6. Summary of Clinical Data

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.

The Zenith Alpha™ Thoracic Endovascular Graft has been the subject of several documented clinical evaluations, including two pivotal studies (one international) that evaluated the safety and effectiveness of the Zenith Alpha™ Thoracic Endovascular Graft in patients with thoracic aneurysm/ulcer and blunt thoracic aortic injury (BTAI), as summarized in Table 6-1. It should be noted that while the study to evaluate use of the device for the treatment of patients with BTAI initially supported approval for an indication inclusive of BTAI in September 2015, subsequent results from longer-term follow-up in combination with results from commercial use suggest an increased risk for in-graft thrombus with use of the device to treat patients with BTAI (refer to the Annual Clinical Update available at www.cookmedical.com for a complete summary of this information). Therefore, the indication for BTAI was removed in June 2017. Additional clinical evaluations include a continued access study for the aneurysm/ulcer indication (see Section 6.2.2) and a European post-market survey (see Section 6.2.3) to further confirm performance of a user interface modification to the introduction system (rotation handle).

Table 6-1. Summary of primary pivotal studies

Pivotal Study	Study Design	Objective	Number of Sites with Enrollment	Number of Patients
Aneurysm/ Ulcer	Prospective, nonrandomized, single-arm, multinational (US, Japan, Germany, England, Sweden) study	To evaluate safety and effectiveness of the Zenith Alpha™ Thoracic Endovascular Graft for the treatment of patients with aneurysms/ulcers of the descending thoracic aorta.	23	110
BTAI	Prospective, nonrandomized, noncomparative, single-arm, US multicenter study	To evaluate safety and effectiveness of the Zenith Alpha™ Thoracic Endovascular Graft for the treatment of BTAI	17	50

6.1. Clinical Study for the Aneurysm/Ulcer Indication

The Zenith Alpha™ Thoracic Endovascular Graft clinical 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. The data presented herein was collected on 110 patients through April 7, 2015. 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 endpoint was 30-day freedom from major adverse events (MAEs), and the performance goal was 80.6%. MAEs were defined as the following: all-cause death; Q-wave MI; 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.

The primary effectiveness endpoint was device success at 12-month. Device success at 12 months was defined as: Technical Success, with none of the following at 12 months:

- Type I or type III endoleaks requiring re-intervention
- Aneurysm rupture or conversion to open surgical repair
- Aneurysm enlargement greater than 0.5 cm

Technical success was defined as successful access of the aneurysm site and deployment of the Zenith Alpha™ Thoracic Endovascular Graft in the intended location. The endovascular graft must be patent at the time of deployment completion as evidenced by intraoperative angiography.

The effectiveness hypothesis of the study was that device success at 12 months met the performance goal of 80.7%.

An independent core laboratory analyzed all patient imaging. An independent clinical events committee (CEC) adjudicated all major adverse events (MAEs), including all patient deaths; additionally the CEC also adjudicated core laboratory reports of migration and device integrity loss. An independent data safety monitoring board (DSMB) monitored the clinical trial according to an established safety monitoring plan.

The study follow-up schedule (Table 6.1-1) consisted of both clinical and imaging (CT and X-ray) assessments at post-procedure (pre-discharge), 30 days, 6 months, 12 months, and yearly thereafter through 5 years.

Table 6.1-1. Study follow-up schedule

Study Schedule							
	Pre-op	Intra-op	Post-procedure	30-Day	6-Month	12-Month	24-Month[d]
Clinical exam	X		X	X	X	X	X
Blood tests	X		X	X	X	X	X
CT scan	X[a]			X[c]	X[c]	X[c]	X[c]
Thoracic x-ray				X	X	X	X
Angiography	X[b]	X					

[a]It is recommended that imaging be performed within 6 months before the procedure.
[b]Required only to resolve any uncertainties in anatomical measurements necessary for graft sizing.
[c]MR imaging may be used for those patients experiencing renal failure or who are otherwise unable to undergo contrast-enhanced CT scan, with TEE being an additional option in the event of suboptimal MR imaging.
[d]Yearly thereafter through 5 years.

At the time of the database lock, of 110 patients enrolled in the study, 90% (99/110) were eligible for follow-up at 12 months (Table 6.1-2). All patients were evaluable for the primary safety endpoint (freedom from MAE at 30 days). All patients were also evaluable for the primary effectiveness endpoint (12-month device success) based on a component of the composite measure having been assessed at the time of the procedure, consistent with the performance goal development. Two patients, although enrolled in the study, did not receive the device due to an inability to advance/gain access to the target treatment site. Although the primary safety and effectiveness endpoints were evaluated at 30 days and 12 months, respectively, patient data presented herein include

longer-term follow-up that was available at the time of the data lock (April 7, 2015). Table 6.1-2 reports the percent of follow-up data available through 4 years.

Table 6.1-2. 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			
		Patients with Data for that Visit	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	110	110/110 (100%)	NA	NA	0	NA	NA	NA	NA	0	0	0	0
30-day	110[e]	106/110 (96.4%)	105/108 (97.2%)	98/108 (90.7%)	0	105/108 (97.2%)	102/108 (94.4%)	NA	105/108 (97.2%)	3	0	0	2[e]
6-month	105	99/105 (94.3%)	97/105 (92.4%)	92/105 (87.6%)	0	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%)	0	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%)	8	77/89 (86.5%)	73/89 (82.0%)	77/89 (86.5%)	77/89 (86.5%)	3	0	7	45
3-year	34	23/34 (67.6%)	20/34 (58.8%)	18/34 (52.9%)	11	17/34 (50.0%)	15/34 (44.1%)	17/34 (50.0%)	17/34 (50.0%)	0	0	0	26
4-year	8	6/8 (75.0%)	6/8 (75.0%)	6/8 (75.0%)	2	6/8 (75.0%)	6/8 (75.0%)	6/8 (75.0%)	6/8 (75.0%)	0	0	0	8

NA – Not assessed.
LTF/WTHD – Lost-to-follow-up and withdrawn.
[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 due to renal failure.
[d]Patients still within follow-up window, but data not yet available.
[e]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.

Demographics and Patient Characteristics

The demographics and patient characteristics are presented in Table 6.1-3.

Table 6.1-3. Demographics and patient characteristics

Demographic	Mean ± SD (n, range) or Percent Patients (number/total number)
Age (years)	
All patients	72.2 ± 9.8 (n=110, 42 – 92)
Male	70.7 ± 9.9 (n=64, 42 – 85)
Female	74.3 ± 9.4 (n=46, 44 – 92)
Gender	
Male	58.2% (64/110)
Female	41.8% (46/110)
Ethnicity	
White	53.6% (59/110)
Hispanic or Latino	0
Black or African American	8.2% (9/110)
American Indian or Alaska Native	0
Asian	38.2% (42/110)
Native Hawaiian or other Pacific Islander	0
Other	0
Height (in)	65.3 ± 4.5 (n=110, 55.1 – 75.2)
Weight (lbs)	161.7 ± 44.3 (n=110, 79.2 – 330.0)
Body mass index	26.5 ± 6.0 (n=110, 16.4 – 50.0)

The medical history and comorbid medical conditions for the patient cohort are presented in Table 6.1-4.

