# Annual Clinical Update

## Abstract

Cook is pleased to provide you with this clinical update on the Zenith® Fenestrated AAA Endovascular Graft, which was commercially approved by FDA on April 4, 2012. **Section I** provides an update on results from the long-term post-approval study for the Zenith® Fenestrated AAA Endovascular Graft as of March 02, 2016. The long-term study consists of 88 patients total, including the patients enrolled premarket (67 patients) and patients enrolled postmarket (21) with enrollment now complete. Follow-up through 5 years is ongoing. Survival from aneurysm-related mortality at 60 months is 97.3% thus far. To date, no death was found to be related to failure of a component of the device. There have been no ruptures or conversions to open surgical repair. Freedom from major morbidity at 60 months is 95.5% thus far. There have been no patients with Type I or Type III endoleak based on core laboratory analysis. There have been 4 reports of an increase in aneurysm size, all in conjunction with a Type II endoleak. There were 2 reports of migration, both in patients with evidence of disease progression at follow-up (without aneurysm pressurization); one patient had associated fenestration stent compression requiring secondary intervention. Three patients were noted to have fracture of a fenestrated stent. The first patient was noted to have fracture of a fenestration stent and the seal stent on the Zenith® Fenestrated AAA Endovascular Graft, neither of which resulted in endoleak, a clinical renal event, or the need for secondary intervention. This patient also exhibited disease progression at follow-up in the absence of aneurysm pressurization. The second patient with a fenestration stent fracture also did not have endoleak, a clinical renal event, or the need for secondary intervention. The third patient with fenestration stent fracture was found to also have renal artery occlusion, but has not required reintervention. The majority of patients who underwent reintervention following treatment with the Zenith® Fenestrated Graft AAA Endovascular Graft (11 of 21) did so for renal artery or device stenosis. **Section II** summarizes commercial experience. A total of 6,653 components have been sold in the US since April 4, 2012. A total of 2,265 components have been sold in the same time outside the US (OUS) – note: there are minor differences between Fenestrated devices available in the US and OUS (e.g., difference in graft diameter, number and location of stents relative to the graft material). There have been 90 procedural and follow-up complaints reported during this time. **Section III** summarizes the findings from explant analysis. To date, one explant has undergone analysis. **Section IV** is reserved for any new notes or general instructions to clinicians, of which there are none at this time beyond those already covered as part of the indications, warnings, and precautions from the Instruction for Use (IFU). **Section V** provides a brief summary of the indications, warnings, and precautions from the IFU.

## Device Description

The Zenith® Fenestrated AAA Endovascular Graft is a modular system consisting of three components, a proximal body graft, a distal bifurcated body graft, and one iliac leg. The graft modules are constructed of full-thickness woven polyester fabric sewn to self-expanding stainless steel Cook-Z® stents with braided polyester and monofilament polypropylene suture. These materials are identical to the materials used to construct the standard Zenith Flex® AAA Endovascular Graft, with the Zenith® Fenestrated AAA Endovascular Graft also having a nitinol wire ring around the small graft fenestrations.

Unlike the standard Zenith Flex® AAA Endovascular Graft, the Zenith® Fenestrated AAA Endovascular Graft has fenestrations or scallops in the graft material, which allow the proximal edge of graft material to be placed above the renal arteries while still permitting blood flow to vessels accommodated by the fenestrations or scallops. In order to account for anatomical variation, each proximal body graft is made to order for a specific patient. Ancillary endovascular components (proximal body extensions and distal leg extensions) are also available. Please refer to the IFU for a more detailed description of the components and the delivery system, as well as the indications, warnings, and precautions (also summarized in Section V).

## Introduction

One of the conditions of approval of the Zenith® Fenestrated AAA Endovascular Graft was to provide a clinical update to physician users annually. This update has been formatted in accordance with a template that was agreed upon by FDA, industry, and clinicians during a meeting at FDA in October 2008. Accordingly, the clinical update is comprised of the following sections: Clinical Study Experience (Section I); Worldwide Commercial Experience (Section II); Explant Analysis (Section III); Notes to Clinicians (Section IV); and Brief Summary of Indications, Warnings, and Precautions from IFU (Section V).

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# Section I – Clinical Study Experience

## Description of Study

The long-term follow-up study is a prospective, observational, single-arm study to evaluate the primary endpoint of 5-year aneurysm-related mortality in patients with aortic or aortoiliac aneurysms who were treated with the Zenith® Fenestrated AAA Endovascular Graft. Additional study endpoints include rupture, conversion, morbidity, device integrity, device patency, changes in aneurysm size, endoleak, migration, and secondary interventions. The study will also evaluate training plan effectiveness, as measured by the composite freedom from the following events at 30 days in up to the first 3 postmarket patients from each site: technical failure, loss of patency, rupture, secondary intervention, conversion, and Type I or III endoleak. The long-term study cohort consists of 88 total patients, including patients enrolled premarket (67) as well as patients enrolled postmarket (21). This update reflects data received as of March 2, 2016.

## Patient Availability

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

**Table 1: Follow-up Availability**

| | | Percent of Data Available[a] | | | Adequate Imaging to Assess the Parameter[b] | | | | Events Occurring Before Next Interval | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Follow-up Visit** | **Patients Eligible for Follow-up[c]** | **Clinical** | **CT** | **KUB (device X-ray)** | **Size Increase** | **Endoleak** | **Migration** | **Fracture** | **Death** | **Conversion** | **Lost to Follow-up (LTF) or Withdrawal** | **Refused Consent for 3-5 Year Follow-up[d]** | **Not Due for Next Visit** |
| Pre-discharge | 88 (0) | 100% (88/88) | 76.1% (67/88) | 78.4% (69/88) | N/A[e] | 69.3% (61/88) | N/A[e] | 84.1% (74/88) | 1 | 0 | 0 | N/A | 0 |
| 30-day | 87 (0) | 98.9% (86/87) | 97.7% (85/87) | 75.9% (66/87) | 73.6% (64/87) | 86.2% (75/87) | 94.3% (82/87) | 94.3% (82/87) | 2 | 0 | 2 | N/A | 0 |
| 6-month | 83 (2) | 94.0% (78/83) | 91.6% (76/83) | 78.3% (65/83) | 89.2% (74/83) | 83.1% (69/83) | 88.0% (73/83) | 90.4% (75/83) | 1 | 0 | 2 | N/A | 2 |
| 12-month | 78 (4) | 89.7% (70/78) | 88.5% (69/78) | 71.8% (56/78) | 83.3% (65/78) | 74.4% (58/78) | 85.9% (67/78) | 84.6% (66/78) | 2 | 0 | 2 | N/A | 9 |
| 24-month | 65 (2) | 89.2% (58/65) | 89.2% (58/65) | 78.5% (51/65) | 86.2% (56/65) | 69.2% (45/65) | 86.2% (56/65) | 87.7% (57/65) | 4 | 0 | 3 | 6 | 4 |
| 36-month | 48 (0) | 95.8% (46/48) | 95.8% (46/48) | 81.3% (39/48) | 91.7% (44/48) | 77.1% (37/48) | 93.8% (45/48) | 93.8% (45/48) | 0 | 0 | 1 | N/A | 0 |
| 48-month | 47 (6) | 80.9% (38/47) | 76.6% (36/47) | 70.2% (33/47) | 76.6% (36/47) | 55.3% (26/47) | 74.5% (35/47) | 78.7% (37/47) | 0 | 0 | 5 | N/A | 15 |
| 60-month | 27 (1) | 96.3% (26/27) | 85.2% (23/27) | 77.8% (21/27) | 81.5% (22/27) | 55.6% (15/27) | 81.5% (22/27) | 81.5% (22/27) | N/A | N/A | N/A | N/A | N/A |

[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] Number in parentheses indicates the number of patients without submitted data who are still eligible for follow-up.
[d] Initial cohort of 30 patients consented only for 2-year follow-up and therefore were asked to reconsent for 3 through 5 year follow-ups.
[e] Pre-discharge represents baseline for comparison at subsequent time points.

