Annual Clinical Update

Abstract

Cook is pleased to provide you with this second clinical update on the Zenith Alpha™ Thoracic Endovascular Graft, which was commercially approved by FDA on September 15, 2015 (initially for the treatment of isolated lesions of the descending thoracic aorta, not including dissections) and is currently indicated (as of July 28, 2017) for the treatment of aneurysms or ulcers of the descending thoracic aorta. **Section I** provides an update on the results from two multicenter clinical trials, reflecting data received as of August 1, 2018 and therefore two years of additional data collection since the previous (2016) clinical update, which reflected data received as of July 28, 2016. Briefly, a thoracic aneurysm/ulcer study was designed to compare the 30-day major adverse event (MAE) rate and the 12-month device success rate with the Zenith Alpha™ Thoracic Endovascular Graft to performance goals derived from a study of its predecessor device, the Zenith® TX2® TAA Endovascular Graft. The original safety and effectiveness of the Zenith Alpha™ Thoracic Endovascular Graft to treat blunt thoracic aortic injury (BTAI) was evaluated in a separate pivotal study. In total, 178 patients were enrolled as follows: 110 in the pivotal phase of the aneurysm/ulcer study, 18 patients in the continued access phase of the aneurysm/ulcer study, and 50 patients in the BTAI study. These studies were designed to collect follow-up data through 5 years. Since approval of the original PMA, there have been no new TAA-related deaths or conversions reported in the aneurysm/ulcer study within 5 years, although follow-up is ongoing.

Between July 28, 2016 to July 28, 2017 there have been 2 reports of rupture (both in the pivotal study after five years (1 patient adjudicated by CEC to be related and 1 patient reported to not be related), 1 newly reported patient with Type I or III endoleak (1 pivotal with distal Type I endoleak). Additionally, there have been 4 new reports of aneurysm growth (2 pivotal, 2 continued access). There have been no new reports of CEC-confirmed migration or losses in either patency or device integrity.

Between July 29, 2017 to August 1, 2018, there have been no new reports of CEC-confirmed migration, loss in either patency or device integrity, Type III endoleak, or rupture in either the pivotal study or continued access study. There have been four newly reported patients with Type I endoleak (three pivotal study patients with distal Type I endoleak and one continued access patient with proximal Type I endoleak). Additionally, there have been six new reports of aneurysm growth (all pivotal).

While BTAI was initially included in the approved indications for the device, as discussed in Section IV below, this indication was withdrawn following reports of thrombosis/occlusion within the graft in patients treated for BTAI with the device. In the

BTAI study, there have been no new aortic injury-related deaths, Type I or III endoleaks, device integrity observations, or conversions since approval of the PMA. There remain no reports of rupture, migration, or loss of patency. However, as reported in the 2016 clinical update, there has been one patient with device compression, who underwent reintervention in the absence of symptoms, and 13 other patients with incidental findings of thrombus typically within the distal portion of the graft (one underwent reintervention in the absence of symptoms). The patients with thrombus tended to have smaller graft diameters and greater distal oversizing when compared to the patients without thrombus. Overall, the results continue to support the safety and effectiveness of the Zenith Alpha Thoracic Endovascular Graft for the treatment of patients with aneurysms or ulcers of the descending thoracic aorta, whereas the BTAI clinical study results were not consistent with worldwide experience for BTAI, which observed a risk of in-graft thrombus when used to treat BTAI. **Section II** summarizes worldwide commercial experience through July 31, 2018. A total of 23,242 components have been sold worldwide (including 8,178 sold in the US) since September 15, 2015. There have been 153 procedural and follow-up complaints reported since approval, including 62 new complaints between July 28, 2016 and July 28, 2017 (during which 8,045 components were sold) and 57 new complaints between July 29, 2017 and August 1, 2018 (during which 9,644 components were sold). Among the reported complaints since approval, there have been 16 for thrombosis in the graft following treatment for BTAI/trauma/penetrating aortic injury (0 new reports occurring between July 28, 2016 and July 28, 2017; 8 new reports occurring between July 29, 2017 and August 1, 2018). **Section III** summarizes the findings from explant analysis. To date, 2 explants have undergone analysis. **Section IV** is reserved for any new notes or general instructions to clinicians and therefore discusses the prior field actions from 2017 pertaining to BTAI (as also provided in the 2016 clinical update) and also a communication from 2018 to reiterate the device indications for use. **Section V** provides a brief summary of the indications, warnings, and precautions from the IFU.

Device Description

The Zenith Alpha™ Thoracic Endovascular Graft is predicated on the Zenith® TX2® Endovascular Graft. The Zenith Alpha™ Thoracic Endovascular Graft is a two-piece cylindrical endovascular graft consisting of a proximal component and an overlapping distal component. Also available are distal extensions for use in increasing the length of overlap between components or extending graft coverage distally; additional proximal components can be used to extend graft coverage proximally. All components are constructed of self-expanding nitinol stents sewn to denser, more tightly woven polyester

graft material (as compared to the stainless steel stents and the polyester graft material used in the Zenith® TX2® Endovascular Graft) with braided polyester and monofilament polypropylene sutures, intended for improving the compatibility with magnetic resonance imaging over the predicate device. The most proximal covered stent of the proximal component and the distal bare stent of the distal component contain barbs to augment fixation of the device. The endovascular graft design has been modified with the intent to improve conformability with respect to the predicate design, has the ability to accommodate steep curvature of the aortic arch (a minimum aortic arch radius of curvature of 20 mm as compared to 35 mm for the predicate device), and is available in a wider range of graft diameters (now 24 mm to 46 mm as compared to 28 mm to 42 mm for the predicate device) in smaller profile endovascular graft introduction systems (16, 18, and 20 Fr as compared to 20 - 22 Fr for the predicate device). 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 Alpha™ Thoracic Endovascular Graft was to provide a clinical update to physician users annually. This update incorporates the information specified in the September 15, 2015 approval order for P140016. 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).

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Section I – Clinical Study Experience

ANEURYSM/ULCER STUDY

Description of Study

Pivotal Phase

The Zenith Alpha™ Thoracic Endovascular Graft pivotal study was a prospective, nonrandomized, single-arm, multinational study that was conducted to evaluate the safety and effectiveness of the Zenith Alpha™ Thoracic Endovascular Graft for the treatment of patients with aneurysms/ulcers of the descending thoracic aorta. Patients were treated between March 17, 2010 (first US enrollment on October 1, 2010) and January 16, 2013. There were 23 investigational sites, including centers in the US (51 patients at 14 sites), Japan (43 patients at 3 sites), Germany (13 patients at 4 sites), Sweden (3 patients at 1 site), and England (1 patient at 1 site). The presenting anatomy, based on core laboratory analysis of pre-procedure imaging, was a thoracic aneurysm in 81.8% (90/110) of patients and a thoracic ulcer in 18.2% (20/110) of patients.

The pivotal study endpoints were established based on performance goals derived from the pivotal study of the previous device, the Zenith® TX2® TAA Endovascular Graft. Similar inclusion/exclusion criteria were used between the two studies. A post hoc analysis was performed comparing demographic, comorbid, and baseline anatomical characteristics between the present study and the previous Zenith® TX2® TAA Endovascular Graft study used to derive the performance goals for hypothesis testing. Of the few variables that were found to be different between studies, none appeared to be relevant with respect to assessing the safety and effectiveness endpoints, thus confirming that comparing to performance goals derived from the previous study remained appropriate. The primary safety (freedom from major adverse events at 30 days) and effectiveness (device success at 12 months) endpoints were met.

Continued Access Phase

At the completion of enrollment in the pivotal study and prior to commercial availability, continued access to the Zenith Alpha™ Thoracic Endovascular Graft was offered to investigators under a study expansion that followed the same inclusion/exclusion criteria, follow-up schedule, definitions, and data collection as for the pivotal study. A total of 18 patients were enrolled between April 19, 2013 and January 19, 2015.

Patient Availability for Follow-up

Patient availability for follow-up as of August 1, 2018 is summarized in Table 1 for the pivotal phase and Table 2 for continued access.

Table 1. Follow-up availability - Pivotal

Follow-up Visit	Patients Eligible for Follow-up	Percent of Data Available[a]			Adequate Imaging to Assess the Parameter[b]				Events Occurring Before Next Interval			
		Clinical Assess-ment	CT[c]	X-ray	Size Increase	Endoleak	Migration	Fracture	Death	Conversion	LTF/ WTHD	Not Due for Next Visit
Operative	110	110/110 (100%)	NA	NA	NA	NA	NA	NA	0	0	0	0
30-day	110[d]	106/110 (96.4%)	105/108 (97.2%)	98/108 (90.7%)	105/108 (97.2%)	102/108 (94.4%)	NA	105/108 (97.2%)	3	0	0	2[d]
6-month	105	99/105 (94.3%)	96/105 (91.4%)	92/105 (87.6%)	96/105 (91.4%)	91/105 (86.7%)	94/105 (89.5%)	98/105 (93.3%)	2	0	4	0
12-month	99	91/99 (91.9%)	92/99 (92.9%)	84/99 (84.8%)	92/99 (92.9%)	83/99 (83.8%)	92/99 (92.9%)	92/99 (92.9%)	7	1	2	0
2-year	89	78/89 (87.6%)	79/89 (88.8%)	75/89 (84.3%)	80/89 (89.9%)	76/89 (85.4%)	80/89 (89.9%)	80/89 (89.9%)	4	0	7	0
3-year	78	73/78 (93.6%)	71/78 (91.0%)	66/78 (84.6%)	71/78 (91.0%)	63/78 (80.8%)	72/78 (92.3%)	72/78 (92.3%)	1	0	5	0
4-year	72	67/72 (93.1%)	67/72 (93.1%)	66/72 (91.7%)	68/72 (94.4%)	60/72 (83.3%)	68/72 (94.4%)	68/72 (94.4%)	6	0	3	0
5-year	63	57/63 (90.5%)	54/63 (85.7%)	54/63 (85.7%)	54/63 (85.7%)	43/63 (68.3%)	56/63 (88.9%)	56/63 (88.9%)	N/A[e]	N/A	N/A[f]	N/A

NA – Not assessed. LTF/WTHD – Lost-to-follow-up or withdrawn. N/A – Not applicable

[a]Site-submitted data.

[b]Based on core laboratory analysis.

[c]Includes MRI or TEE imaging, which is allowed per protocol when the patient is unable to receive contrast medium.

[d]Two patients did not receive the device at the time of the implant procedure and therefore only 30-day clinical follow-up was applicable before the patients exited the study, with no further follow-up due thereafter.

[e] Three patients died >1825 days after the index procedure.

[f] Five patients were lost to follow-up or withdrew >1825 days after the index procedure.

Table 2. Follow-up availability - Continued Access

Follow-up Visit	Patients Eligible for Follow-up	Percent of Data Available[a]				Adequate Imaging to Assess the Parameter[b]				Events Occurring Before Next Interval			
		Clinical Assess-ment	CT[c]	X-ray	Patients with Follow-up Pending[d]	Size Increase	Endoleak	Migration	Fracture	Death	Conversion	LTF/ WTHD	Not Due for Next Visit
Operative	18	18/18 (100%)	NA	NA	0	NA	NA	NA	NA	0	0	0	0
30-day	18	18/18 (100.0%)	17/18 (94.4%)	13/18 (72.2%)	0	17/18 (94.4%)	17/18 (94.4%)	NA	18/18 (100.0%)	0	0	0	0
6-month	18	18/18 (100.0%)	18/18 (100.0%)	15/18 (83.3%)	0	18/18 (100.0%)	17/18 (94.4%)	17/18 (94.4%)	18/18 (100.0%)	0	0	0	0
12-month	18	15/18 (83.3%)	13/18 (72.2%)	13/18 (72.2%)	0	13/18 (72.2%)	12/18 (66.7%)	13/18 (72.2%)	13/18 (72.2%)	3	0	1	0
2-year	14	12/14 (85.7%)	10/14 (71.4%)	9/14 (64.3%)	0	10/14 (71.4%)	10/14 (71.4%)	10/14 (71.4%)	10/14 (71.4%)	0	0	0	0
3-year	14	9/14 (64.3%)	9/14 (64.3%)	6/14 (42.9%)	1	9/14 (64.3%)	8/14 (57.1%)	9/14 (64.3%)	9/14 (64.3%)	2	0	0	2
4-year	10	6/10 (60.0%)	6/10 (60.0%)	6/10 (60.0%)	3	6/10 (60.0%)	6/10 (60.0%)	6/10 (60.0%)	6/10 (60.0%)	1	0	0	6
5-year	3	1/3 (33.3%)	1/3 (33.3%)	1/3 (33.3%)	2	1/3 (33.3%)	1/3 (33.3%)	1/3 (33.3%)	1/3 (33.3%)	N/A	N/A	N/A	N/A

NA – Not assessed.
LTF/WTHD – Lost-to-follow-up or withdrawn.
N/A – Not applicable
[a]Site-submitted data.
[b]Based on core laboratory analysis.
[c]Includes MRI or TEE imaging, which is allowed per protocol when the patient is unable to receive contrast medium.
[d]Patients still within follow-up window, but data not yet available.

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).