Table 6.1-4. Pre-existing comorbid medical conditions

Medical History	Percent Patients (number/total number)
Cardiovascular	
Myocardial infarction (MI)	12.7% (14/110)
Angioplasty/stent	10.0% (11/110)
Cardiac or thoracic surgery	16.4% (18/110)
Prior diagnosis of symptomatic congestive heart failure (CHF)	10.0% (11/110)
Angina	16.4% (18/110)
Prior diagnosis of arrhythmia	23.6% (26/110)
Hypertension	88.2% (97/110)
Coronary artery bypass graft	11.8% (13/110)

Medical History	Percent Patients (number/total number)
Vascular	
Thromboembolic event	0.9% (1/110)
Peripheral vascular disease	21.8% (24/110)
Symptomatic carotid disease warranting intervention	1.8% (2/110)
Any aneurysm (other than the study lesion)	45.5% (50/110)
Thoracic aortic aneurysm	2.7% (3/110)
Abdominal aortic aneurysm	26.4% (29/110)
Other aneurysm[a]	16.4% (18/110)
Degenerative or atherosclerotic ulcer (other than the study lesion)	0.9% (1/110)
Any dissection	9.1% (10/110)[b]
Thoracic aortic dissection	6.4% (7/110)[c]
Abdominal aortic dissection	0
Other dissection[d]	2.7% (3/110)
Thoracic trauma	3.6% (4/110)[e]
Aortobronchial fistula	0.9% (1/110)
Aortoesophageal fistula	0
Bleeding diathesis or uncorrectable coagulopathy	0
Endarterectomy	1.8% (2/110)
Diagnosed or suspected congenital degenerative collagen disease	0
Pulmonary	
Chronic obstructive pulmonary disease (COPD)	25.5% (28/110)
Home oxygen	1.8% (2/110)
Renal	
Chronic renal failure	10.0% (11/110)
Hemodialysis	1.8% (2/110)
Chronic peritoneal dialysis	0
Endocrine	
Diabetes	19.1% (21/110)
Hypercholesterolemia	73.6% (81/110)
Infectious disease	
Systemic infection	0
Gastrointestinal	
Gastrointestinal disease	34.5% (38/110)
Hepatobiliary	
Liver disease	12.7% (14/110)
Neoplasms	
Cancer	24.5% (27/110)
Neurologic	
Stroke	10.9% (12/110)
Substance use	
Past or current smoker	71.8% (79/110)
Allergies	
Allergies	41.8% (46/110)

[a]The "other" aneurysm category includes patients with aneurysms in different locations (i.e., not descending thoracic or abdominal aorta) and patients with aneurysms in multiple locations.
[b]All patients had a history of aortic dissection but at the time of enrollment had no radiographic evidence of aortic dissection.
[c]The treated aneurysm/ulcer was located in the same aortic segment as the previously diagnosed dissection in four patients.
[d]The "other" dissection category includes patients with dissection in different locations (i.e., not descending thoracic or abdominal aorta) and patients with dissections in multiple locations.
[e]All patients had a history (> 1 year) of traumatic thoracic injury.

Table 6.1-5 reports the ASA classification.

Table 6.1-5. ASA physical status classification

ASA Classification	Percent Patients (number/total number)
Healthy patient (1)	8.2% (9/110)
Mild systemic disease (2)	55.5% (61/110)
Severe systemic disease (3)	26.4% (29/110)
Incapacitating systemic disease (4)	10.0% (11/110)
Moribund patient (5)	0

Table 6.1-6 reports the SVS-ISCVS risk score.

Table 6.1-6. SVS-ISCVS risk score classification

SVS-ISCVS Category	Percent Patients (number/total number)
Diabetes risk score	
0	83.6% (92/110)
1	5.5% (6/110)
2	9.1% (10/110)
3	1.8% (2/110)
4	0
Smoking risk score	
0	47.3% (52/110)
1	30.0% (33/110)
2	13.6% (15/110)
3	9.1% (10/110)
Hypertension risk score	
0	11.8% (13/110)
1	29.1% (32/110)
2	31.8% (35/110)
3	27.3% (30/110)
Hyperlipidemia risk score	
0	26.4% (29/110)
1	17.3% (19/110)
2	1.8% (2/110)
3	54.5% (60/110)
Cardiac status risk score	
0	70.0% (77/110)
1	18.2% (20/110)
2	11.8% (13/110)
3	0
Carotid disease risk score	
0	84.5% (93/110)
1	13.6% (15/110)
2	0.9% (1/110)
3	0.9% (1/110)

SVS-ISCVS Category	Percent Patients (number/total number)
Renal status risk score	
0	87.3% (96/110)
1	10.9% (12/110)
2	0
3	1.8% (2/110)
Pulmonary status risk score	
0	66.4% (73/110)
1	26.4% (29/110)
2	6.4% (7/110)
3	0.9% (1/110)
Total SVS/ISCVS risk score	5.9 ± 2.6 (n=110, 1 – 14)

The majority of patients (81.8%) had fusiform aneurysms and the remaining 18.2% had penetrating atherosclerotic ulcers. Table 6.1-7 reports the presenting morphology.

Table 6.1-7. Presenting morphology type per the core laboratory

Morphology	Percent Patients (number/total number)
Aneurysm	81.8% (90/110)
Ulcer	18.2% (20/110)

Table 6.1-8 reports presenting anatomical dimensions of the aneurysm/ulcer, the proximal and distal aortic necks, and the right and left iliac arteries.

Table 6.1-8. Presenting anatomical dimensions reported per the core laboratory

Measure	Mean ± SD (n, range)
Aneurysm dimensions	
Major diameter (mm)	60.9 ± 11.4 (n=90, 41 – 99)
Minor diameter (mm)	51.7 ± 11.1 (n=90, 30 – 92)
Length (mm)	113.5 ± 63.0 (n=90, 25.4 – 324.0)
Ulcer dimensions	
Ulcer depth (mm)	14.1 ± 3.7 (n=20, 8 – 25)
Length (mm)	34.8 ± 20.3 (n=20, 11.0 – 85.7)
Proximal neck diameter	
Left common carotid artery	
Major (mm)	34.0 ± 3.0 (n=110, 24 – 42)
Minor (mm)	31.1 ± 3.5 (n=110, 18 – 39)
20 mm distal to left common carotid artery	
Major (mm)	33.3 ± 4.3 (n=110, 22 – 54)
Minor (mm)	30.6 ± 4.3 (n=110, 20 – 49)

Measure	Mean ± SD (n, range)
Distal neck diameter	
20 mm proximal to celiac artery	
Major (mm)	31.0 ± 5.1 (n=110, 20 – 48)
Minor (mm)	28.9 ± 4.7 (n=110, 19 – 42)
Celiac artery	
Major (mm)	29.5 ± 4.4 (n=110, 20 – 44)
Minor (mm)	27.3 ± 3.8 (n=110, 19 – 38)
Proximal neck length	
Left common carotid artery to distal part of neck (mm)	94.7 ± 57.8 (n=110, 14.4 – 276.7)
Distal neck length	
Celiac artery to proximal part of neck (mm)	105.2 ± 63.2 (n=110, 5.6 – 268.5)
Right iliac artery diameter	
Narrowest segment (mm)	6.7 ± 1.6 (n=105, 3 – 10)[a]
Left iliac artery diameter	
Narrowest segment (mm)	6.9 ± 1.8 (n=104, 0 – 11)[a]

[a]CT imaging was not always adequate for measurement of the iliac arteries.