## AAA-Related Mortality

AAA-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).

Figure 1 and Table 2 show the Kaplan-Meier estimates for survival from aneurysm-related mortality. To date, no death was found to be related to failure of a component of the device.

**Figure 1: Freedom from AAA-Related Mortality**

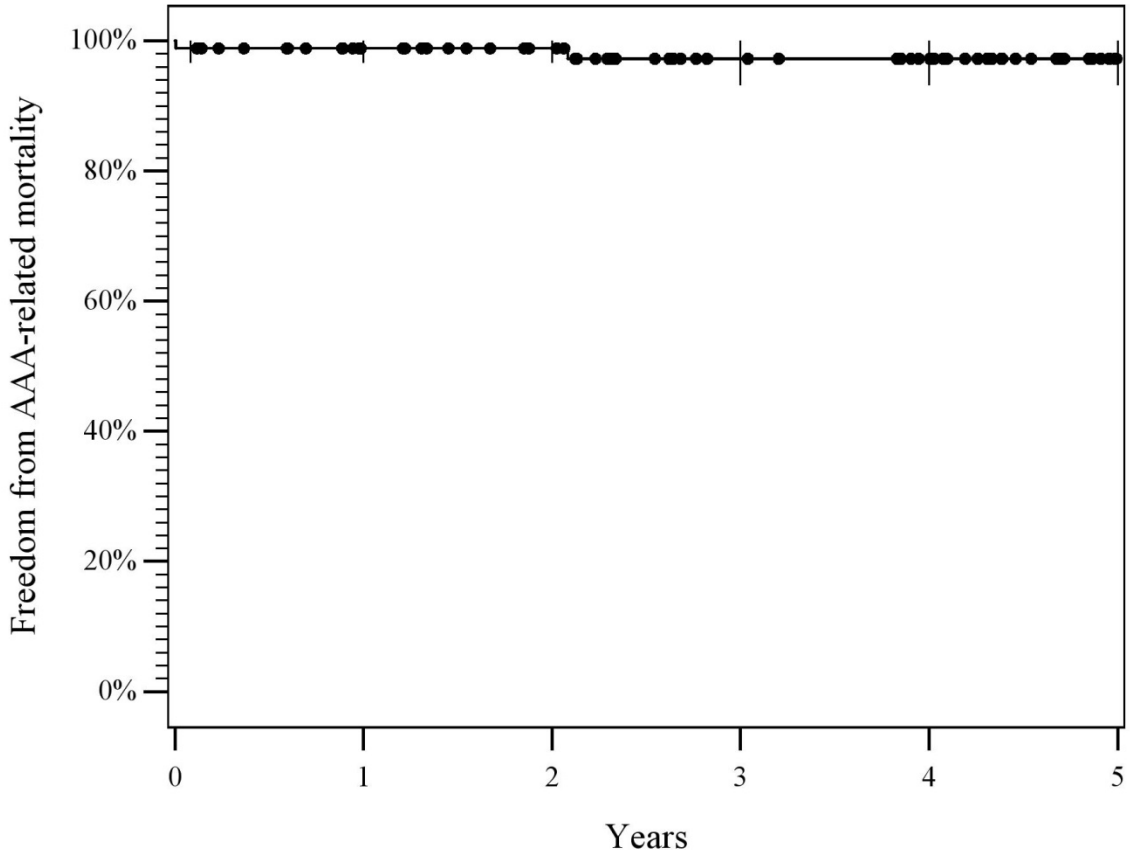


**Table 2: Kaplan-Meier AAA-Related Mortality Survival Estimates**

| Parameter | 30 Days | 365 Days | 730 Days | 1095 Days | 1460 Days | 1825 Days |
|---|---|---|---|---|---|---|
| Kaplan-Meier estimate | 98.9% | 98.9% | 98.9% | 97.3% | 97.3% | 97.3% |
| Standard error | 1.1% | 1.1% | 1.1% | 2.1% | 2.1% | 2.1% |
| Cumulative events | 1[a] | 1 | 1 | 2[b] | 2 | 2 |
| Cumulative censored | 0 | 14 | 23 | 37 | 43 | 68 |
| Number at risk | 87 | 73 | 64 | 49 | 43 | 18 |

[a] Patient 0911108: Bowel ischemia on postoperative day (POD 0) and death on (POD 2); CEC adjudicated death as AAA-related (procedure related).

[b] Patient 0111010: Death on POD 761 according to social security index; cause of death was unknown, therefore, the CEC was unable to adjudicate, but death was conservatively counted as AAA-related for purpose of Kaplan-Meier analysis.

## All-Cause Mortality

Figure 2 and Table 3 show the Kaplan-Meier estimates for freedom from all-cause mortality.