Pivotal

The following data summarize survival from aneurysm-related mortality in the pivotal aneurysm/ulcer study. As presented in Table 3, survival from aneurysm-related mortality at 1825 days is thus far 99.0% for the overall cohort, 98.8% in the aneurysm group, and 100.0% in the ulcer group. There has been one TAA-related death reported to date within 5 years (no new CEC-confirmed TAA-related deaths within 5 years since the original PMA).

Table 3. Kaplan-Meier aneurysm-related mortality survival estimates - Pivotal

Event	Parameter	30 Days			180 Days			365 Days			730 Days			1095 Days			1460 Days			1825 Days		
		Aneur	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**
TAA-related mortality	Number at risk[a]	89	20	109	86	19	105	80	18	98	69	18	87	60	17	77	**52**	16	**68**	**46**	**16**	**62**
	Cumulative events[b]	0	0	0	0	0	0	1[e]	0	1	1	0	1	1	0	1	1	0	1	1	0	1
	Cumulative censored[c]	1	0	1	4	1	5	9	2	11	20	2	22	29	3	32	**37**	4	**41**	**43**	**4**	**47**
	KM estimate[d]	1.000	1.000	1.000	1.000	1.000	1.000	0.988	1.000	0.990	0.988	1.000	0.990	0.988	1.000	0.990	0.988	1.000	0.990	0.988	1.000	0.990
	Standard error	0.000	0.000	0.000	0.000	0.000	0.000	0.012	0.000	0.010	0.012	0.000	0.010	0.012	0.000	0.010	0.012	0.000	0.010	0.012	0.000	0.010

Note: New information since the last reporting period is bolded.
[a]Number of patients at risk at the beginning of the interval.
[b]Total events up to and including the specific interval represents all patients who have had the event.
[c]Total censored patients up to and including the specific interval represents all patients who have met a study exit criteria or for whom data are not available at the specific interval.
[d]At end of interval.
[e]Death due to aspiration pneumonia, which the CEC adjudicated as procedure-related due to the pneumonia having likely been related to a stroke that occurred the day of procedure (1040069).

One patient died from rupture after 5 years (>1825 days), which the CEC adjudicated as TAA-related, as further described below:

1030050 – This patient was treated at the time of the index procedure with a single proximal component. On post-operative day 504, the patient underwent endovascular AAA repair for a newly-diagnosed infrarenal aortic aneurysm. On post-operative day 1852, the patient presented with back pain and shortness of breath. Findings from CT were most consistent with a ruptured thoracic aortic aneurysm. The patient was taken to the operating room for treatment but died in transit on post-operative day 1853. The site-reported cause of death was cardiac arrest. The CEC adjudicated the death as TAA-related, noting an enlarged aneurysm and no intervention.

Continued Access

There have thus far been two TAA-related deaths according to the CEC [1030130 – death from hemorrhagic shock 351 days post-procedure, which the CEC specifically adjudicated as procedure-related rather than related to technique, a failure of the device, or some other reason (additional details regarding this patient include the core laboratory noting on the 30-day CT scan an irregular hazy appearance that extended above the proximal seal zone, which did not represent an endoleak; and at 266 days post-procedure, the site performed an angiogram that demonstrated an enlarging

pseudoaneurysm located off of the lesser curvature of the arch, proximal to the endograft); 1030137 – death from intra-abdominal bleeding 411 days post-procedure, which the CEC specifically adjudicated as procedure-related rather than related to technique, a failure of the device, or some other reason (additional details regarding this patient include the core laboratory noting on the 12-month CT scan air within the TAA and endograft with an associated increase in size of the aorta just below the device and fuzziness of tissue planes at the margins of the aorta at the same level, which abuts the stomach; an EGD was performed 391 days post-procedure that demonstrated stent erosion into the stomach), neither of which are new since the original PMA. There have been no new CEC-adjudicated aneurysm-related deaths in the continued access portion of the study reported since the 2016 Annual Clinical Update. One new death occurring between July 29, 2017 and August 1, 2018 (1030145 – acute hypoxic respiratory failure secondary to community-acquired pneumonia with COPD/pulmonary fibrosis, occurring 1485 days post-procedure) has been adjudicated by the CEC after the August 1, 2018 data lock to not be TAA related (attributed to pneumonia).

All-cause Mortality

Pivotal

The following data summarize survival from all-cause mortality in the aneurysm and ulcer groups. As presented in Table 4, survival from all-cause mortality at 1825 days is thus far 75.9% for the overall cohort, 71.3% in the aneurysm group, and 95.0% in the ulcer group.

Table 4. Kaplan-Meier all-cause mortality survival estimates - Pivotal

Event	Parameter	30 Days			180 Days			365 Days			730 Days			1095 Days			1460 Days			1825 Days		
		Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All
All-cause mortality	Number at risk[a]	89	20	109	86	19	105	80	18	98	69	18	87	60	17	77	**52**	16	**68**	**46**	**16**	**62**
	Cumulative events[b]	0	0	0	2	1	3	4	1	5	11	1	12	15	1	16	19	1	20	**22**	1	**23**
	Cumulative censored[c]	1	0	1	2	0	2	6	1	7	10	1	11	15	2	17	**19**	3	**22**	**22**	**3**	**25**
	KM estimate[d]	1.000	1.000	1.000	0.977	0.950	0.972	0.954	0.950	0.953	0.869	0.950	0.884	0.816	0.950	0.841	**0.759**	0.950	**0.795**	**0.713**	0.950	**0.759**
	Standard error	0.000	0.000	0.000	0.016	0.049	0.016	0.023	0.049	0.021	0.037	0.049	0.032	0.045	0.049	0.038	**0.052**	0.049	**0.044**	**0.056**	0.049	**0.047**

Note: New information since the last reporting period is bolded.

[a]Number of patients at risk at the beginning of the interval.

[b]Total events up to and including the specific interval represents all patients who have had the event.

[c]Total censored patients up to and including the specific interval represents all patients who have met a study exit criteria or for whom data are not available at the specific interval.
[d]At end of interval.

As previously reported, one additional patient died from rupture after 5 years (>1825 days), which the CEC adjudicated as unrelated, as further described below:

1030052 – This patient with prior open repair involving the ascending and descending thoracic aorta (secondary to giant cell aortitis) was treated at the time of the index procedure with a proximal component, distal component, and distal extension. On post-operative day 1862, the patient underwent additional thoracic graft placement due to reported growth in the descending thoracic aorta distal to the originally treated segment. Two days later, the patient died from left hemothorax due to rupture. The CEC adjudicated the death as unrelated, noting there was aneurysm growth below the endograft.

Continued Access

There have thus far been six total deaths in the continued access portion of the study. Two were adjudicated as related, one was adjudicated as unrelated, two in which the CEC was unable to adjudicate relatedness (one newly reported between July 29, 2017 and August 1, 2018). One was also newly reported between July 29, 2017 and August 1, 2018 and was recently adjudicated by the CEC to be unrelated after the datalock.

Endoleak

Pivotal

Table 5 reports the percentage of patients with endoleak (by type) at each follow-up time point based on the results from core laboratory analysis. Patients who underwent a secondary intervention for endoleak or who had associated aneurysm size increase are indicated by footnotes, as are any patients with Type I or III endoleak. There was one patient with a newly reported endoleak occurring between July 28, 2016 and July 28, 2017 (1030022 with distal Type I endoleak at 5-years). There have been three patients with newly-reported endoleak occurring between July 29, 2017 and August 1, 2018 (1030046, 1030052, and 1040062, all with distal Type I endoleak at 5 years). Thus far, there have been thirteen patients with Type I

endoleak (all were distal Type I endoleaks, two of which were determined to be unknown endoleak types at subsequent follow-up, while nine were observed in aneurysm patients who did not receive a distal component, whereas it is recommended that aneurysm patients be treated with a proximal and distal component combination, as also described in Section V), six patients with Type IIa endoleak, eight patients with Type IIb endoleak, two patients with Type II (unknown) endoleak, two patients with Type III endoleak (both Type IIIb), and six patients with unknown endoleak type.

Table 5. Endoleak based on results from core laboratory analysis – Pivotal

Type	Percent Patients (number/total number)																				
	30-day			6-month			12-month			2-year			3-year			4-year			5-year		
	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All
Any (new only)	8.5% (7/82)	10.0% (2/20)	8.8% (9/102)	4.1% (3/73)	5.6% (1/18)	4.4% (4/91)	4.5% (3/66)	0	3.6% (3/83)	8.2% (5/61)	0	6.6% (5/76)	2.0% (1/50)	0	1.6% (1/63)	**8.7% (4/46)**	0	**6.7% (4/60)**	**12.1% (4/33)**	**10.0%** (1/**10**)	**11.6% (5/43)**
Any (new and persistent)	8.5% (7/82)	10.0% (2/20)	8.8% (9/102)	11.0% (8/73)	11.1% (2/18)	11.0% (10/91)	10.6% (7/66)	0	8.4% (7/83)	16.4% (10/61)	0	13.2% (10/76)	10.0% (5/50)	0	7.9% (5/63)	**19.6% (9/46)**	0	**15.0% (9/60)**	**27.3% (9/33)**	**10.0%** (1/**10**)	**23.3% (10/43)**
Multiple	2.4% (2/82)[a]	0	2.0% (2/102)	2.7% (2/73)[a]	0	2.2% (2/91)	1.5% (1/66)	0	1.2% (1/83)	0	0	0	0	0	0	0	0	0	**3.0% (1/33)**	0	**2.3% (1/43)**
Proximal Type I	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Distal Type I (new and persistent)	2.4% (2/82)[a,b]	0	2.0% (2/102)	4.1% (3/73)[a,b,d]	0	3.3% (3/91)	4.5% (3/66)[b,d,e]	0	3.6% (3/83)	8.2% (5/61)[b,e,g-i]	0	6.6% (5/76)	2.0% (1/50)[j]	0	1.6% (1/63)	**4.3% (2/46)**[b,k]	0	**3.3% (2/60)**	**18.2% (6/33)** [b,k,**l,m,n,o**]	0	**14.0% (6/43)**
Number new	2	0	2	1	0	1	1	0	1	3	0	3	1	0	1	1	0	1	4	0	4
Type II	7.3% (6/82)[a]	0	5.9% (6/102)	9.6% (7/73)[a,b]	5.6% (1/18)	8.8% (8/91)	6.1% (4/66)[b, k]	0	4.8% (4/83)	6.6% (4/61) [k]	0	5.3% (4/76)	8.0% (4/50)[k]	0	6.3% (4/63)	**8.7% (4/46)**	0	**6.7% (4/60)**	**9.1% (3/33)**	0	**7.0% (3/43)**
IIa	2	0	2	1	0	1	1	0	1	2	0	2	3	0	3	**1**	0	**1**	**1**	0	**1**
IIb	4	0	4	5	0	5	2	0	2	2	0	2	1	0	1	**3**	0	**3**	**2**	0	**2**
Unknown	0	0	0	1	1	2	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Type IIIb (new and persistent)	0	5.0% (1/20)[c]	1.0% (1/102)	0	5.6% (1/18)[c]	1.1% (1/91)	1.5% (1/66)[f]	0	1.2% (1/83)	0	0	0	0	0	0	0	0	0	0	0	0
Number new	0	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0

Type	Percent Patients (number/total number)																				
	30-day			6-month			12-month			2-year			3-year			4-year			5-year		
	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All
Type IV	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unknown	1.2% (1/82)	5.0% (1/20)	2.0% (2/102)	0	0	0	0	0	0	1.6% (1/61)	0	1.3% (1/76)	0	0	0	**6.5% (3/46)**[i]	0	**5.0% (3/60)**	**3.0% (1/33)**	**10.0%** (1/**10**)	**4.7% (2/43)**

Note: New information since the last reporting period is bolded.

Note: Type IIa = flow from subclavian, celiac, and/or anomalous vertebral arteries; Type IIb = flow from bronchial and/or intercostal arteries.

[a] Patient 0463776 – Distal Type I and Type IIb endoleaks were noted at the 1-month and 6-month follow-ups. The endoleak type was noted as unknown at the last follow-up (unscheduled follow-up at day 300); a decrease in aneurysm size was also noted at the last follow-up. No secondary interventions were performed, and the patient has since withdrawn from the study.

[b] Patient 1040045 –A distal Type I endoleak was noted at the 1-month, 6-month, 12-month, 2-year, 4-year, **and 5-year** follow-ups. A Type IIb endoleak was also identified at the 6-month and 12-month follow-ups. The patient was treated at the time of the index procedure with a single proximal component. The patient also had aneurysm growth (Table 6). **A secondary intervention (ancillary component placement) was performed 1827 days post-procedure to treat persistent distal Type I endoleak**. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests a distal seal length < 20 mm.

[c] Patient 1040051 – The Type III (nonjunctional) endoleak noted at the 1-month and 6-month follow-ups was no longer present at the 12-month follow-up. The location of the endoleak coincided with an area of prominent calcification in the aorta. No secondary interventions have been performed to date and the patient has not demonstrated an increase in ulcer size.