Table 6.1-9 reports the distribution in aneurysm diameter/ulcer depth.

Table 6.1-9. Distribution in range of maximum aneurysm diameter or ulcer depth per the core laboratory

Type	Size Range[a]	Percent Patients (number/total number)
Aneurysm	40 mm – < 50 mm	8.9% (8/90)
	50 mm – < 60 mm	40.0% (36/90)
	60 mm – < 70 mm	36.7% (33/90)
	70 mm – < 80 mm	6.7% (6/90)
	80 mm – < 90 mm	4.4% (4/90)
	90 mm – < 100 mm	3.3% (3/90)
Ulcer	< 20 mm	95.0% (19/20)
	20 mm – < 30 mm	5.0% (1/20)
	30 mm – < 40 mm	0
	40 mm – < 50 mm	0
	50 mm – < 60 mm	0
	60 mm – < 70 mm	0
	70 mm – < 80 mm	0

[a]Diameter for aneurysms and depth for ulcers.

Table 6.1-10 provides the distribution in location of the aneurysm/ulcer.

Table 6.1-10. Location of the primary aneurysm/ulcer as determined by the core laboratory

Location	Percent Patients (number/total number)		
	Aneurysm Patients	Ulcer Patients	All Patients
Location in the thoracic aorta			
Proximal	26.7% (24/90)	50.0% (10/20)	30.9% (34/110)
Middle	53.3% (48/90)	30.0% (6/20)	49.1% (54/110)
Distal	20.0% (18/90)	20.0% (4/20)	20.0% (22/110)

Procedural Information

The majority (71.8%) of procedures were performed under general anesthesia, followed by local anesthesia in 21.8% of procedures. Vascular access was gained via femoral artery cutdown in 62.7% of patients, percutaneously in 36.4% of patients and by using a conduit 0.9% of patients. The mean procedure time was 99.4 ± 53.6 minutes (range 31-362) and the mean procedural blood loss was 121.8 ± 137.7 ml. The mean anesthesia time was 162.7 ± 61.4 minutes and the mean fluoroscopy time was 20.0 ± 20.1 minutes.

Adjunctive procedures for spinal cord protection to prevent paraplegia were performed in 40.0% of patients (72.7% of the adjunctive procedures were cerebral spinal fluid (CSF) drainage), and induced hypotension to ease deployment was performed in 7.3% of patients. The left subclavian artery (LSA) was covered completely in 13% of patients. No LCCA to LSA bypass or LSA transposition were performed.

The access method used to insert the Zenith Alpha™ Thoracic Endovascular Graft is presented in Table 6.1-11. Three types of methods were used: percutaneous (direct needle puncture of the access vessel), cutdown (surgical exposure of the access vessel), and conduit (surgical technique used to bypass prohibitive access vessels). For the percutaneous access method, the procedure time was 88.8 ± 44.7 minutes, blood loss was 128.5 ± 136.4 cc, and incidence of access site complications was 7.3%. For the cutdown/conduit access method, the procedure time was 105.4 ± 57.6 minutes, blood loss was 118.0 ± 139.3 cc, and incidence of access site complications was 5.7%. These data support the use of either method of access for the device.

Table 6.1-11. Access method used to insert the endovascular graft

Type	Percent Patients (number/total number)		
	Aneurysm Patients	Ulcer Patients	All Patients
Percutaneous	31.1% (28/90)	60.0% (12/20)	36.4% (40/110)
Cutdown	67.8% (61/90)	40.0% (8/20)	62.7% (69/110)
Conduit	1.1% (1/90)	0	0.9% (1/110)

The location of the graft components relative to an identified site is provided as percent of patients in Table 6.1-12.

Table 6.1-12. Graft location per core laboratory

Location	Percent Patients (number/total number)		
	Aneurysm Patients	Ulcer Patients	All Patients
Proximal aspect of graft			
Above LCCA	0	0	0
Below LCCA, above LSA	9.1% (8/88)	30.0% (6/20)	13.0% (14/108)
Below LSA	83.0% (73/88)	60.0% (12/20)	78.7% (85/108)
Unable to assess[a]	8.0% (7/88)	10.0% (2/20)	8.3% (9/108)
Distal aspect of graft			
Above celiac artery	95.5% (84/88)	90.0% (18/20)	94.4% (102/108)
Below celiac artery	0	0	0
Unable to assess[a]	4.5% (4/88)	10.0% (2/20)	5.6% (6/108)

LCCA = left common carotid artery; LSA = left subclavian artery.
[a]All patients had post-procedure angiography but not all imaging was adequate for core laboratory review.

Two patients required axillary-axillary bypasses prior to the index procedure (both from a Japanese site). Additional procedures performed after graft deployment included use of a vessel closure device in 26 patients, LCCA stent placement in 1 patient, LSA stent in 1 patient, LSA coil embolization in 5 patients, femoral endarterectomy in 2 patients, thrombo-endarterectomy and patch right femoral in1 patient, iliac artery stents in 3 patients, and chimney stent to maintain blood flow to the LCCA and LSA coil embolization in one patient. Table 6.1-13 reports additional procedures performed either before or after graft implantation.

Table 6.1-13. Additional procedures

Procedure	Percent Patients (number/total number)	
	Before Graft Deployment	After Graft Deployment
Left carotid artery stent	0	0.9% (1/110)
Left subclavian artery stent	0	0.9% (1/110)
Iliac artery angioplasty	0.9% (1/110)	0
Iliac artery stent	0	2.7% (3/110)
Vessel closure device	0	23.6% (26/110)
Other	1.8% (2/110)[a]	8.2% (9/110)[b]

[a]Two patients from Japan (1040051 and 1040069) underwent axillary-axillary bypass prior to the index procedure.
[b]Two patients (1030005 and 1030044) underwent right femoral endarterectomy after the index procedure. One patient (0465997) underwent thromboendarterectomy and patch right femoral after the index procedure. Five patients (1040023, 1040033, 1040039, 1040051, and 1040069) underwent coil embolization of the left subclavian artery after the index procedure. One patient (1040080) had a chimney

stent placed to maintain blood flow to the left common carotid artery and coil embolization of the left subclavian artery after the index procedure.

The device was successfully implanted in 98.2% of patients (2 patients did not receive the device due to the inability to insert/advance the introduction system) and all patients (100%) survived the endovascular procedure. Overall, the procedural results were as expected for the treatment of patients with aneurysms or ulcers of the descending thoracic aorta.

Clinical Utility Measures

The clinical utility results are presented in Table 6.1-14.