**Figure 2: Freedom from All-Cause Mortality**

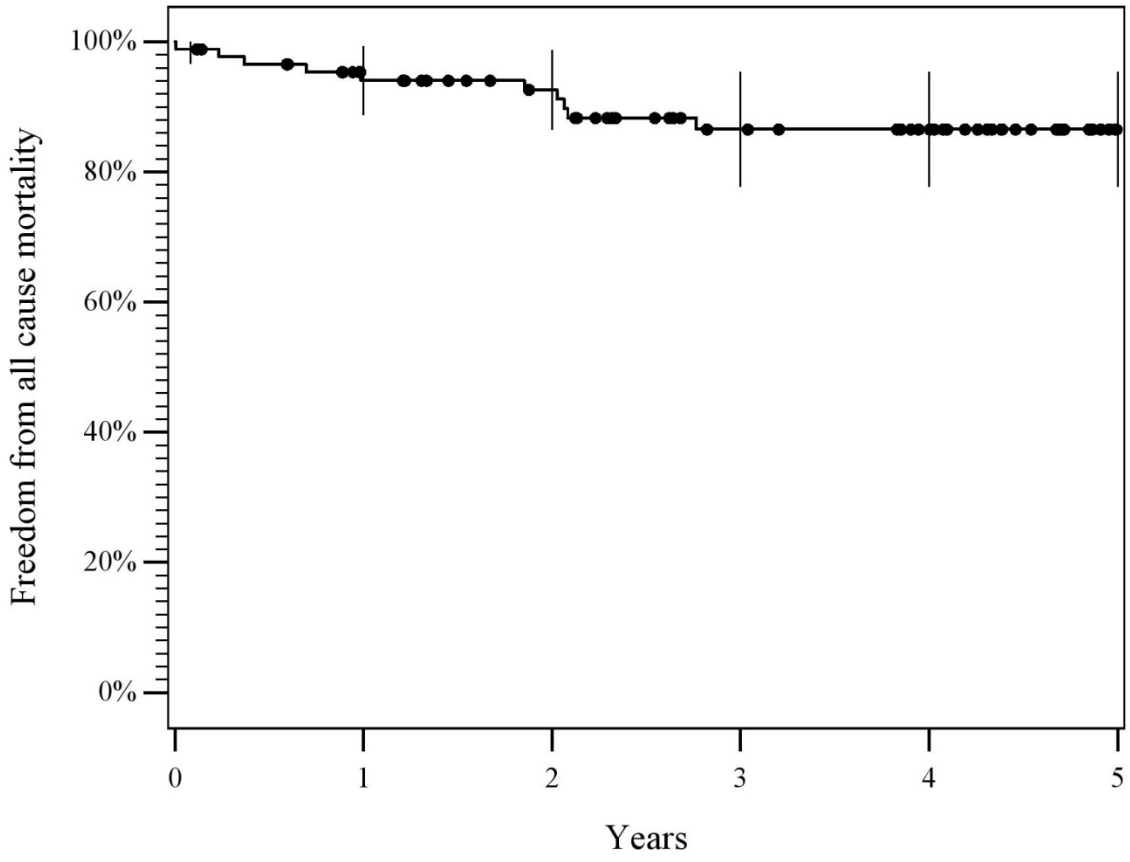


**Table 3: Kaplan-Meier All-Cause Mortality Survival Estimates**

| Parameter | 30 Days | 365 Days | 730 Days | 1095 Days | 1460 Days | 1825 Days |
|---|---|---|---|---|---|---|
| Kaplan-Meier estimate | 98.9% | 94.1% | 92.6% | 86.6% | 86.6% | 86.6% |
| Standard error | 1.1% | 2.7% | 3.1% | 4.5% | 4.5% | 4.5% |
| Cumulative events | 1 | 5 | 6 | 10 | 10 | 10 |
| Cumulative censored | 0 | 10 | 18 | 29 | 35 | 60 |
| Number at risk | 87 | 73 | 64 | 49 | 43 | 18 |

## Rupture

There have been no reports of rupture at any time point.

## Conversion

There have been no reports of conversion to open surgical repair at any time point.

## Major Morbidity

Figure 3 and Table 4 show the Kaplan-Meier estimates for freedom from major morbidity (Q-wave MI, bowel ischemia, paralysis, stroke, reintubation, renal failure requiring dialysis). Events determined by the CEC to be related to a pre-existing condition are not included. No new events have been reported after 30 days.

