FDA Panel Questions (Draft)

Cordis's INCRAFT AAA Stent Graft System

June 12, 2018

Question #1: Transrenal Stent Fractures

The bare transrenal stent contributes to the fixation of the endovascular graft to the abdominal aorta. To date, 10% of INSPIRATION study subjects (19/190) have been identified with at least one stent strut fracture in the bare transrenal stent, resulting in a complete discontinuation in a stent strut. Seven of the 19 subjects (7/190, 3.7%) have had multiple fractures identified, 5 of which had fracture propagation (i.e., additional points of complete breaks in the continuity of the stent strut) noted at subsequent follow-up visits. The sponsor states that there have been no clinical sequelae associated with the observation of stent fracture(s) to-date. One subject was implanted prophylactically at the index procedure with a commercially available aortic cuff in addition to the INCRAFT device. This subject was identified with 8 transrenal stent fractures in the INCRAFT device and a Type 1a endoleak. The Medical Monitor stated that the Type 1a endoleak was likely not associated with the fractures as the aortic bifurcate component has only migrated 1.6 mm from its position at 1-month follow-up visit.

As length of follow-up increases in the clinical study, additional stent fractures and fracture propagations are being reported. As no specific patient population and/or characteristics have been identified as more likely to experience a fracture, all subjects may be at-risk for developing a transrenal stent fracture and subsequently may be at-risk for device migration, Type I endoleak, aneurysm expansion, aortic rupture, and/or death in the long-term. Cordis completed acute bench testing to provide insight into the migration resistance of the implant in the presence of fracture; however, it is not clear how these results translate to the clinic due to limitations in extrapolating bench testing to clinical conditions.

As noted in the INSPIRATION study, 18 of the 19 subjects with transrenal stent fractures were first identified by the Core Lab and not the investigational sites, suggesting that patients treated with the INCRAFT device may experience fractures that would not be detected by their following physicians.

Table: Transrenal Stent Fractures

	1-month	6-month	1-year	2-year	3-year	4-year	5-year
# of subjects w/imaging adequate to assess fracture	183	172	163	144	132	108	38
# of subjects newly identified with at least 1 fracture[&]	-	3	5	2	3	4	2
Cumulative # of subjects with a fracture[$$]	-	3	8	10	13	17	19
Cumulative # of fractures[&&]	-	7	14	22	26	31	**38**

Visit windows are defined based on imaging windows: Procedure (day 0), 1 Month (1 - 90 days), 6 Months (91 - 270 days), 1 Year (271 – 540 days), 2 Years (541 - 900 days), 3 Years (901 - 1260 days), 4 Years (1261 - 1620 days), and 5 Years (1621 - 1980 days).
$$ - Subjects with fractures identified will continue to be included in the numerator and denominator for later time points.
& - Number of subjects newly identified with at least 1 fracture indicates those subjects that were not previously reported as having at least 1 transrenal stent fracture
&& - Cumulative number of total fractures observed – once a fracture is reported, it will continue to be reported for later time points

- *Please comment on the following:*
    - *Please comment on whether the lack of clinical sequelae reported to-date (e.g., implant migration, Type I endoleaks, perforation) and acute migration resistance bench testing are sufficient to mitigate the concerns for long-term clinical sequelae associated with the observed fracture rate.*
    - *Standard imaging evaluation by physicians is unlikely to detect fractures. Please comment on whether fracture detection would be needed for appropriate follow-up of patients treated with the INCRAFT device, given the high rate of fractures that were identified during the clinical study. Alternatively, would standard follow-up to evaluate aneurysm exclusion, device position, and aneurysm size be sufficient, particularly as the fractures have yet to be associated with clinical sequelae.*

Question #2: Aneurysm expansion

Twenty-nine (29) subjects (15.3%) have been observed with aneurysm expansion in the study to-date. Three (3) aneurysm expansions (3/29, 10.34%) were deemed likely attributable to a Type I endoleak. One aneurysm expansion (1/29, 3.45%) was attributed to endotension. Twenty-five (25) of the 29 aneurysm expansions were deemed likely attributable to Type II endoleaks, which are caused by retrograde flow from patent branch arteries.

One hundred and nine (109) Type II endoleaks were identified in 101 subjects in the study to-date (101/190, 53.2%). Therefore, 24.8% of subjects with a Type II endoleak (25/101) were observed with aneurysm expansion. It is difficult to ascertain if Type II endoleaks can be attributed to the device or the

individual patient anatomy. However, there have been high rates of aneurysm expansion observed in this study that are associated with Type II endoleaks, indicating that treatment with the INCRAFT device has not prevented aneurysm growth in these subjects. While there have not been any ruptures reported in the study to-date, the aneurysm sac is pressurized and subjects are at risk for rupture.

Aneurysm size increase has been observed in approximately 16% of study subjects in previous endovascular graft studies through 5-years. Previous endovascular graft studies (as noted in the annual clinical updates and Summary of Safety and Effectiveness Documents of commercially available endovascular grafts) have observed early rates of Type II endoleaks (41%) with the rates decreasing over the 5-years of follow-up. The majority of aneurysm expansions were attributed to Type II endoleaks.