Table 6.1-14. Clinical utility measures

Clinical Utility Measure	Mean ± SD (n, range)[a]		
	Aneurysm	**Ulcer**	**All patients**
Duration of ICU stay (days)	2.6 ± 9.9 (n=88, 0 – 91)	0.8 ± 0.6 (n=20, 0 – 2)	2.3 ± 8.9 (n=108, 0 – 91)
Days to resumption of oral fluid intake	0.4 ± 0.6 (n=89, 0 – 3)	0.5 ± 0.8 (n=20, 0 – 3)	0.4 ± 0.6 (n=109, 0 – 3)
Days to resumption of regular diet	1.3 ± 1.1 (n=89, 0 – 6)	1.5 ± 3.1 (n=19, 0 – 14)	1.3 ± 1.6 (n=108, 0 – 14)
Days to resumption of bowel function	2.3 ± 1.5 (n=70, 0 – 8)	2.0 ± 2.1 (n=15, 0 – 8)	2.3 ± 1.6 (n=85, 0 – 8)
Days to ambulation	1.6 ± 1.3 (n=88, 0 – 9)	1.8 ± 2.2 (n=20, 0 – 10)	1.6 ± 1.5 (n=108, 0 – 10)
Days to hospital discharge	7.4 ± 19.6 (n=90, 1 – 185)	5.0 ± 5.3 (n=20, 1 – 19)	7.0 ± 17.8 (n=110, 1 – 185)

[a]Not all clinical utility measures were assessed for all 110 patients.

Devices Implanted

Table 6.1-15 shows the percent of patients who received each type of Zenith Alpha™ Thoracic Endovascular Graft component (proximal, distal, or distal extension) during the initial implant procedure. Also included is the graft diameter range implanted for each component type.

Table 6.1-15. Stent-graft component type deployed

Type	Percent Patients (number/total number)[a]			Graft Diameter Range (All Patients)
	Aneurysm Patients	Ulcer Patients	All patients	
Proximal component (nontapered or tapered)	100% (88/88)	100% (20/20)	100% (108/108)	28 to 46 mm
Distal component	37.5% (33/88)	0	30.6% (33/108)	32 to 46 mm
Ancillary component	27.3% (24/88)[b]	5.0% (1/20)	23.1% (25/108)	28 to 46 mm
Additional proximal component	13.6% (12/88)	5.0% (1/20)	12.0% (13/108)	
Distal extension	14.8% (13/88)[c]	0	12.0% (13/108)	

[a]Two aneurysm patients did not receive a device as the introduction system could not be successfully advanced; therefore, the denominator is 108, not 110.
[b]One patient received both an additional proximal component and a distal extension.
[c]Includes 12 patients who received 1 distal extension, and 1 patient who received 2 distal extensions.

Table 6.1-16 further summarizes the total number of components placed during the initial implant procedure.

Table 6.1-16. Total number of components placed during the initial implant procedure

Main Body Design	Percent Patients (number/total number)[a]		Percent Patients (number/total number)		
			1	2	3
One-piece (proximal only)	Aneurysm Patients	62.5% (55/88)	69.1% (38/55)	29.1% (16/55)	1.8% (1/55)
	Ulcer Patients	100% (20/20)	95.0% (19/20)	5.0% (1/20)	0
	All Patients	69.4% (75/108)	76.0% (57/75)	22.7% (17/75)	1.3% (1/75)
Two-piece (proximal and distal)	Aneurysm Patients	37.5% (33/88)	N/A	78.8% (26/33)	21.2% (7/33)
	Ulcer Patients	N/A	N/A	N/A	N/A
	All Patients	30.6% (33/108)	N/A	78.8% (26/33)	21.2% (7/33)

[a]Two aneurysm patients did not receive a device as the introduction system could not be successfully advanced; therefore, the denominator is 108, not 110.

Table 6.1-17 reports the sizes (diameters and lengths) of the nontapered proximal components used during the initial implant procedure.

Table 6.1-17. Diameters and lengths of nontapered proximal component (ZTLP-P) sizes used

Diameter (mm)	Length (mm)	n
28	132	2
	155	2
30	132	8
	155	2

Diameter (mm)	Length (mm)	n
32	132	7
	155	4
	201	5
34	137	3
	161	6
	209	2
36	137	10
	161	6
	209	1
38	142	7
	167	3
	217	6
40	142	2
	167	3
	217	1
42	121	3
	173	4
44	125	2
	233	1
46	179	4

Table 6.1-18 reports the sizes (diameters and lengths) of the tapered proximal components used during the initial implant procedure.

Table 6.1-18. Diameters and lengths of tapered proximal component (ZTLP-PT) sizes used

Diameter (mm)	Length (mm)	n
34	161	4
	209	1
36	161	7
	209	4
38	167	1
	217	3
42	173	5
44	179	1
46	179	1

Table 6.1-19 reports the sizes (diameters and lengths) of the distal components used during the initial implant procedure.

Table 6.1-19. Diameters and lengths of distal component (ZTLP-D) sizes used

Diameter (mm)	Length (mm)	n
32	160	4
	229	1
34	142	2
	190	1

Diameter (mm)	Length (mm)	n
36	142	3
	190	1
38	147	4
	197	5
40	147	1
42	152	6
44	157	3
46	157	2

Table 6.1-20 reports the size (diameters and lengths) of the ancillary components used during the initial implant procedure.

Table 6.1-20. Diameters and lengths of ancillary component sizes used

Diameter (mm)	Length (mm)	n
28	108	1
32	108	2
34	112	2
36	112	1
38	91	4
42	94	3
46	97	1

Safety Results

The analysis of safety was based on the 110 patients enrolled in the Zenith Alpha™ Thoracic Endovascular Graft pivotal study for the treatment of aneurysms/ulcers of the descending thoracic aorta. Table 6.1-21 presents the results of hypothesis testing for the primary safety endpoint (30-day freedom from MAEs). MAEs were defined as the following: 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.

Table 6.1-21. Results from primary safety hypothesis testing (MAE endpoint)

Performance Goal	30-day Freedom from MAE Rate	*P*-value	95% Confidence Interval	Performance Goal Met
80.6%	96.4% (106/110)	< 0.001	(91%, 99%)	Yes

The 30-day freedom from MAE rate was 96.4% for the present study, which met the performance goal of 80.6% ($p < 0.001$). Four patients experienced MAEs: 1 patient had a stroke (1040045), 2 patients required ventilation > 72 hours/reintubation (1030062, 1030041), and 1 patient had a stroke and required ventilation > 72 hours/reintubation (1040069).

Death, Rupture, Conversion and MAE

Table 6.1-22 provides the results from Kaplan-Meier analysis for freedom from death (all-cause and TAA-related), rupture, conversion and MAEs through 2 years. 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 CEC. There has been one TAA-related death (1040069) that occurred at 253 days post-procedure due to aspiration pneumonia, which the CEC had indicated was likely related to the severely debilitating stroke that the patient had suffered on the same day as the procedure. There has been one conversion to open surgical repair (1040073), which occurred at 330 days post-procedure due to aortoesophageal fistula.