**Figure 3: Freedom from Major Morbidity**

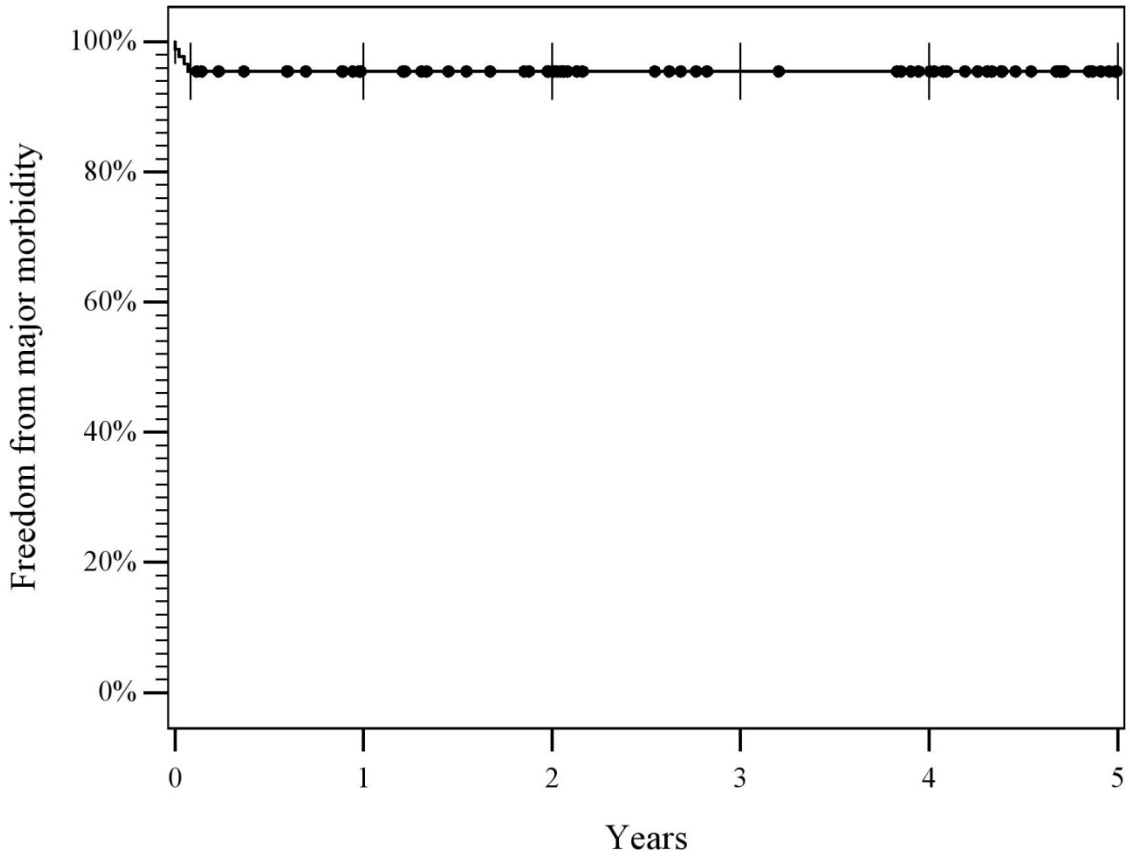

**Table 4: Kaplan-Meier Estimates for Freedom from Major Morbidity**

| Event | Parameter | 30 Days | 365 Days | 730 Days | 1095 Days | 1460 Days | 1825 Days |
|---|---|---|---|---|---|---|---|
| Major Morbidity (any) | Kaplan-Meier estimate | 95.5% | 95.5% | 95.5% | 95.5% | 95.5% | 95.5% |
| | Standard error | 2.2% | 2.2% | 2.2% | 2.2% | 2.2% | 2.2% |
| | Cumulative events | 4 | 4 | 4 | 4 | 4 | 4 |
| | Cumulative censored | 0 | 14 | 25 | 38 | 43 | 67 |
| | Number at risk | 84 | 70 | 59 | 46 | 41 | 17 |
| Q-wave MI | Kaplan-Meier estimate | 100% | 100% | 100% | 100% | 100% | 100% |
| | Standard error | 0% | 0% | 0% | 0% | 0% | 0% |
| | Cumulative events | 0 | 0 | 0 | 0 | 0 | 0 |
| | Cumulative censored | 0 | 8 | 17 | 21 | 25 | 43 |
| | Number at risk | 88 | 80 | 71 | 67 | 63 | 45 |
| Bowel ischemia | Kaplan-Meier estimate | 96.6% | 96.6% | 96.6% | 96.6% | 96.6% | 96.6% |
| | Standard error | 1.9% | 1.9% | 1.9% | 1.9% | 1.9% | 1.9% |
| | Cumulative events | 3[a,b,c] | 3 | 3 | 3 | 3 | 3 |
| | Cumulative censored | 0 | 8 | 17 | 21 | 25 | 42 |
| | Number at risk | 85 | 77 | 68 | 64 | 60 | 43 |
| Spinal cord ischemia/ Paralysis | Kaplan-Meier estimate | 100% | 100% | 100% | 100% | 100% | 100% |
| | Standard error | 0% | 0% | 0% | 0% | 0% | 0% |
| | Cumulative events | 0 | 0 | 0 | 0 | 0 | 0 |
| | Cumulative censored | 0 | 8 | 17 | 21 | 25 | 43 |
| | Number at risk | 88 | 80 | 71 | 67 | 63 | 45 |
| Stroke | Kaplan-Meier estimate | 100% | 100% | 100% | 100% | 100% | 100% |
| | Standard error | 0% | 0% | 0% | 0% | 0% | 0% |
| | Cumulative events | 0 | 0 | 0 | 0 | 0 | 0 |
| | Cumulative censored | 0 | 8 | 17 | 21 | 25 | 43 |
| | Number at risk | 88 | 80 | 71 | 67 | 63 | 45 |
| Re-intubation | Kaplan-Meier estimate | 100% | 100% | 100% | 100% | 100% | 100% |
| | Standard error | 0% | 0% | 0% | 0% | 0% | 0% |
| | Cumulative events | 0 | 0 | 0 | 0 | 0 | 0 |
| | Cumulative censored | 0 | 8 | 17 | 21 | 25 | 43 |
| | Number at risk | 88 | 80 | 71 | 67 | 63 | 45 |
| Renal failure requiring dialysis | Kaplan-Meier estimate | 98.9% | 98.9% | 98.9% | 98.9% | 98.9% | 98.9% |
| | Standard error | 1.1% | 1.1% | 1.1% | 1.1% | 1.1% | 1.1% |
| | Cumulative events | 1[d] | 1 | 1 | 1 | 1 | 1 |
| | Cumulative censored | 0 | 8 | 17 | 20 | 24 | 42 |
| | Number at risk | 87 | 79 | 70 | 67 | 63 | 45 |

[a] Patient 0211011: Bowel ischemia on (POD 25); recovered following treatment with IV fluids and antibiotics.
[b] Patient 0911108: Bowel ischemia on (POD 0) and death on (POD 2).
[c] Patient 1111102: Bowel ischemia on (POD 8); recovered following treatment with antibiotics.
[d] Patient 1350027: Renal failure requiring dialysis on (POD 18).

## Device Integrity

The percent of patients with device integrity findings at each follow-up time point based on the results of from core laboratory analysis is presented in Table 5. As indicated in the footnotes to the table, isolated observations of device integrity findings have been noted, where the need for associated reintervention was infrequent.

**Table 5: Percent of Patients with Device Integrity Findings Based on Core Laboratory Analysis (Date of First Occurrence)**

| Finding | Post-procedure | 1-month | 6-month | 12-month | 24-month | 36-month | 48-month | 60-month | Total Number of Patients |
|---|---|---|---|---|---|---|---|---|---|
| Stent-graft | | | | | | | | | |
| Barb separation | 0% (0/74) | 0% (0/82) | 1.3% (1/75)[a] | 1.5% (1/66)[b] | 1.8% (1/57)[c] | 0% (0/45) | 2.7% (1/37)[m] | 4.5% (1/22)[n] | 5 |
| Stent fracture (single) | 0% (0/74) | 0% (0/82) | 0% (0/75) | 3.0% (2/66)[d,j] | 0% (0/57) | 0% (0/45) | 0% (0/37) | 0% (0/22) | 2 |
| Stent fracture (multiple) | 0% (0/74) | 0% (0/82) | 0.00% (0/75) | 0% (0/66) | 0% (0/57) | 0% (0/45) | 0% (0/37) | 0% (0/22) | 0 |
| Component separation | 0% (0/74) | 0% (0/82) | 0% (0/75) | 0% (0/66) | 0% (0/57) | 0% (0/45) | 0% (0/37) | 0% (0/22) | 0 |
| Limb separation | 0% (0/74) | 0% (0/82) | 0% (0/75) | 0% (0/66) | 0% (0/57) | 0% (0/45) | 0% (0/37) | 0% (0/22) | 0 |
| Stent-to-graft separation | 0% (0/74) | 0% (0/82) | 0% (0/75) | 0% (0/66) | 0% (0/57) | 0% (0/45) | 0% (0/37) | 0% (0/22) | 0 |
| Other | 0% (0/74) | 0% (0/82) | 0% (0/75) | 0% (0/66) | 0% (0/57) | 0% (0/45) | 0% (0/37) | 0% (0/22) | 0 |
| Fenestration stent | | | | | | | | | |
| Fracture | 0% (0/74) | 0% (0/83) | 2.7% (2/75)[e,k] | 1.5% (1/66)[d] | 0% (0/57) | 0% (0/46) | 0% (0/36) | 0% (0/22) | 3 |
| Separation | 0% (0/74) | 0% (0/83) | 0% (0/75) | 0% (0/66) | 0% (0/57) | 0% (0/46) | 0% (0/36) | 0% (0/22) | 0 |
| Other | 0% (0/74) | 0% (0/83) | 4.0% (3/75)[f,g,h] | 1.5% (1/66)[i] | 0% (0/57) | 2.2% (1/46)[l] | 0% (0/36) | 0% (0/22) | 5 |

Note: Grey shading indicates 0 device integrity findings.

[a] Patient 0421003: Separation of a single fixation barb. No clinical sequelae related to the barb separation have been reported.

[b] Patient 0111009: Separation of a single fixation barb. No clinical sequelae related to the barb separation have been reported.

[c] Patient 0511008: Separation of two barbs. No clinical sequelae related to the barb separation have been reported, although radiographic migration (approximately 10 mm over 5 years) was observed and was likely due to longitudinal progression of disease with further aortic neck dilatation.

[d] Patient 0411001: Fracture of sealing stent (at the distal edge of the scallop fenestration) and left renal fenestration stent (uncovered, balloon-expandable 316L stainless steel biliary/iliac stent), but in a patient with progressive aneurysmal disease within and proximal to the treated segment, which likely resulted in uncharacteristic tension/loading of the stents. No subsequent renal events, endoleak, or secondary interventions were reported in this patient.

[e] Patient 0511010: Fracture of left renal fenestration stent (Zenith® Alignment Stent) not readily confirmed based on subsequent bench top CT imaging studies that showed the same appearance of fracture, but in an entirely intact stent.

[f] Patient 1111011: Deformation of right renal fenestration stent (Zenith® Alignment Stent) with no measurable graft movement > 5 mm. On POD 398, a secondary intervention was performed to treat worsening renal function and an angiogram was performed to attempt to cannulate the right renal artery; cannulation was unsuccessful. On POD 435, the patient had a hepatic artery to right renal artery bypass using reverse greater saphenous vein to treat an occlusion caused by the crushed right renal stent. This secondary intervention was successful.