[d] Patient 1030072 – A distal Type I endoleak was noted at the 6-month and 12-month follow-ups. A secondary intervention has occurred (for the site-reported reason of distal Type I endoleak after 12-month follow-up). The patient has not experienced an increase in aneurysm size. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing and a distal seal length < 20 mm. The patient underwent a secondary intervention on post-operative day 420 (Table 9) and there was no endoleak detected at the 2-year follow-up.

[e] Patient 1030047 –A distal Type I endoleak was first noted at the 12-month follow-up (and again at an unscheduled CT [596 days post procedure]) and the 2-year follow-up, at which time the patient underwent secondary intervention (ancillary component placement) 727 days post-procedure (Table 9). The patient was treated at the time of the index procedure with a single proximal component. The patient also had aneurysm growth (Table 6) and CEC-confirmed migration (Table 8). Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing and a distal seal length < 20 mm. There was no endoleak detected at the 3-year follow-up.

[f] Patient 1030095 –A Type III (nonjunctional) endoleak was noted at the 12-month follow-up (a secondary intervention involving distal component placement was performed after the 12-month follow-up for the site-reported reason of distal Type I endoleak; Table 9). The patient was treated at the time of the index procedure with a single proximal component. The patient has not experienced an increase in aneurysm size. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) in combination with the site-reported reason for secondary intervention (distal Type I, not Type III, endoleak) suggest graft undersizing. Patient has subsequently withdrawn from the study on post-operative day 695.

[g] Patient 1030051 –A distal Type I endoleak was noted at the 2-year follow-up. The patient also had aneurysm growth (Table 6) and underwent a secondary intervention beyond 2 years (ancillary component placement 753 days post-procedure for the site-reported reasons of distal Type I endoleak and device migration). The patient was treated at the time of the index procedure with a single proximal component. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests a distal seal length < 20 mm as well as graft undersizing.

[h] Patient 1030100 – Per core laboratory evaluation, a Type II endoleak was identified at the 1-month and 6-month follow-ups. A distal Type I endoleak was identified at 2 years. The patient also had aneurysm growth (Table 6). A distal component was placed 984 days after the index procedure for the site-reported reason of distal Type I endoleak. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing. The patient was treated at the time of the index procedure with a single proximal component.

[i] Patient 1040044 –**Core laboratory evaluation identified a distal Type I endoleak at the 2-year follow-up visit**. The patient was treated at the time of the index procedure with a single proximal component. The patient also had aneurysm growth (Table 6) and CEC-confirmed migration (Table 8) and underwent a secondary intervention beyond 2 years (ancillary component placement 798 days post-procedure for the site-reported reasons of distal Type I endoleak and device migration). Review of core laboratory measurements at first follow-up (relative to the location of the actual graft placement) suggests graft undersizing.

[j] Patient 1030107 – A distal Type I endoleak was noted on the procedural angiogram, but was not seen on the 1-month, 6-month, 12-month, or 2-year follow-up CT. A distal Type I endoleak was noted on the 3-year CT, **and an unknown-type endoleak was noted on the 4-year CT**. This patient was treated at the time of the index procedure with a proximal and distal component. Review of core laboratory measurements of graft location at first follow-up (relative to the location of actual graft placement) suggests potential graft undersizing**.**

[k] Patient 1040036 – A Type IIA endoleak was noted at the 12-month, 2-year, and 3-year follow-ups. Lengthening of the distal aorta and an increase in aneurysm diameter from 59 mm at the 1-month follow-up visit to 63 mm at the 3-year follow-up visit was also noted, likely owing to the distal Type I endoleak (and aneurysm growth) subsequently noted at the 4-year and 5-year follow-up. This patient was treated at the time of the index procedure with a single proximal component. This patient also underwent pre-planned endovascular treatment of an AAA 46 days post-procedure.

[l] Patient 1030022 – A distal Type I endoleak was first noted by the core laboratory at the 5-year follow-up visit. This patient was treated at the time of the index procedure with a single proximal component. No secondary interventions were performed, the patient did not demonstrate an increase in aneurysm size, and the patient exited the study after the 5-year follow-up visit. Review of core laboratory measurements at first follow-up (relative to the location of the actual graft placement) suggests a distal seal length <20mm and potential graft undersizing.

[m] Patient 1030046 – A distal Type I endoleak was first noted by the core laboratory at the 5-year follow-up visit. This patient was treated at the time of the index procedure with a single proximal component. The patient had previously had a secondary intervention (ancillary component placement 594 days post-procedure to treat the site-reported progression of disease). Following this secondary intervention, at the 2-year timepoint the core laboratory noted that the distal seal zone remained tenuous. The patient had demonstrated an increase in aneurysm size (compared to baseline) from the 6-month through the 5-year follow-up visit (in the setting of graft undersizing and a proximal seal length < 20 mm). The patient exited study after completing follow-up at the 5-year visit.

[n] Patient 1030052 – A distal Type I endoleak was first noted by the core laboratory at the 5-year follow-up visit; the core lab reported diameter at the most distal aspect of the graft was notable for an approximately 20 mm increase from 1 month to 5 years. This patient was treated at the time of the index procedure with a proximal component, distal component, and distal extension. The patient did not demonstrate an increase in aneurysm size during the study per core laboratory review. The patient subsequently had a secondary intervention (ancillary component placement 1862 days post-procedure to treat the site-reported reason of aneurysm growth in the descending thoracic aorta distal to the originally treated segment). The patient died two days after the intervention of aneurysm rupture which was CEC-adjudicated as not-related to the device or procedure.

[o] Patient 1040062 – A type IIb endoleak was first noted by the core laboratory at the 1-month visit and at each subsequent follow-up visit until the 5-year, at which point the core laboratory also noted distal Type I endoleak. This patient was treated at the time of the index procedure with two proximal components. No secondary intervention has been performed to date. The patient had demonstrated an increase in aneurysm size (compared to baseline) from the 3-year through the 5-year follow-up visit. The patient exited the study after completing the 5-year follow-up visit. Review of core laboratory measurements of graft location at first follow-up (relative to the location of actual graft placement) suggests a distal seal length < 20 mm.

Continued Access

There have been six patients with core lab-reported endoleak in the continued access portion of the study, including four patients (1030124, 1030130, 1030136, and 1030144) with Type I endoleak (three proximal, one distal (1030136)). Of the three patients with proximal type I endoleak, two (1030124 and 1030130) also had Type III endoleak reported at one timepoint. Between July 28, 2016 and July 28, 2017, there were no new patients with Type I or III endoleaks, only new time points for some patients with previously reported endoleak, as follows: proximal Type I endoleak in 2, including 1(1030130) at 6 months in the setting of graft undersizing also with aneurysm growth without further intervention and subsequently died as noted in the TAA-related Mortality Section, and 1(1030124) at 3 years; Type III endoleak in 2, both nonjunctional (Type IIIb), including 1(1030124) at 30 days, and 1 (1030130) at 6 months; Type II in 2, including 1(1030149) with Type IIb at 30 days, and 1(1030141) with Type IIa at 30 days and Type IIb at 6 months; and unknown endoleak in 1(1030124) at 6 months and 12 months. Between July 29, 2017 and August 1, 2018, one patient (1030144) was newly-reported for a proximal Type I endoleak. Additionally, one patient (1030124) with previously reported proximal Type I endoleak persisted at the 4-year follow-up visit.

Change in Size

Pivotal

Table 6 reports the percentage of patients with an increase (> 5 mm), decrease (> 5 mm), or no change (≤ 5 mm) in aneurysm diameter (or ulcer depth) by core laboratory analysis at each follow-up time point subsequent to 1-month, which represents baseline. In total there were 20 patients that had aneurysm growth at one or more follow-up time points. The following is a count of patients as to when the first occurrence of growth was observed [6-months (n=3), 12 months (n=1), 2 years (n=7), 3 years (n=2), 4 years (n=4), 5 years (n=3)]. Additional details for these patients are provided in the footnotes under Table 6.

There have been two patients with aneurysm growth reported between July 28, 2016 and July 28, 2017, both were new and occurred in the setting of Type II endoleak (1040079, 0467042). There have been six patients with aneurysm growth reported between July 29, 2017 and August 1, 2018 , two of whom (1030102 and 1040046) are newly-reported and had no evidence of endoleak. Among the other four patients with growth reported between July 29, 2017 and August 1, 2018 (1030046, 1040045, 1040062, 1040079), two had distal Type I endoleak (1030046, 1040045), one had Type IIb endoleak (1040079), and one had both distal Type I and Type IIb endoleak (1040062). Reintervention for growth has thus far been reported by the site in nine patients (0460145, 1030017, 1030047, 1030051, 1030100, 1040024, 1040044, 1040045, 1040073) with core lab-reported aneurysm growth (one of which had continued aneurysm growth following reintervention without evidence of endoleak). The remaining eleven patients with growth and no reintervention for growth have exited the study.

All patients with growth at one or more follow-up time points (n=20) were treated for an aneurysm, often without use of a distal main body component (n=17). Additionally, while the percentage of aneurysm patients enrolled in this study (81.8%) was comparable to that from the previous study for the Zenith TX2 TAA Endovascular Graft (85.6%), a proximal and distal main body component pair was used in only 37.5% of the aneurysm patients in the present study compared to nearly 70% of the aneurysm patients in the previous study, which had 7.0% of patients with aneurysm growth at 5 years. Therefore, the labeling for the Zenith Alpha Thoracic Endovascular Graft was specifically updated subsequent to completion of enrollment in the present study in order to emphasize the use of a proximal main body component and distal main body component together when treating an aneurysm in order to best ensure adequate fixation and seal proximal and distal to the aneurysm (as also described in the Device Selection portion of Section V of this Clinical Update).

Table 6. Change in aneurysm diameter/ulcer depth based on results from core laboratory analysis – Pivotal

Item	Percent Patients (number/total number)					
	Aneurysm					
	6-month	12-month	2-year	3-year	4-year	5-year
Increase (> 5 mm)	4.2% (3/72) [a,b,c]	4.2% (3/71) [a,c,d]	14.3% (9/63)[a,d,e-k]	11.5% (6/52)[a,d,h,k-m]	**23.4**% (11/**47**)[a,d,e,**h**,l-q]	**34.2**% (**13**/**38**)[**a**,d,e,**k-t**]
Decrease (> 5 mm)	19.4% (14/72)	31.0% (22/71)	27.0% (17/63)	26.9% (14/52)	**25.5**% (12/**47**)	**18.4**% (**7**/**38**)
No change (≤ 5 mm)	76.4% (55/72)	64.8% (46/71)	58.7% (37/63)	61.5% (**32**/52)	**51.1%** (**24**/**47**)	**47.4**% (**18**/**38**)
Item	**Percent Patients (number/total number)**					
	Ulcer					
	6-month	**12-month**	**2-year**	**3-year**	**4-year**	**5-year**
Increase (> 5 mm)	0	0	0	0	0	0
Decrease (> 5 mm)	33.3% (6/18)	52.9% (9/17)	66.7% (10/15)	46.2% (6/13)	**53.8% (7/13)**	**45.5**% (**5**/**11**)
No change (≤ 5 mm)	66.7% (12/18)	47.1% (8/17)	33.3% (5/15)	53.8% (7/13)	**46.2% (6/13)**	**54.5**% (**6**/**11**)
Item	**Percent Patients (number/total number)**					
	All					
	6-month	**12-month**	**2-year**	**3-year**	**4-year**	**5-year**
Increase (> 5 mm)	3.3% (3/90)	3.4% (3/88)	11.5% (9/78)	9.2% (6/65)	**18.3**% (11/**60**)	**26.5**% (**13**/**49**)
Decrease (> 5 mm)	22.2% (20/90)	35.2% (31/88)	34.6% (27/78)	30.8% (20/65)	**31.7**% (19/**60**)	**24.5**% (**12**/**49**)
No change (≤ 5 mm)	74.4% (67/90)	61.4% (54/88)	53.8% (42/78)	**60.0**% (**39**/65)	**50.0**% (**30**/**60**)	**49.0**% (**24**/**49**)

Note: New information since the last reporting period is bolded.

Note: the number of patients with adequate imaging to assess for size increase reflects the number of exams in which aneurysm diameter/ulcer depth was able to be assessed at each specified time point, whereas the denominators in this table also take into account the availability of a baseline exam to which to compare.

[a] Patient 1030046 – The patient was treated at the time of the index procedure with a single proximal component. The patient underwent a secondary intervention prior to the 2-year follow-up (Table 9) to treat the unexplained aneurysm growth (i.e., no detectable endoleaks). **Aneurysm growth was noted by core laboratory evaluation at the 6-month follow-up visit and at each subsequent follow-up visit up to 5 years.** Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing and a proximal seal length < 20 mm. **The patient has since exited the study.**

[b] Patient 1040060 – The patient did not require a secondary intervention. Per core laboratory evaluation, no endoleaks have been identified in this patient. Aneurysm size was stable at 12 months (< 5 mm increase). **The patient has since exited the study.**

[c] Patient 1040073 – The patient was treated at the time of the index procedure with a single proximal component. The patient had a Type IIb endoleak, which was treated prior to the 12-month follow-up (Table 9). **The patient was converted to an open repair (Table 10) and exited the study.**

[d] Patient 1030017 – The patient was treated at the time of the index procedure with a single proximal component. The patient had no evidence of detectable endoleak. The patient underwent a secondary intervention beyond 2 years (placement of a distal component 922 days post-procedure for aneurysm growth). Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing and a distal seal length < 20 mm. **The patient has since exited the study.**

[e] Patient 1040034 – The patient did not have a secondary intervention and core laboratory results indicate no growth at 3 years. **The patient has since exited the study.**

[f] Patient 1030047 – The patient was treated at the time of the index procedure with a single proximal component. The patient also had distal Type I endoleak (Table 5) and CEC-confirmed migration (Table 8). A secondary intervention was performed (ancillary component placement) on post-operative day 727 (Table 9) and no growth was noted at 3 years.

Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing as well as a distal seal length < 20 mm. **The patient has since exited the study due to death.**

[g] Patient 1030051 – The patient was treated at the time of the index procedure with a single proximal component. A distal Type I endoleak was also noted at the 2-year follow-up (Table 5). The patient underwent a secondary intervention beyond 2 years (ancillary component placement 753 days post-procedure for the site-reported reasons of distal Type I endoleak and device migration. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests a distal seal length < 20 mm as well as graft undersizing. **The patient has since exited the study.**

[h] Patient 1030100 – The patient was treated at the time of the index procedure with a single proximal component. Per core laboratory evaluation, a Type II endoleak was identified at the 1-month and 6-month follow-up visits. A distal Type I endoleak (Table 5) was identified in the patient at 2 years (previous endoleaks identified were Type II). A distal component was placed 984 days after the index procedure for the site-reported reason of distal Type I endoleak. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing. The patient has since exited the study.

[i] Patient 1040041 – The patient was treated at the time of the index procedure with a single proximal component. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing as well as a distal seal length < 20 mm. The patient withdrew from the study 906 days post-procedure.

[j] Patient 1040044 – The patient was treated at the time of the index procedure with a single proximal component. The patient also had a distal Type I endoleak (Table 5) and CEC-confirmed migration (Table 8). The patient underwent a secondary intervention beyond 2 years (ancillary component placement 798 days post-procedure for the site-reported reasons of distal Type I endoleak and device migration). Review of core laboratory measurements at first follow-up (relative to the location of the actual graft placement) suggests graft undersizing. **The patient has since exited the study.**

[k] Patient 1040045 – The patient was treated at the time of the index procedure with a single proximal component. A distal Type I endoleak was noted at the 1-month, 6-month, 12-month, 2-year**, 4-year, and 5-year** follow-up visits (Table 5). A Type IIb endoleak was also identified at the 6-month and 12-month follow-ups. **A secondary intervention (distal extension placement) for distal type I endoleak was performed 1827 days post-procedure.** Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests a distal seal length < 20 mm. **The patient has since exited the study.**

[l] Patient 1040024 – This patient was treated at the time of the index procedure with a single proximal component. No endoleaks or migration were noted at any follow-up point. At the 6-month follow-up, the core laboratory noted that the distal seal zone was extremely short and the patient was at risk for loss of distal seal. At the 3-year follow-up, the core laboratory noted that the device was in jeopardy of losing the distal seal completely. A secondary intervention was completed 1212 days post-procedure with the placement of both a proximal and a distal extension (Gore TAG devices). Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests a distal seal length < 20 mm. The patient has since exited the study.

[m] Patient 1040062 – This patient was treated at the time of the index procedure with two proximal components. A Type IIb endoleak was noted at all follow-up visits from 1-month through **5-year**, **with a distal type I endoleak also noted at the 5-year timepoint** (Table 5). At the 3-year follow-up, growth of > 5 mm was noted (maximum aneurysm diameter increased by 7 mm from 68 mm at 1 month to 75 mm at 3 years). **Aneurysm growth continued to be noted by core laboratory at the 4-year and 5-year follow-up visits.** No secondary interventions were performed.

[n] Patient 0460145 – This patient was treated at the time of the index procedure with a single proximal component. No endoleaks or migration were noted at any follow-up point by core laboratory. **Patient had aneurysm growth at 4 years (8 mm by site, 9 mm by core laboratory) which the site attributed to persistent Type IV endoleak (first noted by site at 4 years). The patient was treated with placement of an additional stent-graft at 1719 days after the index procedure. The core laboratory did not identify any endoleaks and could not identify a cause for aneurysm growth.** Review of core laboratory measurements at first follow-up (relative to the location of the actual graft placement) suggests graft undersizing. **The patient has since exited the study.**

[o] Patient 1040017 – This patient was treated at the time of the index procedure with one proximal component and two distal extensions. Growth was noted at the 4-year follow-up although no endoleaks or migration have been noted. Review of core laboratory measurements at first follow-up (relative to the location of the actual graft placement) suggests graft undersizing. **The patient has since exited the study.**

[p] Patient 1040036 – This patient was treated at the time of the index procedure with a single proximal component. A Type IIa endoleak was noted at the 12-month, 2-year, and 3-year follow-ups. Lengthening of the distal aorta and an increase in aneurysm diameter from 59 mm at 1-m to 63 mm at 3 years also noted, likely owing to the aneurysm growth

(and distal Type I endoleak) subsequently noted at the 4-year follow-up. This patient also underwent pre-planned endovascular treatment of an AAA 46 days post-procedure. **The patient has since exited the study.**

[q] **Patient 1040079- This patient was treated at the time of the index procedure with two proximal components. An unknown Type II endoleak was observed at 6 and 12-months, a type IIb endoleak was observed at 2 and 4-years and a type IIa endoleak was observed at 3-years. Aneurysm growth was noted by core laboratory at the 4-year and 5-year follow-up visits. No secondary interventions were performed.**

[r] **Patient 0467042- This patient was treated at the time of the index procedure with proximal, distal, and distal extension components. At 433 days post procedure the patient underwent a secondary intervention for a distal dissection and an additional distal extension was placed. A Type IIb endoleak was noted at the 4-year follow-up visit and type IIA endoleak was observed at the 5-year follow-up visit. Aneurysm growth was noted by the core laboratory at the 5-year visit. No secondary intervention for growth was reported and the patient exited the study after their 5-year follow-up visit.**

[s] **Patient 1030102 – This patient was treated at the time of the index procedure with a single proximal component and distal extension. Aneurysm growth was first noted by the core laboratory at the 5-year follow-up visit. No endoleak was noted, and the patient did not have a secondary intervention. The patient exited the study after completing follow-up at the 5-year follow-up visit. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests a distal seal length < 20 mm and potential undersizing. Additionally, there was less than the minimum recommended amount of overlap between components initially.**

[t] **Patient 1040046 – This patient was treated at the time of the index procedure with two proximal components. Aneurysm growth was first noted by core laboratory at the 5-year follow-up visit. No secondary intervention was performed, and the patient exited the study after completing follow-up at the 5-year follow-up visit. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests proximal and distal graft undersizing.**

Continued Access

Core laboratory-reported increases in aneurysm size (> 5 mm) have thus far occurred in five patients. Three of the patients with growth (2 of which were newly reported between July 28, 2016 and July 28, 2017) were aneurysm patients treated initially with only a single proximal component.. There were no reported increases in aneurysm size occurring between July 29, 2017 and August 1, 2018. The breakdown of when each of these five patients experienced aneurysm growth is as follows: one at 6 months (patient also had core laboratory-reported proximal Type I and Type III endoleaks at the same time point, which was subsequent to earlier reintervention involving distal extension placement for the site-reported reason of new ulcer, and the patient has since died); one at 12 months (patient also had Type IIa and Type IIb endoleaks based on core laboratory analysis, no reintervention, and has since died); one at 2 years, 3 years, and 4 years (patient also had core laboratory-reported distal Type I endoleak on subsequent unscheduled follow-up imaging and underwent reintervention involving additional main body component placement for the site-reported reasons of migration and distal Type I endoleak); and two at 36 months (one patient with no endoleak reported and one patient who also experienced aneurysm growth at 4 years, who had core laboratory-reported Type III endoleak at 1 month, unknown endoleak at 6 and 12 months, and proximal type I endoleak at 3 and 4 years,). Three of the patients with growth were aneurysm patients treated initially with only a single proximal component.

Rupture

Pivotal

No ruptures have been reported to date in the pivotal cohort within 5 years (1825 days). Between July 28, 2016 and July 28, 2017 two ruptures were reported after 5 years (1030050, 1030052). No additional ruptures have been reported between July 29, 2017 and August 1, 2018.

Continued Access

No ruptures have been reported to date in continued access.

Graft Patency

Pivotal

No occlusions and three patients with confirmed presence of thrombus in the graft (each in the setting of excessive graft oversizing) have been reported to date in the pivotal cohort.

Continued Access

No occlusions and one patient with confirmed presence of thrombus in the graft (in the setting of pre-existing aortic neck thrombus) have been reported to date in continued access.

Device Integrity

Pivotal

The percentage of patients with CEC-confirmed device integrity findings at each follow-up time point based on the results from core laboratory analysis are presented in Table 7. There have been no new device integrity findings since the original PMA.

Table 7. CEC-confirmed loss of device integrity – Pivotal

Finding	Percent Patients (number/total number)																				
	30-day			6-month			12-month			2-year			3-year			4-year			5-year		
	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All
Barb separation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stent fracture	1.2% (1/85)[a]	0	1.0% (1/105)	1.3% (1/80)[a]	0	1.0% (1/98)	1.3% (1/75)[a]	0	1.1% (1/92)	1.5% (1/65)[a]	0	1.3% (1/80)	1.8% (1/57)[b]	0	1.4% (1/72)	2.0% (1/**52**)[b]	0	1.5% (1/**68**)	0	0	0
Component separation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

[a] Patient 1030069 – Per core laboratory, a single stent fracture (of the second covered stent in the proximal device) was noted on the 1-month, 6-month, 12-month, and 2-year x-rays. Nothing uncharacteristic regarding the anatomy or deployment of the graft was observed. This patient has had no clinical sequelae from the stent fracture. No secondary interventions were performed. **The patient withdrew from the study 1153 days post-procedure.**

[b] Patient 1030028 – Per core laboratory, a single fracture of the proximal bare stent of the device was noted on the 3-year and 4-year x-rays. Nothing uncharacteristic regarding the anatomy or deployment of the graft was observed. This patient has had no clinical sequelae from the stent fracture**. No secondary interventions were performed, and the patient exited the study after completing follow-up at the 5-year follow-up visit.**

Continued Access

No CEC-confirmed device integrity observations have been identified on the exams analyzed to date.

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; clinically significant migration was defined as migration resulting in the need for secondary intervention.

Pivotal

Table 8 reports the percentage of patients with migration (clinically significant and radiographic) based on date of first occurrence. There have been three reports of CEC-confirmed migration to date (no new reports since the original PMA), all of which appeared to have occurred in patients with graft undersizing.

Table 8. Percent of patients (aneurysm and ulcer) with CEC-confirmed migration (date of first occurrence) – Pivotal

Item	Percent Patients (number/total number)					
	6-month	12-month	2-year	3-year	4-year	5-year
Migration (> 10 mm)	0% (0/98)	0% (0/92)	3.8% (3/80)[a,b,c]	0% (0/72)	0% (0/68)	0% (0/56)

[a] Patient 1030012 – The patient was treated at the time of the index procedure with a single proximal component. The patient had cranial migration of the distal end of the proximal component first confirmed by the CEC at 2 years. There was no evidence of endoleak, and the aneurysm size has continuously decreased from 61 mm at 1 month to 40 mm at 2 years and 38 mm at 3 years. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing.

[b] Patient 1030047 – The patient was treated at the time of the index procedure with a single proximal component. The patient had cranial migration of the distal end of the proximal component first confirmed by the CEC at 2 years. The patient also had aneurysm growth (Table 6), distal Type I endoleak (Table 5), and underwent a secondary intervention (Table 9). Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing and a distal seal length < 20 mm.

[c] Patient 1040044 – The patient was treated at the time of the index procedure with a single proximal component. The patient had cranial migration of the distal end of the proximal component first confirmed by the CEC at 2 years. The patient also had aneurysm growth (Table 6), a distal Type I endoleak (Table 5), and underwent a secondary intervention beyond 2 years (ancillary component placement 798 days post-procedure for the site-reported reasons of distal Type I endoleak and device migration). Review of core laboratory measurements at first follow-up (relative to the location of the actual graft placement) suggests graft undersizing.

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There have been no reports of CEC-confirmed migration to date.

Secondary Interventions

Pivotal

The site-reported reasons for reintervention are provided in Table 9. Nineteen patients in total have undergone a secondary intervention, nine of which occurred in patients with either core lab observed or the site-reported reason of growth of the treated aneurysm. There was one new patient with reintervention reported between July 28, 2016 and July 28, 2017 (0460145, for Type IV endoleak). There were two new patients with reintervention reported between July 29, 2017 and August 1, 2018 (1040045 for distal type I endoleak, and 1030052 for aneurysm growth in the descending thoracic aorta distal to the originally treated segment).