Table 6.1-22. Kaplan-Meier estimates freedom from death (all-cause and TAA-related), rupture, conversion, and MAEs

Event	Parameter	30 Days			180 Days			365 Days			730 Days		
		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
	Cumulative events[b]	0	0	0	2	1	3	4	1	5	11	1	12
	Cumulative censored[c]	1	0	1	2	0	2	6	1	7	10	1	11
	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
	Standard error	0.000	0.000	0.000	0.016	0.049	0.016	0.023	0.049	0.020	0.037	0.049	0.032
TAA-related mortality	Number at risk[a]	89	20	109	86	19	105	80	18	98	69	18	87
	Cumulative events[b]	0	0	0	0	0	0	1[e]	0	1	1	0	1
	Cumulative censored[c]	1	0	1	4	1	5	9	2	11	20	2	22
	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
	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
Rupture	Number at risk[a]	89	20	109	86	19	105	80	18	98	69	18	87
	Cumulative events[b]	0	0	0	0	0	0	0	0	0	0	0	0
	Cumulative censored[c]	1	0	1	4	1	5	10	2	12	21	2	23
	KM estimate[d]	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Standard error	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Conversion	Number at risk[a]	89	20	109	86	19	105	80	18	98	69	18	87
	Cumulative events[b]	0	0	0	0	0	0	1[f]	0	1	1	0	1
	Cumulative censored[c]	1	0	1	4	1	5	9	2	11	20	2	22
	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
	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
MAE[g]	Number at risk[a]	85	20	105	81	19	100	74	18	92	60	18	78
	Cumulative events[b]	4	0	4	7	1	8	12	1	13	24	1	25
	Cumulative censored[c]	1	0	1	2	0	2	4	1	5	6	1	7
	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
	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

[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]Death due to aspiration pneumonia (1040069).
[f]Conversion due to aortoesophageal fistula, adjudicated by the CEC as procedure-related (1040073).

[g]MAEs were defined as the following: 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.

All Adverse Events

Table 6.1-23 presents the Kaplan-Meier estimates for freedom from adverse events according to organ system category.

Table 6.1-23. Kaplan-Meier estimates (freedom from morbidity, by category)

Category	Parameter	30 Days			180 Days			365 Days			730 Days		
		Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All
Access site/incision[a]	Number at risk[i]	84	19	103	78	18	96	72	17	89	62	17	79
	Cumulative events[j]	5	1	6	8	1	9	8	1	9	8	1	9
	Cumulative censored[k]	1	0	1	4	1	5	10	2	12	20	2	22
	KM estimate[l]	0.944	0.950	0.945	0.910	0.950	0.917	0.910	0.950	0.917	0.910	0.950	0.917
	Standard error	0.024	0.049	0.022	0.030	0.049	0.026	0.030	0.049	0.026	0.030	0.049	0.026
Cardiovascular[b]	Number at risk[i]	84	20	104	82	19	101	74	18	92	63	18	81
	Cumulative events[j]	5	0	5	5	0	5	7	0	7	8	0	8
	Cumulative censored[k]	1	0	1	3	1	4	9	2	11	19	2	21
	KM estimate[l]	0.944	1.000	0.955	0.944	1.000	0.955	0.921	1.000	0.935	0.907	1.000	0.924
	Standard error	0.024	0.000	0.020	0.024	0.000	0.020	0.029	0.000	0.024	0.032	0.000	0.026
Cerebrovascular/ neurological[c]	Number at risk[i]	86	20	106	83	19	102	76	18	94	66	18	84
	Cumulative events[j]	3	0	3	4	0	4	6	0	6	6	0	6
	Cumulative censored[k]	1	0	1	3	1	4	8	2	10	18	2	20
	KM estimate[l]	0.967	1.000	0.973	0.955	1.000	0.963	0.931	1.000	0.943	0.931	1.000	0.943
	Standard error	0.019	0.000	0.016	0.022	0.000	0.018	0.027	0.000	0.022	0.027	0.000	0.022
Gastrointestinal[d]	Number at risk[i]	88	19	107	81	18	99	76	17	93	66	17	83
	Cumulative events[j]	1	1	2	5	2	7	6	2	8	8	2	10
	Cumulative censored[k]	1	0	1	4	0	4	8	1	9	16	1	17
	KM estimate[l]	0.989	0.950	0.982	0.943	0.900	0.935	0.931	0.900	0.926	0.906	0.900	0.905
	Standard error	0.011	0.049	0.013	0.025	0.067	0.024	0.027	0.067	0.025	0.032	0.067	0.029

Category	Parameter	30 Days			180 Days			365 Days			730 Days		
		Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All	Aneur	Ulcer	All
Pulmonary[e]	Number at risk[i]	85	20	105	81	19	100	74	18	92	66	18	84
	Cumulative events[j]	4	0	4	5	0	5	6	0	6	8	0	8
	Cumulative censored[k]	1	0	1	4	1	5	10	2	12	16	2	18
	KM estimate[l]	0.955	1.000	0.964	0.944	1.000	0.954	0.931	1.000	0.944	0.905	1.000	0.923
	Standard error	0.022	0.000	0.018	0.024	0.000	0.020	0.027	0.000	0.022	0.032	0.000	0.026
Renal[f]	Number at risk[i]	86	20	106	79	19	98	73	18	91	64	18	82
	Cumulative events[j]	3	0	3	7	0	7	10	0	10	12	0	12
	Cumulative censored[k]	1	0	1	4	1	5	7	2	9	14	2	16
	KM estimate[l]	0.967	1.000	0.973	0.921	1.000	0.935	0.885	1.000	0.905	0.859	1.000	0.855
	Standard error	0.019	0.000	0.16	0.029	0.000	0.024	0.034	0.000	0.029	0.038	0.000	0.031
Vascular[g]	Number at risk[i]	85	20	105	80	18	98	71	17	88	55	16	71
	Cumulative events[j]	4	0	4	6	1	7	10	1	11	18	2	20
	Cumulative censored[k]	1	0	1	4	1	5	9	2	11	17	2	19
	KM estimate[l]	0.955	1.000	0.963	0.933	0.950	0.936	0.884	0.950	0.896	0.789	0.894	0.801
	Standard error	0.022	0.000	0.018	0.027	0.049	0.024	0.035	0.049	0.030	0.046	0.071	0.040
Miscellaneous/ other[h]	Number at risk[i]	59	13	72	43	10	53	33	9	42	26	9	35
	Cumulative events[j]	28	7	35	44	10	54	54	10	64	61	10	71
	Cumulative censored[k]	1	0	1	1	0	1	1	1	2	1	1	2
	KM estimate[l]	0.681	0.650	0.675	0.497	0.500	0.497	0.381	0.500	0.402	0.300	0.500	0.335
	Standard error	0.050	0.107	0.045	0.054	0.122	0.048	0.052	0.122	0.048	0.049	0.112	0.046