[g] Patient 0511003: Slight compression of left renal fenestration stent (uncovered, balloon-expandable 316L stainless steel biliary stent) with no measurable graft movement > 5 mm. Due to stenosis, on POD 1539, the patient underwent angioplasty and stent placement. Restenosis was identified at the 60-month follow-up and a successful secondary intervention was performed on POD 1844. The CEC adjudicated this event as unrelated.

[h] Patient 0511007: Slight compression of the left renal fenestration stent (uncovered, balloon-expandable 316L stainless steel biliary stent) with no measurable graft movement > 5 mm and not requiring secondary intervention.

[i] Patient 0511006: Compression of the right renal fenestration stent (uncovered, balloon-expandable 316L stainless steel biliary stent) associated with graft migration (approximately 12 mm by 24 months) due likely to longitudinal progression of disease with further aortic neck dilatation. Due to stenosis, on POD 883, the patient underwent angioplasty and stent placement.
[j] Patient 0611101: Single stent fracture in the proximal graft, approximately at the level of the renal arteries, was observed on the 12-month KUB. No clinical sequelae related to the stent fracture have been reported.
[k] Patient 0211103: Fracture and deformity of left renal fenestration stent (Zenith® Alignment Stent). On POD 1124, the patient was reported to have an occlusion of a fenestrated renal vessel, but the occlusion is not being treated at this time (secondary intervention for stenosis on the right side was performed on POD 1582). The patient was noted to have creatinine rise greater than 2 mg/dl from baseline during two follow-up periods. The CEC adjudicated this event as AAA- related (procedure-related and device-related due to progression of the left renal artery stenosis to occlusion).
[l] Patient 1111102: Compression of left renal stent due to angulation. No other renal events were reported, and the patient has not required a secondary intervention for this event.
[m] Patient 0111017: Separation of one barb at 48 months. Barb separation was confirmed by the CEC, noted for the first time at 48 months following retrospective review of imaging.
[n] Patient 1111013: Separation of one barb observed at 60 months. Barb separation was confirmed by the CEC. No clinical sequelae related to the barb separation have been reported.

## Patency

The percent of patients with patency loss involving either the stent-graft or a vessel accommodated by a fenestration is provided in Table 6.

**Table 6: Percent of Patients with Loss of Patency Based on Core Laboratory Analysis or As Reported by the Site (Date of First Occurrence)**

| Post-procedure | 1-month | 6-month | 12-month | 24-month | 36-month | 48-month | 60-month |
|---|---|---|---|---|---|---|---|
| 0% (0/63) | 0% (0/77) | 2.8% (2/71)[a,b] | 3.4% (2/59)[c,d] | 0% (0/46) | 2.7% (1/37)[e] | 0% (0/27) | 0% (0/15) |

[a] Patient 0211008 had renal artery occlusion; the patient underwent secondary intervention, as described in Table 10.
[b] Patient 0911115 had accessory renal artery occlusion; no secondary intervention was performed.
[c] Patient 0611003 had renal artery occlusion; no secondary intervention was performed.
[d] Patient 1111011 had renal artery occlusion; the patient underwent secondary intervention, as described in Table 10.
[e] Patient 0211103 had renal artery occlusion and fenestration stent fracture. This patient had serum creatinine rise > 2.0 mg/dL and > 30% above baseline during two follow-up periods and no secondary intervention was performed for left renal occlusion.

## Change in Aneurysm Size

Table 7 reports the percent of patients with an increase (> 5 mm), decrease (> 5 mm), or no change (≤ 5 mm) in aneurysm diameter based on core laboratory analysis at each follow-up time point subsequent to pre-discharge, which represents baseline. Any patient with size increase and associated endoleak and/or requiring a secondary intervention is indicated by a footnote.

**Table 7: Percent of Patients with an Increase, Decrease, or No Change in Aneurysm Size Based on Core Laboratory Analysis**

| Item | 1-month | 6-month | 12-month | 24-month | 36-month | 48-month | 60-month |
|---|---|---|---|---|---|---|---|
| Increase (> 5mm) | 0% (0/64) | 0% (0/74) | 0% (0/65) | 0% (0/56) | 6.8% (3/44)[a,b,d] | 8.3% (3/36)[b,c,d] | 4.5% (1/22)[d] |
| Decrease (> 5mm) | 1.6% (1/64) | 52.7% (39/74) | 66.2% (43/65) | 75.0% (42/56) | 77.3% (34/44) | 80.6% (29/36) | 81.8% (18/22) |
| No change (≤ 5 mm) | 98.4% (63/64) | 47.3% (35/74) | 33.8% (22/65) | 25.0% (14/56) | 15.9% (7/44) | 11.1% (4/36) | 13.6% (3/22) |

[a] Patient 0511004 had persistent type II endoleak requiring secondary intervention on POD 1393, with no additional growth as of the 5-year follow-up.
[b] Patient 0111016 had a persistent Type II endoleak reported at the 3 and 4-year visits. A secondary intervention (coil embolization) was performed on POD 1490.
[c] Patient 0211010 had a persistent Type II endoleak requiring secondary intervention on POD 239, but the endoleak was still evident at the 48-month follow-up visit. The patient refused to return for the 5-year follow-up visit.
[d] Patient 0211011 had a persistent Type II endoleak at the 3, 4 and 5-year visits. A secondary intervention had not been performed as of the 5-year follow-up.

## Endoleak

Table 8 reports the percent of patients with endoleak (by type) at each follow-up time point based on the results of core laboratory analysis. No Type I or Type III endoleaks have been detected by the core laboratory.

**Table 8: Percent of Patients with Endoleak Based on Core Laboratory Analysis**

| Type | Pre-discharge | 1-month | 6-month | 12-month | 24-month | 36-month | 48-month | 60-month | Total Number of Patients |
|---|---|---|---|---|---|---|---|---|---|
| Any (new only) | 31.1% (19/61) | 6.7% (5/75) | 7.2% (5/69) | 3.4% (2/58) | 2.2% (1/45) | 0% (0/37) | 0% (0/26) | 0% (0/15) | 32 |
| Any (new and persistent) | 31.1% (19/61) | 24.0% (18/75) | 26.1% (18/69) | 27.6% (16/58) | 24.4% (11/45) | 21.6% (8/37) | 15.4% (4/26) | 6.7% (1/15) | |
| Multiple | 0% (0/61) | 0% (0/75) | 0% (0/69) | 0% (0/58) | 0% (0/45) | 0% (0/37) | 0% (0/26) | 0% (0/15) | 0 |
| Proximal Type I | 0% (0/61) | 0% (0/75) | 0% (0/69) | 0% (0/58) | 0% (0/45) | 0% (0/37) | 0% (0/26) | 0% (0/15) | 0 |
| Distal Type I | 0% (0/61) | 0% (0/75) | 0% (0/69) | 0% (0/58) | 0% (0/45) | 0% (0/37) | 0% (0/26) | 0% (0/15) | 0 |
| Type II | 29.5% (18/61) | 24.0% (18/75) | 23.2% (16/69) | 22.4% (13/58) | 17.8% (8/45) | 18.9% (7/37) | 15.4% (4/26) | 6.7% (1/15) | 30[a] |
| Type III | 0% (0/61) | 0% (0/75) | 0% (0/69) | 0% (0/58) | 0% (0/45) | 0% (0/37) | 0% (0/26) | 0% (0/15) | 0 |
| Type IV | 0% (0/61) | 0% (0/75) | 0% (0/69) | 0% (0/58) | 0% (0/45) | 0% (0/37) | 0% (0/26) | 0% (0/15) | 0 |
| Unknown | 1.6% (1/61) | 0% (0/75) | 2.9% (2/69) | 5.2% (3/58) | 6.7% (3/45) | 2.7% (1/37) | 0% (0/26) | 0% (0/15) | 6[a] |

Note: Grey shading indicates 0 endoleaks.
[a] Includes one patient who had a Type II endoleak at pre-discharge and an unknown endoleak type at 6, 12, 24, and 36 months; one patient who had a type II endoleak at pre-discharge, 1 month, and 6 months, and an unknown endoleak type at 24 months; and one patient who had an unknown endoleak type at 12 months and a Type II endoleak at 24 months; and one patient who had a Type II endoleak at 1 month and an unknown endoleak type at 6 months.

