcer enlargement, or increased risk of thrombosis.

Note: Refer to the IFU for complete warnings and precautions