[a]Access site/incision events included: hematoma (n=5), hernia (n=1), infection (n=2), lymph fistula (n=0), pseudoaneurysm (n=0), seroma (n=1), and wound complication requiring return to operating room (n=0).
[b]Cardiovascular events included: cardiac arrhythmia (n=4), cardiac arrest (n=0), cardiac ischemia (n=1), congestive heart failure (n=1), myocardial infarction (n=3), and refractory hypertension (n=0).
[c]Cerebrovascular/neurological events included: paralysis (n=0), paraplegia (n=0), paraparesis > 30 days (n=1), spinal cord shock (n=0), transient ischemic attack (n=0), and stroke (n=5).
[d]Gastrointestinal events included: bleeding (n=4), bowel ischemia (n=2), infection (n=4), mesenteric ischemia (n=1), and paralytic ileus > 4 days (n=0).
[e]Pulmonary events included: COPD (n=1), hemothorax (n=0), pleural effusion (n=1), pneumonia (n=6), pneumothorax (n=0), pulmonary edema (n=0), pulmonary embolism (n=1), and pulmonary embolism involving hemodynamic instability or surgery (n=0).
[f]Renal events included: renal failure (n=4), UTI (n=6), serum creatinine rise > 30% above baseline resulting in a persistent value > 2.0 mg/dl (n=2).
[g]Vascular events included: aneurysm (n=11), aortobronchial fistula (n=1), aortoesophageal fistula (n=1), aortoenteric fistula (n=0), coagulopathy (n=1), deep vein thrombosis (n=0), dissection (n=3), embolism (n=2), hematoma (n=1), pseudoaneurysm (n=1), thrombosis (n=1), and vascular injury (n=5).
[h]Miscellaneous/other events included: hypersensitivity/allergic reaction (n=1), multi-organ failure (n=2), sepsis (n=2), and other (n=70).
[i]Number of patients at risk at the beginning of the interval.

[j]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.
[k]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.
[l]At end of interval.

Effectiveness Results

Table 6.1-24 presents the results of hypothesis testing for the primary effectiveness endpoint (12-month device success) for the Zenith Alpha™ Thoracic Endovascular Graft.

Table 6.1-24. Results from primary effectiveness hypothesis testing (device success endpoint)

Performance Goal	12-month Device Success Rate	*P*-value	95% Confidence Interval	Performance Goal Met
80.7%	92.7% (102/110)[a]	< 0.001	(86.2%, 96.8%)	Yes

[a]The performance goal was originally calculated with a 365-day cutoff for inclusion of events (e.g., secondary interventions) and the results in the present study were analyzed in the same fashion for consistency such that the 12-month device success rate was 95.5% (105/110) with a 95% confidence interval of 89.7%, 98.5%. However, there were 3 additional patients in the present study who had an endoleak detected at the 12-month follow-up and subsequently underwent secondary intervention > 365 days after the index procedure; therefore, a conservative analysis was performed that included these 3 additional patients as failures (as shown in the table).

The 12-month device success rate was 92.7% for the present study (using the conservative analysis shown in Table 6.1-24), which met the performance goal of 80.7% ($p < 0.001$). There were 5 patients who did not meet the effectiveness endpoint of 12-month device success (using the original 365-day cutoff for events), as follows. Two patients (1030014, 1030098) did not receive the device due to an inability to insert/advance the introduction system and were therefore technical failures. In patient 1030014 (87-year-old white female), the introduction system became lodged at the aortic bifurcation in the right common iliac artery despite attempts to increase the diameter of the iliac artery. In patient 1030098 (73-year-old white female), the index procedure was aborted due to difficulty inserting a dilator in the left limb of a previous aneurysm repair; the previous endovascular abdominal aortic aneurysm repair made the patient a poor candidate for a conduit. Three patients (1030017, 1030046, 1040073) experienced aneurysm growth greater than 5 mm at the 12-month follow-up, one of whom (1040073) also underwent conversion to open surgical repair 330 days post-procedure due to an aortoesophageal fistula. There were 3 additional patients who had endoleak detected at 12-month follow-up and subsequently underwent secondary intervention > 365 days after the index procedure (1030047, 1030072, 1030095). Sensitivity to missing data, including a worst-case analysis, was performed, and met the performance goal.

Device Performance

Table 6.1-25 presents changes in aneurysm size, as observed from the 30-day (baseline) measurement to each follow-up exam through 2 years (based on core laboratory evaluation). A total of 11 patients experienced aneurysm growth (> 5 mm) at one or more follow-up time points based on core laboratory analysis through 2 years. Aneurysm growth was associated with detectable endoleak in six patients, four of whom underwent secondary intervention. There was no detectable endoleak in the remaining five patients with aneurysm growth, two of whom had no change in aneurysm size (≤ 5 mm change compared to baseline) as of the last available follow-up without the need for secondary intervention. Among the three other patients with growth and no detectable endoleak, two required secondary intervention and one had growth at the last available follow-up; each growth was associated with an inadequate seal zone length (i.e., length < 20 mm) as well as graft undersizing. Each patient who had growth that did not resolve spontaneously or was not associated with a Type II endoleak was initially treated for an aneurysm using only a proximal component, underscoring the importance of adhering to the sizing guidelines in the Instructions for Use (IFU), both in terms of component diameter as well as component type and length, which includes the use of a two-component repair (proximal and distal component) when treating aneurysms.

Table 6.1-25. Change in aneurysm diameter/ulcer depth based on results from core laboratory analysis

Item	Percent Patients (number/total number)								
	Aneurysm			Ulcer			All		
	6-month	12-month	2-years	6-month	12-month	2-years	6-month	12-month	2-years
Increase (> 5 mm)	4.2% (3/72) [a,b,c]	4.2% (3/71) [a,c,d]	14.8% (9/61) [a,d,e-k]	0	0	0	3.3% (3/90)	3.4% (3/88)	12.0% (9/75)
Decrease (> 5 mm)	19.4% (14/72)	31.0% (22/71)	24.6% (15/61)	33.3% (6/18)	52.9% (9/17)	64.3% (9/14)	22.2% (20/90)	35.2% (31/88)	32.0% (24/75)
No change (≤ 5 mm)	76.4% (55/72)	64.8% (46/71)	60.7% (37/61)	66.7% (12/18)	47.1% (8/17)	35.7% (5/14)	74.4% (67/90)	61.4% (54/88)	56.0% (42/75)

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 6.1-30) to treat the unexplained aneurysm growth (i.e., no detectable endoleaks). 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.

[b]Patient 1040060 – The patient has not required 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).

[c]Patient 1040073 – The patient had a Type IIb endoleak, which was treated prior to the 12-month follow-up (Table 6.1-30).

[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.
[e]Patient 1040034 – The patient has not had a secondary intervention and core laboratory results indicate no growth at 3 years.
[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 6.1-26) and CEC-confirmed migration (Table 6.1-27). A secondary intervention was performed (ancillary component placement) on post-operative day 727 (Table 6.1-30) 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.
[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 6.1-26). 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.
[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-ups. A distal Type I endoleak (Table 6.1-26) has been identified in the patient at 2 years (previous endoleaks identified were Type II). Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing.
[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 6.1-26) and CEC-confirmed migration (Table 6.1-27). 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.
[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 and 2-year follow-ups (Table 6.1-26). A Type IIb endoleak was also identified at the 6-month and 12-month follow-ups. No secondary interventions have been performed to date. Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests a distal seal length < 20 mm.