Table 9. Site-reported reasons for secondary intervention – Pivotal

Reason	0-30 Days	31-365 Days	366-730 Days	731-1095 Days	1096-1460 Days	1461-1825 Days	>1825 Days
Device migration	0	0	1[g]	2[k,l]	0	0	0
Endoleak							
Type I proximal	0	0	0	0	0	1[p]	0
Type I distal	0	0	3[d,g,h]	4[k-n]	1[o]	0	**1[r]**
Type II	0	1[b]	0	0	0	0	0
Type IV (through graft body)	0	0	1[j]	0	0	**1[q]**	0
Other	1[a]	1[c]	2[e,f]	1[i]	0	0	**1[s]**

Note: New information since the last reporting period is bolded.

[a] Patient 1040058 (ulcer) – Patient had pre-planned left subclavian artery embolization and right-to-left subclavian artery bypass 7 days after the index procedure.

[b] Patient 1040073 (aneurysm) – Patient had two separate secondary interventions for Type II endoleak: unsuccessful attempt at placing embolization coils in the intercostal artery, followed by successful direct puncture of the aneurysm with delivery of N-butyl cyanoacrylate.

[c] Patient 1040037 (aneurysm) – Patient had additional component placed for aortic dissection proximal to the study device 324 days after the index procedure.

[d] Patient 1030072 (aneurysm) – Patient had a persistent Type I distal endoleak treated with additional distal components and balloon angioplasty 420 days after the index procedure.

[e] Patient 0467042 (aneurysm) – Patient had a dissection distal to the most distal stent. Ancillary components were placed 433 days after the index procedure.

[f] Patient 1030046 (aneurysm) – Patient had observed progression of disease treated with additional proximal and distal components 594 days after the index procedure.

[g] Patient 1030047 (aneurysm) – Patient had observed device migration and Type I distal endoleak treated with ancillary components 727 days after the index procedure.

[h] Patient 1030095 (aneurysm) – Patient had a persistent Type I distal endoleak treated with additional distal components 534 days after the index procedure.

[i] Patient 1030017 – Patient had observed aneurysm growth without evidence of endoleak treated with ancillary components 922 days after the index procedure.

[j] Patient 1040054 – (aneurysm) Patient had persistent Type IV endoleak per site analysis (unknown type endoleak per core laboratory analysis) treated with ancillary components 599 days after the index procedure.
[k] Patient1030051 – (aneurysm) Patient had a persistent distal Type I endoleak and device migration treated with ancillary components 753 days after the index procedure.
[l] Patient1040044 – (aneurysm) Patient had a persistent distal Type I endoleak and device migration (confirmed by CEC) treated with ancillary components 798 days after the index procedure.
[m] Patient1030100 – (aneurysm) Patient had a persistent distal Type I endoleak treated with additional distal component 984 days after the index procedure.
[n] Patient1030089 – (aneurysm) Patient had a persistent distal Type I endoleak (core laboratory confirmed endoleak on an unscheduled visit after the 2-year visit; core laboratory was unable to confirm endoleak on 2-year visit due to non-contrast CT being performed; however, due to enlarging TAA and lack of distal seal the core laboratory suggested that a distal Type I was inferred at the 2-year visit). The patient was treated with an additional distal component 990 days after the index procedure.
[o] Patient 1040024 – (aneurysm) Patient had a persistent distal Type I endoleak (identified by site during secondary intervention, core laboratory was unable to determine presence or absence of Type I endoleak due to incomplete imaging angiogram) treated with additional distal component 1212 days after the index procedure.
[p] Patient 0467909 – (aneurysm) Patient had a proximal Type I endoleak (identified by the site; core laboratory identified a Type IIA endoleak) treated with proximal and distal extensions at 1576 days after the index procedure.
[q] Patient 0460145 – (aneurysm) Patient had aneurysm growth at 4 years (8 mm by site, 9 mm by core laboratory) which the site attributed to persistent Type IV endoleak (first noted by site at 4 years). The patient was treated with placement of an additional stent-graft at 1719 days after the index procedure. The core laboratory did not identify any endoleaks and could not identify a cause for aneurysm growth.
[r] Patient 1040045 – (aneurysm) Patient had a persistent distal Type I endoleak identified by core laboratory at the 1-month, 6-month, 1-year, 2-year, 4-year, and 5-year follow-up visits, and had aneurysm growth compared to baseline at the 2-year through 5-year follow-up visits. The patient was treated by placement of a distal extension 1827 days after the index procedure.
[s] Patient 1030052 – (aneurysm) This patient had distal Type I endoleak first identified by core laboratory at the 5-year follow-up visit. This patient did not experience aneurysm growth > 5 mm from baseline. The patient was treated for site-reported aneurysm growth in the descending thoracic aorta distal to the originally treated segment. Two additional components were placed 1862 days after the index procedure.

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In total, two patients (1030130, 1030136) have required a secondary intervention (no new patients have required a secondary intervention since the 2016 Annual Clinical Update). Reintervention in patient 1030130 occurred 108 days after the index procedure to treat a new site-reported ulcer at the distal end of the proximal component. The patient was treated with ancillary components and was subsequently noted to have aneurysm growth as well as Type I and Type III endoleaks based on core laboratory analysis of the 6-month follow-up exam without further intervention. The patient presented to the emergency department 350 days post-procedure with hemoptysis and hematemesis and died 351 days post-procedure due to hemorrhagic shock. Reintervention in patient 1030136 occurred at 959 days after the index procedure for the site-reported reasons of migration and distal Type I endoleak. The patient was treated with an additional proximal component and distal extension.

Conversion

Pivotal

As shown in Table 10, there has been one conversion to open surgical repair in the pivotal aneurysm/ulcer group (no new reports since the original PMA).

Table 10. Kaplan-Meier estimates for freedom from conversion – Pivotal

Event	Parameter	30 Days			180 Days			365 Days			730 Days			1095 Days			1460 Days			1825 Days		
		Aneur	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**	**Aneur**	**Ulcer**	**All**
Conversion	Number at risk[a]	89	20	109	86	19	105	80	18	98	69	18	87	60	17	77	**52**	**16**	**68**	**46**	**16**	**62**
	Cumulative events[b]	0	0	0	0	0	0	1[e]	0	1	1	0	1	1	0	1	1	0	1	**1**	0	1
	Cumulative censored[c]	1	0	1	4	1	5	9	2	11	20	2	22	29	3	32	**37**	**4**	**41**	**43**	**4**	**47**
	KM estimate[d]	1.000	1.000	1.000	1.000	1.000	1.000	0.988	1.000	0.990	0.988	1.000	0.990	0.988	1.000	0.990	0.988	1.000	0.990	0.988	1.000	0.990
	Standard error	0.000	0.000	0.000	0.000	0.000	0.000	0.012	0.000	0.010	0.012	0.000	0.010	0.012	0.000	0.010	0.012	0.000	0.010	0.012	0.000	0.010

Note: New information since the last reporting period is bolded.
[a]Number of patients at risk at the beginning of the interval.
[b]Total events up to and including the specific interval represents all patients who have had the event. Note, only the first event is represented in the Kaplan-Meier estimate. A patient may have multiple events in each category.
[c]Total censored patients up to and including the specific interval represents all patients who have met a study exit criteria or for whom data are not available at the specific interval.
[d]At end of interval.
[e]Patient 1040073 (aneurysm) conversion due to aortoesophageal fistula, adjudicated by the CEC as TAA-related.

Continued Access

There have been no conversions to open repair reported in continued access.

Major Adverse Events

Pivotal

Table 11 shows the Kaplan–Meier estimates for freedom from major adverse events (MAE), which were defined as follows: all-cause death; Q-wave myocardial infarction; cardiac event involving arrest, resuscitation, or balloon pump; ventilation > 72 hours or reintubation; pulmonary event requiring tracheostomy or chest tube; renal failure requiring permanent dialysis, hemofiltration, or kidney transplant in a patient with a normal pre-procedure serum creatinine level; bowel resection; stroke; paralysis; amputation involving more than the toes; aneurysm or vessel leak requiring reoperation; deep vein thrombosis requiring surgical or lytic therapy; pulmonary embolism involving hemodynamic instability or surgery; coagulopathy requiring surgery; or wound complication requiring return to the operating room. There were 8 newly reported patients with MAE (within 1825 days) between July 28, 2016 and July 28, 2017. There was one newly-reported patient with MAE within 1825 days between July 29, 2017 and August 1, 2018 (1030107 – Death).

Table 11. Kaplan-Meier estimates for major adverse events – Pivotal

Event	Parameter	30 Days			180 Days			365 Days			730 Days			1095 Days			1460 Days			1825 Days		
		Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All
MAE	Number at risk[a]	85	20	105	81	19	100	74	18	92	60	18	78	49	16	65	**43**	**15**	**58**	**20**	**9**	**29**
	Cumulative events[b]	4	0	4	7	1	8	12	1	13	24	1	25	31	2	33	**35**	2	**37**	**43**	**3**	**46**
	Cumulative censored[c]	1	0	1	2	0	2	4	1	5	6	1	7	10	2	12	**12**	**3**	**15**	**27**	**8**	**35**
	KM estimate[d]	0.956	1.000	0.964	0.922	0.950	0.927	0.864	0.950	0.879	0.722	0.950	0.763	0.634	0.894	0.681	**0.581**	0.894	**0.638**	**0.470**	**0.835**	**0.537**
	Standard error	0.022	0.000	0.018	0.029	0.049	0.025	0.037	0.049	0.032	0.049	0.049	0.042	0.054	0.073	0.047	**0.057**	0.073	**0.050**	**0.058**	**0.091**	**0.052**

Note: New information since the last reporting period is bolded.

[a]Number of patients at risk at the beginning of the interval.

[b]Total events up to and including the specific interval represents all patients who have had the event. Note, only the first event is represented in the Kaplan-Meier estimate. A patient may have multiple events in each category.

[c]Total censored patients up to and including the specific interval represents all patients who have met a study exit criteria or for whom data are not available at the specific interval.

[d]At end of interval.

Continued Access

There have thus far been 8 patients in continued access with MAE (1 new patient occurring between July 28, 2016 and July 28, 2017; 1 new patient occurring between July 29, 2017 and August 1, 2018). The reported MAEs in continued access are as follows: wound complication requiring return to operating room (n=1), death (n=3), stroke (n=1), re-intubation (n=1), and aneurysm or vessel leak requiring re-operation (n=2).

Summary

Longer-term follow-up of patients enrolled in the aneurysm/ulcer study is ongoing with 5-year and 3-year follow-up nearly complete now for the pivotal and continued access cohorts, respectively. Since approval of the original PMA, there have been no new TAA-related deaths within 5 years of the index procedure, conversions, reports of CEC-confirmed migration, loss in either patency or device integrity, or Type III endoleaks for either cohort.

Between July 28, 2016 and July 28, 2017 there has been 1 newly reported patient with Type I or III endoleak (1 pivotal with distal Type I). Additionally, there have been 2 new reports of rupture (both occurring in the pivotal study after 5 years), 4 new reports of aneurysm growth (2 pivotal, 2 continued access), 3 of which were associated with endoleak. Reintervention has thus far been reported in 8 patients with aneurysm growth (1 of which had continued aneurysm growth following reintervention without evidence of endoleak, whom is now exited the study).

Between July 29, 2017 and August 1, 2018 there have been four newly-reported patients with Type I endoleak (three pivotal with distal Type I and one continued access with proximal Type I), no new reports of rupture, six new reports of aneurysm growth (all pivotal), four of which appeared to be associated with endoleak. Reintervention to treat aneurysm growth > 5 mm from baseline has thus far been reported in nine patients (one of which had continued aneurysm growth following reintervention without evidence of endoleak and has now exited the study). In total, there have been nineteen secondary interventions in the pivotal study (two new within this time period) and two in the continued access study (no new reports within this time period).

BLUNT THORACIC AORTIC INJURY (BTAI) STUDY

The BTAI indication has been removed from the indications for use for this device as approved on July 28, 2017 (see the Patency section and Section IV below). The following information is included in this Clinical Update to Physicians to aid in the management of patients who have already been treated with this device for BTAI.

Description of Study

The Zenith Alpha™ Thoracic Endovascular Graft clinical study is a prospective, nonrandomized, noncomparative, single-arm, multicenter study that was conducted to evaluate the safety and effectiveness of the Zenith Alpha™ Thoracic Endovascular Graft for the treatment of patients with BTAI. Enrollment in the clinical trial began on January 23, 2013 and was completed May 7, 2014. Seventeen (17) US institutions enrolled a total of 50 patients.

Patient Availability for Follow-up

Patient availability for follow-up in the BTAI study as of August 1, 2018 is summarized in Table 12.