## Migration

Table 9 reports the percent of patients with CEC-confirmed radiographic migration (≥ 10 mm) or clinically significant migration (measurable movement of the stent-graft > 5 mm and development of a Type I endoleak or renal stenosis/occlusion with demonstrable deformation of the mating renal stent based on core laboratory analysis) at each follow-up time point (date of first occurrence).

**Table 9: Percent of Patients with CEC-Confirmed Migration (Date of First Occurrence)**

| Item | 1-month | 6-month | 12-month | 24-month | 36-month | 48-month | 60-month |
|---|---|---|---|---|---|---|---|
| Radiographic migration | 0% (0/82) | 0% (0/73) | 0% (0/67) | 1.8% (1/56)[a] | 0% (0/45) | 0% (0/35) | 4.5% (1/22)[b] |
| Clinically significant migration | 0% (0/82) | 0% (0/73) | 0% (0/67) | 1.8% (1/56)[a] | 0% (0/45) | 0% (0/35) | 0% (0/22) |

[a] Patient 0511006 had renal stenosis from associated stent compression (uncovered, balloon-expandable 316L stainless steel biliary stent) requiring secondary intervention. Longitudinal progression of disease with further aortic neck dilatation likely resulted in migration. There were no Type I or Type III endoleaks or increase in aneurysm size in this patient. The total amount of graft movement detected at the time of the clinically significant migration was approximately 12 mm (relative to the celiac artery).
[b] Patient 0511008 was without any associated renal stenosis requiring secondary intervention and additionally did not have any endoleak or increase in aneurysm size. Longitudinal progression of disease with further aortic neck dilatation likely resulted in migration. The total amount of graft movement was approximately 10 mm (relative to the celiac artery), which occurred over 60 months. No interventions have been performed for this patient.

## Secondary Interventions

Table 10 summarizes the site reported reasons for and types of secondary interventions.

**Table 10: Reasons for and Types of Secondary Intervention (as Reported by the Site)**

| Reason / Type | 0-30 Days | 31-365 Days | 366-730 Days | 731-1095 Days | 1096-1460 Days | 1461-1825 Days |
|---|---|---|---|---|---|---|
| Aneurysm rupture | 0 | 0 | 0 | 1 | 0 | 0 |
| Ancillary component | -- | -- | -- | q | -- | -- |
| Symptoms | 0 | 0 | 0 | 0 | 0 | 0 |
| N/A | -- | -- | -- | -- | -- | -- |
| Device/renal stenosis | 1 | 2 | 3 | 3 | 1 | 2 |
| Angioplasty/stenting | -- | b,c | g,h,i | h,k,o | l | n,t |
| Other | a | -- | -- | -- | -- | -- |
| Device migration | 0 | 0 | 0 | 1 | 0 | 0 |
| Angioplasty/stenting | -- | -- | -- | h | -- | -- |
| **Device separation** | 0 | 0 | 0 | 0 | 0 | 0 |
| N/A | -- | -- | -- | -- | -- | -- |
| **Occlusion** | 0 | 1 | 1 | 0 | 0 | 0 |
| Bypass | -- | d | j | -- | -- | -- |
| **Device kink** | 0 | 0 | 0 | 0 | 0 | 0 |
| N/A | -- | -- | -- | -- | -- | -- |

| Reason Type | 0-30 Days | 31-365 Days | 366-730 Days | 731-1095 Days | 1096-1460 Days | 1461-1825 Days |
|---|---|---|---|---|---|---|
| **Infection** | 0 | 0 | 0 | 0 | 0 | 0 |
| N/A | -- | -- | -- | -- | -- | -- |
| **Type I proximal** | 0 | 0 | 0 | 1 | 2 | 0 |
| Angioplasty/stenting | -- | -- | -- | p | -- | -- |
| Coil embolization | -- | -- | -- | -- | p | -- |
| Angiogram/catheterization | -- | -- | -- | -- | p | -- |
| **Type I distal** | 0 | 1 | 0 | 0 | 0 | 1 |
| Coil embolization | -- | u | -- | -- | -- | a |
| Ancillary component | -- | -- | -- | -- | -- | a |
| **Type IIA (vessel perfusion)** | 0 | 3 | 0 | 0 | 1 | 1 |
| Coil embolization | -- | e,f,u | -- | -- | -- | r |
| Ligation | -- | -- | -- | -- | m | -- |
| **Type IIB (vessel perfusion)** | 0 | 0 | 0 | 0 | 0 | 0 |
| N/A | -- | -- | -- | -- | -- | -- |
| **Type III (graft overlap joint)** | 0 | 0 | 0 | 0 | 0 | 0 |
| N/A | -- | -- | -- | -- | -- | -- |
| **Type IV (through graft body)** | 0 | 0 | 0 | 0 | 0 | 0 |
| N/A | -- | -- | -- | -- | -- | -- |
| **Unknown type** | 0 | 0 | 0 | 1 | 1 | 0 |
| Ancillary component | -- | -- | -- | q | -- | -- |
| Angioplasty/stenting | -- | -- | -- | -- | s | -- |
| **Other** | 0 | 0 | 1 | 1 | 1 | 0 |
| Angiogram/catheterization | -- | -- | j | -- | m | -- |
| Angioplasty/stenting | -- | -- | -- | k | -- | -- |

[a] Patient 0211011: Angiography revealed that the right renal artery was severely stenosed. Attempted cannulation was unsuccessful, as the fenestration stent (Zenith® Alignment Stent) was not flared at the time of the initial implant procedure. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment. The CEC adjudicated this event as AAA-related. The site reported a distal Type I endoleak and on POD 1746, the patient underwent successful coil embolization and ancillary component placement.

[b] Patient 0111008: The patient experienced right renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent). On POD 238, the patient was successfully treated with angioplasty and additional stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment. Follow-up demonstrated a patent renal artery. The CEC adjudicated this event as AAA-related.

[c] Patient 0111014: The patient experienced bilateral renal artery stenoses (uncovered, balloon-expandable 316L stainless steel biliary stents). On POD 245, the patient was successfully treated with angioplasty and additional stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment. Follow-up demonstrated a patent renal artery. The CEC adjudicated this event as AAA-related.