Endoleaks classified by type, as assessed by the core laboratory at each exam period through 2 years, are reported in Table 6.1-26. In total, there were seven patients found to have a Type I (distal) endoleak and two patients found to have a Type III (nonjunctional) endoleak at one or more time points, two of which (one with Type I and one with Type III) had no evidence of the same endoleak at last available follow-up and without the patients having undergone secondary intervention. Endoleak in the other seven patients (five of which required secondary intervention) was associated with an inadequate seal zone length (i.e., length < 20 mm) and/or graft undersizing, which occurred following aneurysm treatment with only a proximal component in six of the patients, underscoring the

importance of adhering to the sizing guidelines in the IFU, both in terms of component diameter as well as component type and length, including the use of a two-component repair (proximal and distal components) when treating aneurysms.

Table 6.1-26. Endoleak based on results from core laboratory analysis

Type	Percent Patients (number/total number)											
	1-month			6-month			12-month			2-years		
	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)	8.5% (5/59)	0	6.8% (5/73)
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)	16.9% (10/59)	0	13.7% (10/73)
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
Proximal Type I	0	0	0	0	0	0	0	0	0	0	0	0
Distal Type I	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)	8.5% (5/59)[b,e,g-i]	0	6.8% (5/73)
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]	0	4.8% (4/83)	6.8% (4/59)	0	5.5% (4/73)
Type III	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
Type IV	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	1.7% (1/59)	0	1.4% (1/73)

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

[b]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 and 2-year follow-ups. A Type IIb endoleak was also identified at the 6-month and 12-month follow-ups. The patient also had aneurysm growth (Table 6.1-25). No secondary interventions have been performed to date. 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 aneurysm 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 6.1-30) and there was no endoleak detected at the 2-year follow-up.
[e]Patient 1030047 – The patient was treated at the time of the index procedure with a single proximal component. 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. The patient also had aneurysm growth (Table 6.1-25) and CEC-confirmed migration (Table 6.1-27). The patient underwent a secondary intervention (ancillary component placement) 727 days post-procedure (Table 6.1-30). 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 – The patient was treated at the time of the index procedure with a single proximal component. 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 6.1-30). 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 – 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 2-year follow-up. The patient also had aneurysm growth (Table 6.1-25) 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). 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 – 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-ups. A distal Type I endoleak has been identified in the patient at 2 years (previous endoleaks identified were Type II). The patient also had aneurysm growth (Table 6.1-25). Review of core laboratory measurements at first follow-up (relative to the location of actual graft placement) suggests graft undersizing.
[i]Patient 1040044 – The patient was treated at the time of the index procedure with a single proximal component. The patient also had aneurysm growth (Table 6.1- 25) and CEC-confirmed migration (Table 6.1-27) 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.

The results for migration through 2 years, as confirmed by the CEC, are provided in Table 6.1-27. There were three cases of CEC-confirmed migration (two also with aneurysm growth, distal Type I endoleak, and the need for secondary intervention), each of which was associated with an inadequate seal zone length (i.e., length < 20 mm) and/or graft undersizing and occurred following aneurysm treatment with only a proximal component, underscoring the importance of adhering to the sizing guidelines in the IFU, both in terms of component diameter as well as component type and length, including the use of a two-component repair (proximal and distal components) when treating aneurysms.

Table 6.1-27. Percent of patients (aneurysm and ulcer) with CEC-confirmed migration (date of first occurrence)

Item	Percent Patients (number/total number)		
	6-month	12-month	2-year
Migration (> 10 mm)	0% (0/94)	0% (0/92)	3.9% (3/77)[a,b,c]

[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 6.1-25), distal Type I endoleak (Table 6.1-26), and underwent a secondary intervention (Table 6.1-30). 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 6.1-25), a distal Type I endoleak (Table 6.1-26), 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

The results from core laboratory analysis for graft kink/compression through 2 years are summarized in Table 6.1-28.

Table 6.1-28. Core laboratory reports of graft kink/compression

Item	30-day	6-month	12-month	2-year
Kink/compression	0	0	0	1.3% (1/77)[a]

[a]Patient 0468761 – The patient had a kink in the proximal and distal components identified by the core laboratory on the 2-year CT scan. There were no clinical sequelae associated with the kink; at the 2-year follow-up, the aneurysm had decreased in size and the device was patent. The patient died prior to the next follow-up visit.

CEC-confirmed device integrity observations at each exam period through 2 years are summarized in Table 6.1-29.

Table 6.1-29. CEC-confirmed loss of device integrity

Finding	Percent Patients (number/total number)											
	30-day			6-month			12-month			2-years		
	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
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)	1.6% (1/63)[a]	0	1.3% (1/77)
Component separation	0	0	0	0	0	0	0	0	0	0	0	0

[a]Patient 1030069 – Patient had a report of a single stent fracture (of the second covered stent in the proximal device) seen on the 30-day, 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.

Tables 6.1-30 and 6.1-31 summarize the site-reported reasons for secondary intervention and types of secondary intervention, respectively.

Table 6.1-30. Site-reported reasons for secondary intervention (all patients)

Reason	0-30 Days	31-180 Days	181-365 Days	366-730 Days
Device migration	0	0	0	1[g]
Endoleak				
Type I proximal	0	0	0	0
Type I distal	0	0	0	3[d,g,h]
Type II	0	0	1[b]	0
Type III (graft overlap joint)	0	0	0	0
Type III (hole/tear in graft)	0	0	0	0
Type IV (through graft body)	0	0	0	1[i]
Unknown	0	0	0	0
Other	1[a]	0	1[c]	2[e,f]

[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 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.

Table 6.1-31. Types of secondary interventions

Type*	0-30 Days	31-180 Days	181-365 Days	366 – 730 Days
Percutaneous				
Ancillary component placed	0	0	1[b]	6[d-i]
Balloon angioplasty	0	0	0	1[d]
Coil embolization	0	0	0	0
Stent	0	0	0	0
Thrombectomy	0	0	0	0
Thrombolysis	0	0	0	0
Other	0	0	1[b]	0

Type*	0-30 Days	31-180 Days	181-365 Days	366 – 730 Days
Surgical				
Conversion to open repair	0	0	0	0
Surgical bypass procedure	0	0	0	0
Other	1[a]	0	0	0
Other	0	0	1[c]	0

*A patient may have had more than one treatment type.
[a-i]Refer to the footnotes in Table 6.1-30 for additional details.

Gender Subset Analysis

There was nearly an equal proportion of males (n = 64, 58.2%) and females (n = 46, 41.8%) enrolled in this study, allowing for further analysis of outcomes by gender. There was no significant difference in age between male (70.7 ± 9.9 years; 42 – 85 years) and female (74.3 ± 9.4 years; 44 – 92 years) patients. Furthermore, the access method used (cutdown vs. percutaneous vs. conduit) was not significantly different between male (56.3% cutdown, 43.8% percutaneous, 0% conduit) and female (71.7% cutdown, 26.1% percutaneous, 2.2% conduit) patients.