Table 12. Follow-up availability

Follow-up Visit	Patients Eligible for Follow-up	Percent of Data Available[a]			Adequate Imaging to Assess the Parameter[b]			Events Occurring Before Next Interval			
		Clinical	CT[c]	Patients with Follow-up Pending	Endoleak	Migration	Aortic Injury Healing	Death	Conversion to Open Repair	Lost to Follow-up/ Withdrawal	Not Due for Next Visit
Operative	50	50/50 (100%)	NA	0	NA	NA	NA	0[d]	0	0	0
30-day	50[d]	47/50 (94.0%)	43/50 (86.0%)	0	42/50 (84.0%)	10/50 (20.0%)	42/50 (84.0%)	5[d]	0	5	0
6-month	40	33/40 (82.5%)	34/40 (85.0%)	0	34/40 (85.0%)	33/40 (82.5%)	34/40 (85.0%)	0	1	1	0
12-month	38	30/38 (78.9%)	32/38 (84.2%)	0	32/38 (84.2%)	27/38 (71.1%)	32/38 (84.2%)	0	0	6	0
2-year	32	28/32 (87.5%)	29/32 (90.6%)	0	29/32 (90.6%)	28/32 (87.5%)	29/32 (90.6%)	1	0	3	0
3-year	28	25/28 (89.3%)	24/28 (85.7%)	1	23/28 (82.1%)	24/28 (85.7%)	24/28 (85.7%)	0	0	1	1
4-year	26	22/26 (84.6%)	20/26 (76.9%)	0	19/26 (73.1%)	20/26 (76.9%)	20/26 (76.9%)	0	0	3	17
5-year	6	6/6 (100.0%)	4/6 (66.7%)	0	2/6 (33.3%)	2/6 (33.3%)	2/6 (33.3%)	N/A	N/A	N/A	N/A

NA – Not assessed.
[a]Site-submitted data.
[b]Based on core laboratory analysis – Does not include imaging exams received by the core laboratory for analysis, but that have not yet been analyzed.
[c]Includes non-contrast CT, MRI, or TEE imaging, which are allowed per the protocol when a patient is unable to undergo contrast-enhanced CT scan.
[d]Patient 1200054 – The patient underwent 30-day follow-up (CT scan and clinical exam) 22 days post-procedure before exiting the study due to death 24 days post-procedure.

Aortic Injury-related Mortality

Aortic injury-related mortality was defined as any death determined by the independent clinical events committee (CEC) to be causally related to the initial implant procedure, secondary intervention, or rupture of the transected aorta.

As presented in Table 13, there has been 1 aortic injury-related death reported to date (no new reports since the original PMA), corresponding to 97.6% freedom from aortic injury-related mortality thus far.

Table 13. Kaplan-Meier aortic injury-related mortality survival estimates

Event	Parameter	30 Days	180 Days	365 Days	730 Days	1095 Days	1460 Days	1825 Days
Aortic Injury-Related Mortality	Number at risk[a]	48	40	36	32	**28**	**12**	**4**
	Cumulative events[b]	0	1[e]	1	1	1	1	**1**
	Cumulative censored[c]	2	9	13	17	**21**	**37**	**45**
	KM estimate[d]	1.000	0.976	0.976	0.976	0.976	0.976	**0.976**
	Standard error	0.000	0.024	0.024	0.024	0.024	0.024	**0.024**

Note: New information since the last reporting period is bolded.
[a]Number of patients at risk at the beginning of the interval.
[b]Total events up to and including the specific interval represents all patients who have had the event.
[c]Total censored patients up to and including the specific interval represents all patients who have met a study exit criteria or for whom data are not available at the specific interval.
[d]At end of interval.
[e]Death due to exsanguination as a result of aortoesophageal fistula (1200024).

All-cause Mortality

As presented in Table 14, there have been six deaths (1 new report between July 28, 2016 and July 28, 2017; no new reports between July 29, 2017 and August 1, 2018), corresponding to 86.3% freedom from all-cause mortality thus far.

Table 14. Kaplan-Meier all-cause mortality survival estimates

Event	Parameter	30 Days	180 Days	365 Days	730 Days	1095 Days	1460 Days	1825 Days
All-Cause Mortality	Number at risk[a]	48	40	36	32	**28**	**12**	**4**
	Cumulative events[b]	1	5	5	5	6	**6**	**6**
	Cumulative censored[c]	1	5	9	13	**16**	**32**	**40**
	KM estimate[d]	0.980	0.893	0.893	0.893	**0.863**	**0.863**	**0.863**
	Standard error	0.020	0.046	0.046	0.046	**0.059**	**0.059**	**0.059**

Note: New information since the last reporting period is bolded.
[a]Number of patients at risk at the beginning of the interval.
[b]Total events up to and including the specific interval represents all patients who have had the event.
[c]Total censored patients up to and including the specific interval represents all patients who have met a study exit criteria or for whom data are not available at the specific interval.
[d]At end of interval.

Endoleak

Table 15 summarizes the endoleak results based on core laboratory analysis. All three patients with endoleak first had reported endoleak at the 1-month visit, one of whom (1200033) was identified to have endoleak at subsequent time points. There have been no new reports of endoleak since the original PMA.

Table 15. Endoleak based on results from core laboratory analysis

Type	Time point						
	30-day	6-month	12-month	2-year	3-year	4-year	5-year
Any (new only)	7.1% (3/42)	0	0	0	0	0	0
Any (new and persistent)	7.1% (3/42)	2.9% (1/34)	0	0	0	0	0
Multiple	0	0	0	0	0	0	0
Proximal Type I	0	0	0	0	0	0	0
Distal Type I	0	0	0	0	0	0	0
Type IIa	0	0	0	0	0	0	0
Type IIb	2.4% (1/42)[a]	0	0	0	0	0	0
Type III	0	0	0	0	0	0	0
Type IV	0	0	0	0	0	0	0
Unknown	4.8% (2/42)[b,c]	2.9% (1/34)[c]	0	0	0	0	0

Note: Type IIa = flow from subclavian, celiac, and/or anomalous vertebral arteries; Type IIb = flow from bronchial and/or intercostal arteries.
[a] Patient 1200061 – Site did not report an endoleak on the 30-day CT scan. Patient was LTF 59 days after the index procedure.
[b] Patient 1200035 – Site reported a Type IIA endoleak. To date, no treatment has been reported. No endoleaks were noted for this patient between the 1-month CT and 4-year CT.
[c] Patient 1200033 – Site reported the identification and attempted treatment of a proximal Type I endoleak (Table 17) as well as the patient's later conversion to open repair (Table 18).

Rupture

No ruptures have been reported to date in the BTAI study.

Graft Patency

To date, no loss of patency was observed in the BTAI study, as assessed by the core laboratory. Additionally, there remains one patient with device compression based on core laboratory analysis (refer also to Table 16), which was associated with placement of two proximal components at the time of the initial implant procedure, resulting in compression due to the second component having been placed through a suture loop on the first component; this patient underwent a secondary intervention for compression (angioplasty, as noted in Table 17) in the absence of clinical symptoms

In addition to the patient above with device compression, incidental findings of thrombus within the graft have been noted in 13 other patients (no new reports since the 2016 Annual Clinical Update). Each patient was originally treated with a single proximal component, one of which has subsequently undergone a secondary intervention (placement of an additional stent-graft for coverage and stability of thrombus in the absence of distal embolization or adverse problems, as noted in Table 17). Overall, these observations included reports of thrombus formation in grafts that were notable for the following based on independent radiology review separate from the core laboratory:

- one constriction/compression leading to a secondary intervention (angioplasty, as noted in Table 17) in the absence of clinical symptoms;
- six longitudinal bunching/redundancies of fabric, with one leading to a secondary intervention (placement of additional stent-graft, as noted in Table 17) in the absence of clinical symptoms;
- two changes in anatomy/graft position;
- three differential diameters between treated aorta and distal aorta; and
- two only reporting progressive thrombus formation.

There tended to be smaller graft diameters and greater distal oversizing on average in the patients with thrombus compared to the patients without thrombus. A radius of curvature less than the recommended 20 mm minimum was also observed in nearly half the patients with thrombus. Additionally, while approximately 50% of patients in the study had an aorta that was at least 10% smaller at the distal seal site when compared to the proximal seal/fixation site, only 20% of patients were treated with a tapered component.

The observations of thrombus from the clinical trial in combination with reports of thrombus from commercial use (Section II) resulted in Cook removing the indication for BTAI in June 2017, as further described in Section IV.

Device Integrity

Table 16 summarizes the device integrity results based on core laboratory analysis. There have been no new device integrity findings since the original PMA.

Table 16. Device integrity based on results from core laboratory analysis

Finding	Percent Patients (number/total number)						
	30-day	6-month	12-month	2-year	3-year	4-year	5-year
Kink	0	0	0	0	0	0	0
Device compression	2.3% (1/43)[a]	0	0	0	0	0	0
Device infolding	0	0	0	0	0	0	0
Stent fracture	0	0	0	0	0	0	0

[a]Patient 1200012 – Symmetrical compression occurred to the proximal section of the second component that was placed in this patient, due possibly to the component having been deployed through the distal suture loop of the proximal (first) component, which then restricted the second component from fully opening. This finding of compression is considered different from the compression/infolding due to hemodynamic forces commonly associated with the most proximal aspect of a stent-graft. The patient had not experienced any adverse sequelae, but underwent a secondary intervention 335 days post-procedure. Balloon angioplasty was performed and the secondary intervention was deemed successful. Core laboratory analysis of the secondary intervention angiogram revealed no device compression.

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; clinically significant migration was defined as migration resulting in the need for secondary intervention. There have been no core laboratory reports of migration to date.

Secondary Interventions

The site-reported reasons for reintervention are provided in Table 17. Six patients in total have under gone at least one intervention subsequent to the initial procedure (no new reports of secondary intervention since the original PMA).

Table 17. Site-reported reasons for secondary intervention – Blunt thoracic aortic injury

Reason	0-30 Days	31-365 Days	366-730 Days	730-1095 Days	1095-1460 Days	1461-1825 Days
Device compression	0	1[b]	0	0	0	0
Endoleak						
Type I proximal	1[a]	0	0	0	0	0
Type I distal	0	0	0	0	0	0
Type II	0	0	0	0	0	0
Type III (graft component overlap)	0	0	0	0	0	0
Type III (hole/tear in graft)	0	0	0	0	0	0
Type IV (through graft body)	0	0	0	0	0	0
Unknown	0	0	0	0	0	0
Clinical signs/symptoms	0	1[e]	0	0	0	0
Other	0	2[c,d]	1[f]	0	0	0

[a]Patient 1200033 – The patient was treated for a proximal Type I endoleak (per site assessment; core laboratory reported an unknown type of endoleak) 30 days post-procedure; the graft appeared undersized based on core laboratory-assessed aortic diameter measurements. Six Heli-FX™ screws were placed but the endoleak persisted and the secondary intervention was deemed unsuccessful. The patient later underwent conversion to open surgical repair 181 days after the index procedure. The patient survived the surgery and has not experienced any adverse events subsequent to the conversion as of 212 days post-procedure.

[b]Patient 1200012 underwent balloon angioplasty 335 days post-procedure to correct device compression of the proximal section of the second component (with no associated adverse sequelae) noted on the 1-month CT scan. The secondary intervention was deemed successful.

[c]Patient 1200024 underwent two secondary interventions following the index procedure. An unsuccessful secondary intervention (stent-graft placement) was attempted to treat a pseudoaneurysm proximal to the previously placed stent-graft on post-procedure day 74. On post-procedure day 79, the patient underwent a mini-sternotomy, aortic arch debranching, aortic bypass to the innominate and left carotid arteries with Hemashield™ graft, placement of a commercially available endograft, and bilateral chest tube placement to successfully treat the pseudoaneurysm. As described previously, the patient subsequently died on post-operative day 116. The death was adjudicated as procedure-related by the CEC (cause of death was exsanguination due to aortoesophageal fistula).

[d]Patient 1200006 underwent placement of a commercially available stent-graft 219 days post-procedure to treat an area of residual injury or possible endoleak. The injury was incompletely treated during the index procedure due to the device having been placed too far distally (noted on the 6-month CT scan). The patient also required a left subclavian artery bypass. The secondary intervention was deemed successful.

[e]Patient 1200036 was diagnosed with an aortic dissection distal to the previously placed stent-graft on post-operative day 286 after returning to the hospital for chest pain. The site noted that the patient was hypertensive and had stopped taking his blood pressure medication. An additional stent-graft was placed the following day, which resolved the patient's symptoms. The patient was discharged 2 days after the reintervention.

[f]Patient 1200060 required placement of an additional stent-graft (overlapped with the existing graft) 435 days post-procedure to provide coverage and stability of the thrombus noted in the distal stent-graft and native aorta on the 12-month CT scan in the absence of distal embolization or adverse problems. The site reported that the intervention was successful.

Conversion

As presented in Table 18, there has been one conversion to open repair in the BTAI study (no new reports since the original PMA), corresponding to a 97.5% freedom from conversion thus far.

Table 18. Kaplan-Meier estimates for freedom from conversion

Event	Parameter	30 Days	180 Days	365 Days	730 Days	1095 Days	1460 Days	1825 Days
Conversion	Number at risk[a]	48	40	36	32	**28**	**12**	**4**
	Cumulative events[b]	0	0	1[e]	1	1	1	**1**
	Cumulative censored[c]	2	10	13	17	**21**	**37**	**45**
	KM estimate[d]	1.000	1.000	0.975	0.975	0.975	0.975	**0.975**
	Standard error	0.000	0.000	0.025	0.025	0.025	0.025	**0.025**

Note: New information since the last reporting period is bolded.
[a]Number of patients at risk at the beginning of the interval.
[b]Total events up to and including the specific interval represents all patients who have had the event.
[c]Total censored patients up to and including the specific interval represents all patients who have met a study exit criteria or for whom data are not available at the specific interval.
[d]At end of interval.
[e]Patient 1200033 – Conversion to open repair was due to endoleak, adjudicated by the CEC as procedure-related.