[d] Patient 0211008: An angiogram demonstrated an occluded left renal artery with proximal compression of the left renal stent (uncovered, balloon-expandable 316L stainless steel biliary/renal stent). On POD 222, the patient was successfully treated with iliorenal bypass. Compression without evidence of migration was due likely to suboptimal deployment of the renal stent into the middle/upper portion of the fenestration. The CEC adjudicated this event as AAA-related.

[e] Patient 0211010: The patient experienced persistent Type II endoleak. On POD 239, the patient was successful treated with by coil embolization.

[f] Patient 0611101: The patient experienced Type II endoleak, causing an enlarged AAA. On POD 224, the patient was successfully treated with coil embolization and NBCA glue.

[g] Patient 0211007: The patient experienced right renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary/renal stent). On POD 406, the patient was successfully treated by angioplasty and additional stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment. The CEC adjudicated this event as AAA-related.

[h] Patient 0111017: Renal ultrasound demonstrated a right renal artery stenosis (Zenith® Alignment Stent). On POD, 427, the patient was successful treated with stent placement. The CEC adjudicated the event as

AAA- related. Left renal artery in-stent stenosis (Zenith® Alignment Stent) was noted on POD 840 and the patient was successfully treated with stent placement. The core laboratory retrospectively noted separation of one barb observed at 48 months. Barb separation was confirmed by the CEC, noted for the first time at 2 years; however, the site determined the stenosis was due to device migration. The CEC adjudicated the stenosis to be AAA-related and due to the site-reported migration (no migration according to the core laboratory).

[i] Patient 1211109: The patient experienced left renal artery stenosis (Zenith® Alignment Stent). On POD 382, the patient was successfully treated with angioplasty and stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment. Core laboratory analysis of the procedural angiogram noted a patent graft and stented, patent renal arteries with no evidence of an endoleak. CEC adjudicated this event as AAA- related.

[j] Patient 1111011: An angiogram demonstrated an occluded right renal artery (Zenith® Alignment Stent). On POD 398, a percutaneous attempt to cannulate the right renal artery stent was unsuccessful. On POD 435, the patient, who had a right renal stent that was crushed at the orifice of the vessel, was successfully treated with surgical common hepatic artery to right renal artery bypass performed using reverse greater saphenous vein to treat a crushed right renal stent at the orifice of vessel. The CEC adjudicated this event as AAA-related.

[k] Patient 0511006: The patient experienced right renal artery stent compression and subsequent stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent). On POD 883, the patient was successfully treated with angioplasty and stent placement. Compression of the fenestration stent associated with graft migration (approximately 12 mm by 24 months) was likely due to longitudinal progression of disease with further aortic neck dilatation. Intra-operative angiogram demonstrated a patent right renal artery at the end of the procedure. The CEC adjudicated this event as AAA-related.

[l] Patient 0511009: The patient experienced bilateral renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent). On POD 1400, the patient was successfully treated with bilateral angioplasty and stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment. The CEC adjudicated this event AAA-related.

[m] Patient 0511004: The patient underwent diagnostic angiogram for suspected Type IIA and Type III endoleaks, which were not detected at on POD 1137. On POD 1393, the patient underwent additional intervention, which involved laparotomy, a suture ligation of the inferior mesenteric artery (IMA), and exploration of the aneurysm sac to successfully remedy the Type II endoleak with aneurysm growth.

[n] Patient 0511003: The patient experienced left renal artery stenosis (uncovered, balloon-expandable 316L stainless steel biliary stent) from slight compression of the fenestration stent (with no measurable graft movement > 5 mm). On POD 1539, the patient was successfully treated with angioplasty and stent placement. The CEC adjudicated this event as AAA-related.

[o] Patient 0611105: The patient experienced right renal artery stenosis (Zenith® Alignment Stent). On the POD 743, the patient was successfully treated with angioplasty and stent placement. No evidence of graft migration or stent deformation, suggesting the stenosis may have resulted from local thrombus formation or intimal hyperplasia within the stented segment. The CEC adjudicated this event as AAA-related.

[p] Patient 0911006: Based on the site assessment of the imaging, the 2-year CT scan revealed a proximal Type I endoleak at the junction of the Zenith® Fenestrated AAA Endovascular Graft and the Zenith® Alignment Stent; however, core laboratory analysis noted an endoleak of unknown type. On the POD 1003, the patient was successfully treated with a balloon-expandable covered stent. Based on the site assessment of the imaging, the 3 year CT scan revealed a Type I proximal endoleak; however, the core laboratory analysis noted an endoleak of unknown type. On POD 1100, the attempt at coil embolization of the vessel that supplied the endoleak was not successful, as access to the vessel could not be obtained. On POD 1142, the patient underwent a third, successful secondary intervention involving coil embolization (1142 days post-procedure) of the vessel thought to be contributing to the observed endoleak.

[q] Patient 1211106: The patient experienced an unknown type endoleak with reported infrarenal aneurysm sac rupture. On POD 1031, the patient underwent successful placement of two additional components in the iliac arteries and bilateral limb dilatation with a CODA balloon. A repeat angiography revealed no endoleak. The core laboratory noted a Type II endoleak, but no aneurysm sac rupture. The CEC adjudicated this event as AAA-related, and stated they did not consider this to be an aneurysm rupture, but rather a new endoleak.

[r] Patient 0111016: The patient experienced a Type II endoleak. On POD 1490, the patient underwent successful coil embolization.

[s] Patient 1411101: The patient experienced an unknown type endoleak. On POD 1188, the patient underwent successful angioplasty and covered stent placement in the left renal artery.
[t] Patient 0211103: The patient experienced renal stenosis (Zenith® Alignment Stent). On POD 1582, the patient underwent successful renal angioplasty.
[u] Patient 1350021: The patient experienced Type I and Type II endoleaks according to the site. On POD 263, the patient underwent successful coil embolization.

## Summary

Patient enrollment is complete and patient follow-up is ongoing. Survival from aneurysm-related mortality at 60 months is 97.3% thus far. To date, no death was found to be related to failure of a component of the device. There have been no ruptures or conversions to open surgical repair. Freedom from major morbidity at 60 months is 95.5% thus far.

There have been no patients with core laboratory-reported Type I or Type III endoleaks. There have been 4 reports of an increase in aneurysm size, all in conjunction with a Type II endoleak (the origin of the endoleak was IMA in 1 patient, lumbar artery and the lumbar artery in 1 patient; the origin was not further specified in 2). There have been 2 reports of migration, both in patients with evidence of disease progression at follow-up (without aneurysm pressurization); 1 patient had associated fenestration stent compression with stenosis requiring secondary intervention. Three patients were noted to have fracture of a fenestrated stent. The first patient was noted to have fracture of a fenestration stent as well as the seal stent on the Zenith® Fenestrated Graft, but neither fracture resulted in endoleak, a clinical renal event, or the need for secondary intervention. This patient also exhibited disease progression at follow-up in the absence of aneurysm pressurization. The second patient with a fenestration stent fracture was identified without endoleak, subsequent clinical renal event or need for secondary intervention. The third patient with fenestration stent fracture was found to also have renal artery occlusion, but has not required a secondary intervention.