No significant differences between males and females with respect to primary safety and effectiveness endpoints were found. For the primary safety endpoint, the 30-day freedom from MAE rate was 96.9% (62/64) for males and 95.7% (44/46) for females. For the primary effectiveness endpoint, the 12-month device success rate was 96.9% (62/64) for males and 93.5% (43/46) for females. Overall, males and females treated with the Zenith Alpha™ Thoracic Endovascular Graft had similar outcomes, indicating the device is likely to be equally safe and effective for both males and females.

Summary

All but 2 patients received at least one proximal component, and approximately one-third of patients also received a distal component (i.e., a two-piece system), as compared to approximately two-thirds of patients in the previous study who were treated with a two-piece system. Therefore, a two-component repair was less often used in this study compared to the previous study, despite similar percentages of patients from both studies having been treated for aneurysms. The IFU for the Zenith Alpha™ Thoracic Endovascular Graft was therefore updated to emphasize the importance of a two-component repair when treating aneurysms given that the reports of growth, migration, and distal Type I endoleak tended to occur in only aneurysm patients who were treated using a single proximal component.

Two patients did not receive a device in this study due to an inability to advance/gain access to the target treatment site; 2 patients also did not receive a device in the previous study for similar reasons. In patients where access was gained (n = 108), all devices were deployed successfully in the intended location and all vessels were patent at the time of deployment. An access conduit was necessary for graft delivery in 0.9% of patients, and percutaneous access was used in 36% of patients.

There were no deaths within 30 days of endovascular repair. There was one TAA-related death within 365 days, resulting in a 99% freedom from TAA-related mortality at 1 year. There were no ruptures reported at any follow-up time period. One patient underwent conversion to open repair 330 days post-procedure due to an aortoesophageal fistula; the CEC adjudicated the event as related to the procedure. The patient survived the surgical repair and investigational device explant and has since exited the study. Patients experienced adverse events in each of the organ system categories.

A total of 11 patients experienced aneurysm growth (> 5 mm) at one or more follow-up time points based on core laboratory analysis through 2 years. Aneurysm growth was associated with detectable endoleak in six patients, four of whom underwent secondary intervention. There was no detectable endoleak in the remaining five patients with aneurysm growth, two of whom had no change in aneurysm size ($\leq$ 5 mm change compared to baseline) as of the last available follow-up without the need for secondary intervention. Among the three other patients with growth and no detectable endoleak, two required secondary intervention and one had growth at the last available follow-up; each growth was associated with an inadequate seal zone length (i.e., length < 20 mm) as well as graft undersizing.

The majority of endoleaks detected were Type II, and there were no proximal Type I or Type IV endoleaks at 24 months. In total, there were seven patients found to have a Type I (distal) endoleak and two patients found to have a Type III (nonjunctional) endoleak at one or more time points, two of which (one with Type I and one with Type III) had no evidence of the same endoleak at last available follow-up and without the patients having undergone secondary intervention. Endoleak in the other seven patients (five of which required secondary intervention) was associated with an inadequate seal zone length (i.e., length < 20 mm) and/or graft undersizing.

There were three cases of CEC-confirmed migration (two also with aneurysm growth, distal Type I endoleak, and the need for secondary intervention), each of which was associated with an inadequate seal zone length (i.e., length < 20 mm) and/or graft

undersizing. There was one report of loss of device integrity (a single stent fracture) within 24 months, but with no adverse clinical sequelae.

In total, nine patients required a secondary intervention within 24 months for the site reported reasons of left subclavian artery embolization with bypass (n=1), Type II endoleak (n=1), distal Type I endoleak (n=2), distal Type I endoleak and migration (n=1), Type IV endoleak (n=1), disease progression (n=1), and aortic dissection (n=2).

Both the safety (30-day freedom from MAEs) and effectiveness (12-month device success) hypotheses were met. Overall, the results provide a reasonable assurance of the safety and effectiveness of the Zenith Alpha™ Thoracic Endovascular Graft.

6.2. Summary of Supplemental Clinical Information

6.2.1. Longer-term Follow-up (> 2 years) – Aneurysm/Ulcer Pivotal Study

As of April 7, 2015 there were 34 patients eligible for follow-up beyond 2 years (as shown in Table 6.1-2). Three patient deaths have been reported > 730 days following endovascular repair (2 of which were CEC-adjudicated as not related to TAA-repair and 1 which the CEC was unable to adjudicate). There are no reports of rupture or conversion to open surgical repair > 730 days. One additional patient experienced aneurysm growth (> 5 mm) after 2 years, which was associated with an inadequate landing zone length. There were no new reports of migration or Type I or III endoleak beyond 2 years. One new stent fracture was identified at 3 years, without adverse clinical sequelae. Three patients have undergone reintervention beyond 2 years, each of which was described previously due to having exhibited aneurysm growth within 2 years (one patient also had distal Type I endoleak and migration within 2 years, while another also had distal Type I endoleak within 2 years).

6.2.2. Continued Access – Aneurysm/Ulcer Indication

The results from patients treated during the continued access investigation of the aneurysm/ulcer indication (n = 18) were consistent with the results described for the pivotal study cohort, including one patient with aneurysm growth and Type I endoleak (at 6 months) that was associated with graft undersizing following initial treatment of the aneurysm with only a proximal component. Additionally, a portion of the patients enrolled in the continued access investigation (n = 11) were treated with the rotation handle version of the introduction system, which successfully deployed the stent-graft in all cases, consistent with the deployment results based on bench testing.

6.2.3. European Post-market Survey – Delivery System with Rotational Handle

A post-market survey was implemented in Europe to gather additional supportive information regarding clinical performance of the rotation handle introduction system. Physician users in Europe were surveyed on the procedural performance of the rotation handle system beginning March 31, 2014. A total of 38 surveys were completed as of June 30, 2014. Table 6.2.3-1 summarizes the survey results.

Table 6.2.3-1. Results of European post-market survey

Survey Question	Response Percent (number/total number)	
Did the introduction system with the rotation handle successfully retract the release-wires without the use of the alternate sequence?	Yes	100% (38/38)
	No	0
Was the alternate sequence successful in retracting the release-wires?	Yes	Not applicable
	No	Not applicable
	Not applicable	100% (38/38)
Was the graft successfully deployed in the intended location?	Yes	97.4% (37/38)
	No	2.6% (1/38)[a]
Was the graft patent at the completion of the procedure?	Yes	100% (38/38)
	No	0

[a]Slight distal migration of a tapered proximal component was reported.

All grafts were successfully deployed in the intended location using the primary release sequence, as described in the IFU, with the exception of one report of a slight distal migration during deployment. The alternate release sequence, which is also described in the IFU and is intended to be used in situations in which deployment difficulties involving the handle are encountered, was not used in any case. Furthermore, all grafts were patent at the completion of the procedure and no unique findings were observed as compared to the results from the pivotal clinical studies. These results in combination with the results from the preclinical studies and uses of the introduction system with rotation handle during continued access provide a reasonable assurance of safety and effectiveness of the modifications that were made to the user interface since the time of enrollment completion in the pivotal clinical study.