Major Adverse Events

Table 19 shows the Kaplan-Meier estimates for freedom from major adverse events (MAE) for the BTAI study (defined as all-cause death; stroke; paraplegia; Q-wave MI; cardiac event involving arrest or resuscitation; renal failure requiring permanent dialysis, hemofiltration, or kidney transplant in a patient with a normal pre-procedure serum creatinine level; conversion to open repair; pulmonary embolism involving hemodynamic instability or surgery; graft infection; or wound complication requiring return to the operating room). There was 1 new MAE (death, included in the "All-cause Mortality" section) between July 28, 2016 and July 28, 2017. There were no new MAEs between July 29, 2017 and August 1, 2018.

Table 19. Kaplan-Meier estimates for major adverse events

Event	Parameter	30 Days	180 Days	365 Days	730 Days	1095 Days	1460 Days	1825 Days
Major Adverse Events	Number at risk[a]	45	37	34	30	**26**	**10**	**4**
	Cumulative events[b]	3	4	4	4	5	5	**5**
	Cumulative censored[c]	2	9	12	16	**19**	**35**	**41**
	KM estimate[d]	0.939	0.914	0.914	0.914	**0.883**	**0.883**	**0.883**
	Standard error	0.035	0.044	0.044	0.044	**0.058**	**0.058**	**0.058**

Note: New information since the last reporting period is bolded.
[a]Number of patients at risk at the beginning of the interval.
[b]Total events up to and including the specific interval represents all patients who have had the event. Note, only the first event is represented in the Kaplan-Meier estimate. A patient may have multiple events in each category.
[c]Total censored patients up to and including the specific interval represents all patients who have met a study exit criteria or for whom data are not available at the specific interval.
[d]At end of interval.

Summary

There have been no new aortic injury-related deaths, Type I or III endoleaks, device integrity observations, or conversions since approval of the PMA, and there remain no reports of rupture, migration, or loss of patency. There was 1 new report of all-cause mortality and one 1 report of MAE occurring between July 28, 2016 and July 28, 2017 (no new reports occurring between July 29, 2017 and August 1, 2018). Further, there have been no new reports of in-graft thrombus since the 2016 clinical update. The observations of thrombus from the clinical trial in combination with reports of thrombosis/occlusion from commercial use of the device for BTAI (Section II) resulted in Cook removing the indication for BTAI in June 2017, as further described in Section IV.

Section II – Worldwide Commercial Experience

The Zenith Alpha™ Thoracic Endovascular Graft was commercially available in the US soon after marketing approval was granted by FDA on September 15, 2015, and has been in commercial use in other parts of the world since 2013 with more than 27,000 devices sold globally.

As shown in Table 20, a total of 23,242 components (including 8,178 components in the US) have been distributed worldwide between September 15, 2015 and July 31, 2018.

Table 20. Total number of Zenith Alpha Thoracic Endovascular Graft components sold worldwide and in US (between September 15, 2015 and July 31, 2018)

Component	Total Number Sold Globally (subtotal for past year)	Total Number Sold in US (subtotal for past year)
ZTA-P (proximal component)	15,776 (6,354)	5,465 (2,275)
ZTA-PT (proximal tapered component)	5,812 (2,555)	2,048 (913)
ZTA-D (distal component)	1,055 (399)	363 (108)
ZTA-DE (distal extension)	599 (336)	302 (139)
Total	**23,242 (9,644)**	**8,178 (3,435)**

Cook evaluates product performance from this commercial experience based on complaint reporting systems throughout the world. Table 21 summarizes the procedural and follow-up complaints received with known final trend codes during global commercial experience with the Zenith Alpha Thoracic Endovascular Graft between September 15, 2015 and July 31, 2018. All complaints received related to the Zenith Alpha Thoracic Endovascular Graft are processed through the Quality Regulations 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 21. Number of procedure and follow-up complaints from global commercial experience with the Zenith Alpha Thoracic Endovascular Graft between September 15, 2015 and July 31, 2018

Complaint (by final trend code)	Sub-categories		Total since US approval (number new in past year)
Early death (≤ 30 days)			7 (2)[a]
Late death (> 30 days)			6 (2)[b]
Occluded device	Thrombosis in graft	16 (8)	25 (9)
	Not able to flush	3 (0)	
	Not able to introduce wire into introduction system	6 (1)	
Deployment, premature			1 (0)
Infection			1 (0)
Leakage			4 (2)
Difficult to release			15 (4)
Difficult removal from sheath			2 (0)
Unable to deploy			10 (1)
Endoleak	Type of endoleak unknown or not reported	2 (1)	24 (4)
	Endoleak Type I	19 (3)	
	Endoleak Type II	0	
	Endoleak Type III	3 (0)	
Separated			1 (0)
Fitting, separation			2 (1)
Disconnecting			1 (0)
Not a reject-No defect[c]			16 (9)
Dissection/perforation, vessel			1 (0)
Improper graft placement			13 (7)
Advancement difficulty			6 (3)
Components, Not matched			1 (0)
Component, Incorrect			1 (0)
Fistula			1 (0)
Deployment			4 (2)
Adverse physiological response			1 (1)
Incorrect diameter			1 (1)
Incomplete expansion			2 (2)
Perforation of introducer sheath			1 (1)
Rupture			1 (1)
Tissue Breakdown/Damage			1 (1)
Tract length (aorta elongation)			1 (1)
Fitting, damaged			1 (1)
Difficult to remove introduction system from patient			1 (1)
Failure in rotation of handle			1 (1)
Total			**153 (57)**

[a] Reported causes of death included: Anaphylactic shock; Aortic rupture two days after the procedure; Cortical strokes post-op; Dissection/rupture of innominate artery; Unknown; and 2 under investigation.
[b] Reported causes of death included: Occlusion due to thrombosis; Sepsis followed by hypokalemia, renal failure and multiorgan failure; Cardiorespiratory arrest in a context of renal failure, septic shock, neurologic

and thoracic events; Unknown; Occlusion due to thrombosis (died during secondary intervention); Refusal of further treatment except for comfort care in setting of several sacral ulcers and paraplegia.
[c] Complaint was concluded to not be related to Cook device.

As noted in Table 21, there have been 16 patients with thrombosis in the graft, each of which occurred following treatment for BTAI/trauma/penetrating aortic injury, 14 of which also included the use of smaller diameter grafts (18 – 22 mm). In total, there were 2 deaths, 5 paraplegia/paraparesis, and 9 reinterventions reported among the 16 patients with thrombosis/occlusion following treatment for BTAI/trauma/penetrating aortic injury, some of whom experienced more than one of these events. As previously mentioned in the 2016 Annual Clinical Update (and further described in Section IV), the reports of thrombosis/occlusion during commercial use of the device for BTAI in combination with the observations of in-graft thrombus from the BTAI clinical trial (Section I) resulted in Cook voluntarily removing the indication for BTAI as well as smaller diameter grafts (18 – 22 mm) from the market in June 2017.

Except for the risk of thrombosis/occlusion following BTAI treatment, 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 have occurred with unexpected frequency. However, following observations of Type I endoleak with use of the device to treat aortic dissection outside the US, Cook issued a notice to healthcare providers (in August 2018, as also described in Section IV) to reiterate that the Zenith Alpha Thoracic Endovascular Graft is indicated for the treatment of patients with aneurysms or ulcers of the descending thoracic aorta.

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 has been obtained from two explanted devices from patients treated as a part of the multi-center clinical studies (one from the aneurysm/ulcer study and one from the BTAI study). Both explants were from the patients who underwent conversion to open surgical repair.

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, and if applicable, also histological microscopy and/or scanning electron microscopy. The assessment was focused upon graft material wear, suture wear, and metal component fatigue.

The observations from explant analysis as well as the length of time the devices were implanted are listed in Table 22. Of note, neither explant was received in aortic tissue.

Table 22. Observations from grafts explanted during the multi-center clinical studies

Reason for explant	Days implanted	Observations[a]					
		Damaged or broken stents	Barb separation	Graft wear	Cut or broken sutures (green)[b]	Cut or broken sutures (blue)[c]	Suture hole elongation
Conversion due to aorto-esophageal fistula	331	No	No	No	Yes	No	No
Conversion due to Type I endoleak	182	Yes	No	No	Yes	Yes	No

[a] Noted observations may have been due to damage caused during explantation.
[b] Sutures used to attach external stents.
[c] Sutures used to attach internal stents and bare stent.

Worldwide Commercial Experience

There have been no explants analyzed from worldwide commercial experience.

Summary

In total, there have been two explants analyzed. 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. Nonetheless, routine imaging follow-up remains important in detecting any potential compromises in device integrity that might require reintervention.

Section IV – Notes to Clinicians

BTAI

As described in the 2017 Annual Clinical Update (Section IV), in March 2017, Cook sent a voluntary communication (Urgent: Medical Device Correction) to inform customers about reports of thrombus within the Zenith Alpha Thoracic Endovascular Graft during on-going clinical trial follow-up (typically noted by only the core laboratory, not the investigational sites) and commercial use for BTAI (as also summarized in Sections I and II of this Clinical Update), and based on these results, also underscore the importance of careful patient selection, device planning/sizing, and follow-up according to the IFU.

Subsequent to the March 2017 communication, Cook received additional reports of thrombus during commercial use of the product for BTAI (also summarized in Section II of this Clinical Update). Although the additional reports were from patients treated prior to the March 2017 communication, Cook voluntarily withdrew the indication for BTAI and correspondingly also removed from the market smaller graft diameters likely to be used only for BTAI, as described in the June 2017 communication (Urgent: Medical Device Correction and Removal, a copy of which is attached for reference). The resultant changes to the labeling to account for removal of the indication for BTAI as well as the smaller graft diameters are reflected in Section V.

With regards to patients already treated for BTAI, and recognizing the potential clinical significance of graft thrombosis if not addressed, it is particularly important to continue following these patients in accordance with the IFU, including imaging follow-up such as contrast-enhanced CT scans to monitor for thrombus within the graft, which may appear as a contrast void within the lumen of the graft on imaging.

Dissection

In August 2018, Cook sent a voluntary communication (a copy of which is also attached for reference) to reiterate that the Zenith Alpha Thoracic Endovascular Graft is indicated for the treatment of patients with aneurysms or ulcers of the descending thoracic aorta. This communication followed observations of Type I endoleak in patients treated with the device for aortic dissection outside the US, which included three reports of proximal Type I endoleak requiring reintervention. The Zenith Alpha Thoracic Endovascular Graft is not indicated for treatment of aortic dissection in any market and has not been evaluated for safety and effectiveness in this patient population.

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

Indications

The Zenith Alpha Thoracic Endovascular Graft is indicated for the endovascular treatment of patients with aneurysms or ulcers of the descending thoracic aorta having vascular morphology suitable for endovascular repair, including:

- Iliac/femoral anatomy that is suitable for access with the required introduction systems
- Non−aneurysmal aortic segments (fixation sites) proximal and distal to the thoracic aneurysm or ulcer:
    - with a length of at least 20 mm, and
    - with a diameter measured outer-wall-to-outer-wall of no greater than 42 mm and no less than 20 mm

Warnings and Precautions

Patient Selection

- The Zenith Alpha Thoracic Endovascular Graft is designed to treat aortic neck diameters no smaller than 20 mm and no larger than 42 mm. The Zenith Alpha Thoracic Endovascular Graft is designed to treat proximal aortic necks (distal to either the left subclavian or left common carotid artery) of at least 20 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. Graft length should be selected to cover the aneurysm or ulcer as measured along the greater curve of the aneurysm, plus a minimum of 20 mm of seal zone on the proximal and distal ends. A distal aortic neck length of at least 20 mm proximal to the celiac axis is required. These sizing measurements are critical to the performance of the endovascular repair. In patients with a large proximal aortic vessel diameter and aneurysms on the inner curvature, there is a risk that the graft may deploy in an angulated position if the sealing zone is less than 20 mm.
- Key anatomic elements that may affect successful exclusion of the thoracic aneurysm or ulcer include severe angulation (radius of curvature < 20 mm and localized angulation > 45 degrees); short proximal or distal fixation sites (< 20 mm); an inverted funnel shape at the proximal fixation site or a funnel shape at

the distal fixation site (greater than a 10% change in diameter over 20 mm of fixation site length); and circumferential thrombus and/or calcification at the arterial fixation sites. Irregular calcification and/or plaque may compromise the attachment and sealing at the fixation sites. In the presence of anatomical limitations, a longer neck length may be required to obtain adequate sealing and fixation. Necks exhibiting these key anatomic elements may be more conducive to graft migration. In patients with large aneurysms on the outer curvature close to the left subclavian, it may be difficult to track the device around the arch, and extra support may be needed using a brachio-femoral wire.

- In-graft thrombus has been observed when the Zenith Alpha Thoracic Endovascular Graft has been used to treat blunt thoracic aortic injuries. This risk may potentially be associated with excessive oversizing in the distal seal zone of the device.