The majority of patients who underwent reintervention following treatment with the Zenith® Fenestrated AAA Endovascular Graft (11 of 21) did so for renal artery or device stenosis, which was associated with stent compression in 2 patients (one of whom also had graft migration, as noted above). Two patients with renal artery occlusion also underwent secondary intervention; both occlusions were associated with stent compression. Careful patient selection, device planning/sizing, as well as device placement during the initial procedure (e.g., ensuring deployment of the fenestration stent in the lower portion of the graft fenestration), are important to mitigate the potential for reintervention due to stent compression that may result in either renal artery stenosis or occlusion.

# Section II – Worldwide Commercial Experience

The Zenith® Fenestrated AAA Endovascular Graft was commercially available in the US soon after marketing approval was granted by FDA on April 4, 2012. The device has been commercially available OUS since 2002 – note: there are minor differences between Fenestrated devices available in the US and OUS (e.g., difference in graft diameter, number and location of stents relative to the graft material).

As shown in Table 11, a total of 6,653 components in the US (2,265 components OUS) have been distributed between April 4, 2012 and March 31, 2016.

**Table 11: Total Number of Zenith® Fenestrated AAA Endovascular Graft Components Sold Between April 4, 2012 and March 31, 2016**

| Component | US Number Sold | OUS Number Sold |
|---|---|---|
| ZFEN-P (proximal component) | 3,446 | 1,156 |
| ZFEN-D (distal component) | 3,207 | 1,109 |
| **Total** | **6,653** | **2,265** |

Cook evaluates product performance from this commercial experience based on complaint reporting systems throughout the world. Table 12 summarizes the complaints associated with the procedure and follow-up of patients during US commercial experience with the Zenith® Fenestrated AAA Endovascular Graft between April 4, 2012 and March 31, 2016. All complaints received related to the Zenith® Fenestrated AAA Endovascular Graft are processed through the Customer Relations Department at William A. Cook Australia Pty Ltd, the manufacturer of the device, and are subject to a quality engineering and clinical review. Based on this review, additional information may be requested from the user facility at which the event occurred. The Quality Engineering group makes a final determination of root cause, and the findings are evaluated for any necessary corrective action.

**Table 12: Complaints from Commercial Experience with the Zenith® Fenestrated AAA Endovascular Graft Between April 4, 2012 and March 31, 2016**

| Complaint | Quantity |
|---|---|
| Death Early (≤ 30 days) | 7[a] |
| Death Late (> 30 days) | 1[b] |
| Other vessel rupture/dissection | 1 |
| Iliac artery perforation | 1 |
| Renal occlusion/renal infarction/reduced kidney perfusion/kidney loss | 5 |
| Occlusion | 4 |
| Renal stent collapse | 1 |
| Renal stent kink | 2 |
| Secondary intervention – placement of additional stents | 1 |
| Femoral-femoral bypass surgery and/or conversion to unplanned aortouni-iliac procedure | 1 |
| Type I endoleak (proximal) | 9 |
| Type I endoleak (distal) | 1 |
| Type I endoleak (proximal/distal not specified) | 1 |
| Type II endoleak | 2 |
| Type III endoleak | 10 |
| Unspecified endoleak Type | 3 |
| Barb separation | 2 |
| Aborted procedure – graft damaged prior to use | 1 |
| Trigger wire difficulty (removal) | 3 |
| Difficult visualization | 1 |
| Difficulty cannulating | 1 |
| Difficulty removing dilator tip | 1 |
| Wire not advancing | 3 |
| Incorrect alignment/loading/design | 4 |
| Valve leakage/blood leaking from delivery system | 24 |
| **Total** | **90** |

[a] Reported causes of death included: heparin-induced thrombocytopenia resulting in paralysis; stroke; aortic rupture during ballooning; bowel ischemia; death three days following conversion to open repair during initial implant procedure; cardiac issues, renal failure, and bowel ischemia; and iliac artery perforation and open repair.

[b] Death two days following secondary intervention to treat rupture due to retraction of limbs.

# Section III – Explant Analysis

This section summarizes the findings from explant analysis of grafts from clinical study and worldwide commercial experience. Explant analysis is performed using high resolution X-ray, gross examination, histological microscopy, and scanning electron microscopy. The assessment is focused upon graft material wear, suture wear, and metal component fatigue. While damage from surgical instruments during explantation is sometimes obvious in explant analysis, it is not always possible to determine whether observations occurred before explantation or whether the explantation process contributed to, or caused, the observations.

### Clinical Study Experience

There have been no explants analyzed from the multi-center study.

There has been one explant analyzed from non-commercial experiences outside the multi-center study. The implantation time was approximately 170 days. The explant was taken at the time of autopsy from a patient who died following a myocardial infarction. The explant analysis identified barb separations, suture break (green), and cuts in the graft material – there was no evidence of stent fracture or graft material wear.

### Worldwide Commercial Experience

There have been no explants analyzed from worldwide commercial experience.

### Summary

There has been one explant analyzed. While damage from surgical instruments during explantation was sometimes obvious, it was not always possible to determine whether observations occurred before explantation or whether the explantation process contributed to, or caused, the observations. Nonetheless, routine imaging follow-up remains important to detect any potential compromises in device integrity that might require reintervention.

# Section IV – Notes to Clinicians

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

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

## Indications

The Zenith® Fenestrated AAA Endovascular Graft is indicated for the endovascular treatment of patients with abdominal aortic or aortoiliac aneurysms having morphology suitable for endovascular repair, including:

- Adequate iliac/femoral access compatible with required introduction systems
- Nonaneurysmal infrarenal aortic segment (neck) proximal to the aneurysms with:
  - Length ≥ 4 mm and unsuitable for a non-fenestrated graft
  - Diameter ≤ 31 mm and ≥ 19 mm
  - Angle < 45 degrees relative to long axis of aneurysm
  - Angle < 45 degrees relative to axis of suprarenal aorta
- Ipsilateral iliac artery fixation site > 30 mm in length and between 9 – 21 mm in diameter
- Contralateral iliac artery distal fixation site > 30 mm in length and between 7 – 21 mm in diameter

## Warnings and Precautions

Patient Selection

- Key anatomic elements that may affect successful exclusion of the aneurysm include severe proximal neck angulation (> 45 degrees for infrarenal neck to axis of AAA or > 45 degrees for suprarenal neck relative to the immediate infrarenal neck); short proximal aortic neck (< 4 mm); greater than 10% increase in diameter over 15 mm of proximal aortic neck length; and circumferential thrombus and/or calcification at the arterial implantation sites, specifically the proximal aortic neck and distal iliac artery interface. Irregular calcification and/or plaque may compromise the fixation and sealing of the implantation sites. Necks exhibiting these key anatomic elements may be more conducive to graft migration.
- Patients with recurrent aortic aneurysmal disease or with disease above the renal arteries may be prone to further aortic dilation in the renal/visceral segment, which could compromise device integrity/fixation.

Implant Procedure

- Inaccurate placement and/or incomplete sealing of the Zenith® Fenestrated AAA Endovascular Graft within the vessel may result in increased risk of endoleak, migration, or inadvertent occlusion of the renal or internal iliac arteries. Renal artery patency must be maintained to prevent/reduce the risk of renal failure and subsequent complications. It is recommended that all vessels accommodated by a small fenestration be stented in order to secure positive alignment of the graft fenestration with the vessel origin.

Note: Refer to the IFU for complete warnings and precautions