Device Selection

- Graft length should be selected to cover the aneurysm or ulcer as measured along the greater curve of the aneurysm, plus a minimum of 20 mm of seal zone on the proximal and distal ends.
- To treat more focal aortic lesions, such as ulcers/saccular aneurysms, a proximal component can be used alone.
- In aneurysms the graft may settle into the greater curve of the aneurysm over time. Accordingly, extra graft length needs to be planned:
    - A two-component repair (proximal and distal component) is recommended, as it provides the ability to adapt to the length change over time. A two-component repair (proximal and distal component) also provides active fixation at both the proximal and distal seal sites.
    - The minimum required amount of overlap between devices is three stents. Less than a three-stent overlap may result in endoleak (with or without component separation). However, no part of the distal component should overlap the proximal sealing stent of the proximal component, and no part of the proximal component should overlap the distal sealing stent of the distal component, as doing so may cause malapposition to the vessel wall. Device lengths should be selected accordingly.
    - If an acceptable two-component (proximal and distal component) treatment plan cannot be achieved (e.g., excessive aortic coverage, even

with maximal overlap of shortest components), the proximal component must be selected with enough length to achieve and maintain the minimum 20 mm sealing zones at both ends even when positioned in the greater curve of the aneurysm. Failure to do so could result in migration, endoleak, and aneurysm growth, as observed in the clinical study.

Implant Procedure

- Be sure to land the proximal and distal ends of the device in an aortic neck segment with a diameter that matches the initial sizing of the device. Landing in a segment that is different from the location used to size the device may potentially result in inadequate (< 10%) or excessive (> 25%) graft diameter oversizing and therefore migration, endoleak, thoracic aneurysm or ulcer growth, or increased risk of thrombosis.

Note: Refer to the IFU for complete warnings and precautions

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BLOOMINGTON, IN 47402-4195 U.S.A.
PHONE: 812.339.2235 TOLL FREE: 800.457.4500
WWW.COOKMEDICAL.COM

June 22, 2017

URGENT:
MEDICAL DEVICE CORRECTION AND REMOVAL

ATTENTION:
Risk Management/Recall Administration
Our records indicate that you may have received some of the affected products listed below.

Details on Affected Devices:
Zenith Alpha™ Thoracic Endovascular Graft

Product Brand Name	Catalog Identifier*	Lot Number
Zenith Alpha™ Thoracic Endovascular Graft	ZTA-D-/-W	All Lots
	ZTA-DE-/-W	
	ZTA-P-/-W	
	ZTA-PT-/-W	

**Please refer to the complete product listing for further information.*

Description of the Problem:
As described in the March 22, 2017 Device Correction regarding the Zenith Alpha™ Thoracic Endovascular Graft, there were complaints involving thrombosis/occlusion of the product when used to treat blunt thoracic aortic injury (BTAI). Since that time, Cook Medical has received additional complaints for the same problem. Although the complaints were from patients treated prior to issuance of the above noted Device Correction, Cook Medical is initiating a voluntary correction of the Instructions for Use (IFU) and is also voluntarily removing specific sizes of the Zenith Alpha Thoracic Endovascular Graft from the market.

Description of the Correction:
The correction to the IFU for this device removes the indication for use in BTAI, as follows (corrections shown in **bold**):

The Zenith Alpha™ Thoracic Endovascular Graft is indicated for the endovascular treatment of patients with **aneurysms or ulcers** of the descending thoracic aorta having vascular morphology suitable for endovascular repair including:

- Iliac/femoral anatomy that is suitable for access with the required introduction systems
- Nonaneurysmal aortic segments (fixation sites) proximal and distal to the **aneurysm or ulcer**:
  - with a length of at least 20 mm, and
  - with a diameter measured outer-wall-to-outer-wall of no greater than 42 mm and no less than **20 mm**.

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Additionally, the following warning has been added to describe the thrombus risk that has been observed when the device is used to treat BTAI:

- Risk of in-graft thrombus has been observed when the Zenith Alpha Thoracic Endovascular Graft has been used to treat BTAI.

Patients already treated with the Zenith Alpha Thoracic Endovascular Graft for the BTAI indication should be followed according to the current IFU and with considerations outlined in Cook Medical's recent Medical Device Correction of March 22, 2017.

Description of the Removal:
Because of the IFU correction to remove BTAI from the indication, it is necessary to remove specific sizes of this device (grafts with a proximal or distal diameter 18 – 22 mm) that would likely be used only for BTAI. The following table lists the specific catalog numbers for the product sizes that are being removed:

Product Brand Name	Catalog Identifier	Global Product Number	Lot Number
Zenith Alpha™ Thoracic Endovascular Graft	ZTA-P-18-105-W	G35327	All Lots
	ZTA-P-20-105-W	G35329	
	ZTA-P-22-105-W	G35331	
	ZTA-PT-22-18-105-W	G38041	
	ZTA-PT-26-22-105-W	G38055	
	ZTA-DE-22-104-W	G35506	

Potential adverse events that may occur if these devices were used for BTAI include death, paraplegia, and/or surgical intervention.

Actions to be taken:

- Please share this notice with others in your organization who either use this device or follow patients treated with this device. Follow the IFU corrections as provided above.
- Examine inventory and immediately quarantine affected products.
- Complete and return the required Acknowledgement and Receipt Form, as well as any affected recalled products to Cook Medical within 30 days.
- Maintain a copy of this notice for your records.
- Upon availability of the corrected IFU, your Cook Medical Sales Representative will personally follow-up and provide corrected IFUs for your inventory.
- Immediately report any adverse events to Cook Medical Customer Relations at 800.457.4500 or 812.339.2235, Monday through Friday between 7:30 am and 5:00 pm (Eastern Time), or by email at customerrelationsna@cookmedical.com.

Adverse events or quality problems experienced with the use of this product may also be reported to the FDA:

- Online at: http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm (form available to fax or mail
- Call the FDA at: 1-800-FDA-1088

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Transmission of this notice:
This notice must be shared with appropriate personnel, including down to the user level, within your organization or to any organization where the potentially affected devices have been transferred.

This action is being taken with the knowledge of the Food and Drug Administration.

We recognize this situation is a disruption to your normal operations and we sincerely apologize. Thank you again for your immediate assistance in this matter. Should you have any medical questions or concerns, please contact Cook Medical Customer Relations at 800.457.4500 or 812.339.2235. We look forward to your response.

Cook Medical

Rita A. Harden

Rita A. Harden
Director, Customer Relations & Regulatory Reporting

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1025 ACUFF ROAD, P.O. BOX 4195
BLOOMINGTON, IN 47402-4195 U.S.A.
PHONE: 812.339.2235 TOLL FREE: 800.457.4500
WWW.COOKMEDICAL.COM

August 28, 2018

ATTENTION: Healthcare Provider, Chief Executive, Risk Manager, and Purchasing

Details on affected devices:
Zenith Alpha™ Thoracic Endovascular Graft

PRODUCT BRAND NAME	Catalog Identifier*
Zenith Alpha™ Thoracic Endovascular Graft	ZTA-D-/-W
	ZTA-DE-/-W
	ZTA-P-/-W
	ZTA-PT-/-W

**Please refer to the complete product listing for further information.*

Description of the problem:

Cook Medical has become aware that the Zenith Alpha™ Thoracic Endovascular Graft has been used to treat patients with thoracic aortic dissections.

As per the Instructions for Use (IFU), the Zenith Alpha Thoracic Endovascular Graft is indicated for the endovascular treatment for patients with aneurysms or ulcers of the descending thoracic aorta having vascular morphology suitable for endovascular repair, including:

- Iliac/femoral anatomy that is suitable for access with the required introduction systems
- Nonaneurysmal aortic segments (fixation sites) proximal and distal to the thoracic aneurysm or ulcer:
    - With a length of at least 20 mm, and
    - With a diameter measured outer-wall-to-outer-wall of no greater than 42 mm and no less than 20 mm.

To emphasize best practices, Cook Medical would like to reiterate that the Zenith Alpha Thoracic Endovascular Graft and ancillary components should be used as specified in the IFU. The IFU section 4.2 “Patient Selection, Treatment and Follow Up” states that the safety and effectiveness of the Zenith Alpha Thoracic Endovascular Graft and ancillary components have not been evaluated in the patient populations for dissection.

Refer to IFU section 5 for potential adverse events associated with either Zenith Alpha Thoracic Endovascular Graft or the implantation procedure that may occur and/or require intervention.

Actions to be taken:

No devices need to be returned and patients **already treated** for a dissection should receive standard follow-up procedures. Please also do the following:

- Please share this notice with others in your organization who either use this device or follow patients treated with this device. Follow the IFU.
- Maintain a copy of this notice for your records.

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- Report adverse events to Cook Medical Customer Relations by phone at 800.457.4500 or 812.339.2235, Monday through Friday between 7:30 am and 5:00 pm (Eastern Time) or by email to CustomerRelationsNA@CookMedical.com.

Adverse events or quality problems experienced with the use of this product may also be reported to the FDA.

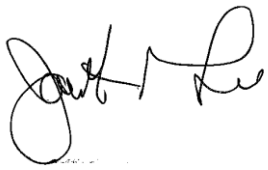
- Visit http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm to obtain a form to fax or mail.
- Call the FDA at 800.FDA.1088.

Transmission of this notice

This notice must be shared with appropriate personnel, including down to the user level, within your organization or with any organization where the potentially affected devices have been transferred.

This action is being taken with the knowledge of the Food and Drug Administration.

Thank you for your immediate attention to this matter. If you have any questions or concerns, please contact Cook Medical Customer Relations at 800.457.4500 or 812.339.2235.



Janet Price-Lutz
Post Market Specialist
Customer Support & Delivery
Cook Medical

ZENITH ALPHA™ THORACIC ENDOVASCULAR GRAFT DEVICES

Reference Part Number	Global Product Number	Reference Part Number	Global Product Number	Reference Part Number	Global Product Number
ZTA-D-28-160-W	G35381	ZTA-P-24-127-W	G35334	ZTA-P-42-225-W	G35368
ZTA-D-30-160-W	G35383	ZTA-P-26-105-W	G35335	ZTA-P-44-125-W	G35369
ZTA-D-32-160-W	G35385	ZTA-P-28-109-W	G35337	ZTA-P-44-179-W	G35371
ZTA-D-34-142-W	G35391	ZTA-P-28-155-W	G35339	ZTA-P-44-233-W	G35372
ZTA-D-34-190-W	G35392	ZTA-P-28-201-W	G35340	ZTA-P-46-125-W	G35373
ZTA-D-36-142-W	G35393	ZTA-P-30-109-W	G35341	ZTA-P-46-179-W	G35375
ZTA-D-36-190-W	G35394	ZTA-P-30-155-W	G35343	ZTA-P-46-233-W	G35376
ZTA-D-38-147-W	G35395	ZTA-P-30-201-W	G35344	ZTA-PT-30-26-108-W	G38072
ZTA-D-38-197-W	G35396	ZTA-P-32-109-W	G35345	ZTA-PT-32-28-178-W	G38075
ZTA-D-40-147-W	G35397	ZTA-P-32-155-W	G35347	ZTA-PT-32-28-201-W	G38171
ZTA-D-40-197-W	G35398	ZTA-P-32-201-W	G35348	ZTA-PT-34-30-161-W	G38172
ZTA-D-42-152-W	G35399	ZTA-P-34-113-W	G35349	ZTA-PT-34-30-209-W	G38173
ZTA-D-42-204-W	G35400	ZTA-P-34-161-W	G35351	ZTA-PT-36-32-161-W	G38178
ZTA-D-44-157-W	G35401	ZTA-P-34-209-W	G35352	ZTA-PT-36-32-209-W	G38179
ZTA-D-44-211-W	G35402	ZTA-P-36-113-W	G35353	ZTA-PT-38-34-167-W	G38180
ZTA-D-46-157-W	G35403	ZTA-P-36-161-W	G35355	ZTA-PT-38-34-217-W	G38190
ZTA-D-46-211-W	G35404	ZTA-P-36-209-W	G35356	ZTA-PT-40-36-167-W	G38191
ZTA-DE-26-104-W	G35511	ZTA-P-38-117-W	G35357	ZTA-PT-40-36-217-W	G38201
ZTA-DE-30-108-W	G35515	ZTA-P-38-167-W	G35359	ZTA-PT-42-38-173-W	G38203
ZTA-DE-34-112-W	G35519	ZTA-P-38-217-W	G35360	ZTA-PT-42-38-225-W	G38204
ZTA-DE-38-91-W	G35523	ZTA-P-40-117-W	G35361	ZTA-PT-44-40-179-W	G38208
ZTA-DE-42-146-W	G38023	ZTA-P-40-167-W	G35363	ZTA-PT-44-40-233-W	G38216
ZTA-DE-42-94-W	G36346	ZTA-P-40-217-W	G35364	ZTA-PT-46-42-179-W	G38220
ZTA-DE-46-97-W	G38027	ZTA-P-42-121-W	G35365	ZTA-PT-46-42-233-W	G38236
ZTA-P-24-105-W	G35333	ZTA-P-42-173-W	G35367		