Table: Aneurysm Expansion

	6-Month	1-Year	2-Year	3-Year	4-Year	5-Year	Total Subjects**
Number of Subjects with Imaging Adequate to Assess Aneurysm Size Change	176	173	155	142	112	42	
Change in Aneurysm Size*							
Increase > 5 mm							
Total New[$]	-	-	11	13	4	1	29
Persistent	-	-	0	10	19	8	
Total (*New + Persistent)*	-	-	11	23	23	9	
	(0%)	(0%)	(7.1%)	(16.2%)	(20.5%)	(21.4%)	

Visit windows are defined based on imaging windows: 6 Months (91 - 270 days), 1 Year (271 - 540 days), 2 Years (541 - 900 days), 3 Years (901 - 1260 days), 4 Years (1261 - 1620 days), and 5 Years (1621 - 1980 days).

* - New and Persistent row results present the number of subjects with an event. Total row results present the number of subjects with an event (percent of total subjects with adequate imaging to assess aneurysm size change) by study visit.

Please comment on the following:

- *Please comment on the possible reasons for the observed rate of Type II endoleaks observed in the INSPIRATION study, for example, could the permeability of the graft material or the amount of wall motion contribute to the development of Type II endoleaks.*
- *Aneurysm expansion represents a failure of the aneurysm treatment. Please comment on how subjects who experience aneurysm expansion in the presence of a Type II endoleak should be considered when evaluating the effectiveness of the device.*

Question #3: Benefit-Risk Analysis

In addition to the observations of transrenal stent fractures and aneurysm expansion, the sponsor has reported effectiveness-related events including device occlusions, other patency-related events, and Type 1 endoleaks. These effectiveness-related events, as well as the associated secondary interventions to address these events should be taken into consideration in the benefit-risk analysis.

Occlusions & Patency-Related Events: Device occlusions and other patency-related events have been observed in the study to-date, including two subjects with complete occlusions of the aortic bifurcate component and both iliac limbs, 1 subject with bilateral limb occlusion, 7 subjects with single limb occlusion, 16 subjects with 18 stent graft stenoses observed in the iliac limbs, and 1 subject with limb kink. These observations have been noted within 1-year and in longer term follow-up. Although caution should be applied in directly comparing rates of events between endovascular graft studies, the frequency of patency-related events during follow-up is not consistent with those reported for other endovascular graft IDE studies (as noted in annual clinical updates, Instructions for Use, and Summary of Safety and Effectiveness documents), particularly the occlusions within 1 year of follow-up (7/189, 3.7% as compared to approximately 1% in the other studies).

Significant secondary interventions were completed to address the device occlusions and stenoses. The secondary interventions included conversion to open repair (2), fem-fem bypass (4), axillo-bifemoral bypass (1), relining of the INCRAFT device with competitor limbs (1), placement of stents (18 stents placed), angioplasty (1), and other adjunctive catheter-based procedures (10). Please note that multiple procedures may have been completed in a single intervention to address an event. Compared to other endovascular graft studies, the rate of secondary interventions completed to address a patency-related events for the INCRAFT (7.9%, 15/190) is higher than what has been reported for other studies (i.e., rates from 2-5%).

Type 1 Endoleaks: Seven (7) subjects were identified with a Type 1a endoleak, which is an endoleak that arises at or from the aortic sealing zone of the endovascular graft. Five (5) subjects underwent secondary intervention to resolve the endoleak, which includes the following: coil embolization (2), placement of commercially available aortic cuff (2), adjunctive EndoAnchors (2), placement of commercially available aortic cuff and chimney (1), adjunctive stent (1), and placement of EndoAnchors (1). Please note that multiple procedures may have been completed in a single intervention to address an event.

Three (3) subjects were identified with Type 1b endoleaks, which is an endoleak that arises at or near one of the iliac seal zones of the endovascular graft. One (1) subject with a Type 1b endoleak was

attributed to proximal limb migration. All 3 subjects underwent a secondary intervention, namely placement of additional stent grafts to resolve the endoleak.

The frequency of Type Ia and Ib endoleaks during follow-up seems to be higher than the reported rate for other endovascular graft IDE studies (i.e., 5.3% as compared to 0 – 2%); however, reported rates at specific follow-up visits for other commercially available devices have approached the over-all rate for the INSPIRATION study (as noted in annual clinical updates and Summary of Safety and Effectiveness documents).

The INSPIRATION study met its pre-defined primary safety and effectiveness endpoints evaluated at 30-days and 1-year, respectively. The results show that there is a low rate of aneurysm-related mortality and safety-related events. However, rates of effectiveness-related events such as transrenal stent fractures, device occlusions and patency-related events, aneurysm expansion, and Type I endoleaks are higher than usually observed in the clinical studies of other commercially available devices (as noted in the annual clinical updates, Instructions for Use, and Summary of Safety & Effectiveness documents). These effectiveness-related observations and events have been reported through both the acute follow-up (i.e., within 1-year) as well as the 5-year follow-up.

Table: Type I Endoleaks, Occlusions, & Patency-Related Events

	1-month	6-months	1-year	2-years	3-years	4-years	5-years	Total
# of subjects with data for that visit	189	182	177	162	148	129	45	
Occlusions								
Complete Occlusion *(aortic bifurcate & both iliac limbs)*	-	1	-	-	1	-	-	2
Occlusion of one or both iliac limb	-	3	3	1	-	1	-	8
Stenosis								
Partial stenosis *(aortic bifurcate and one iliac limb)*	-	-	-	-	-	-	1	1
Stenosis of one or both iliac limbs	-	4	8*	1*	3	1	-	15*
Kink								
Limb Kink	-	-	-	-	1	-	-	1

Total Occlusions & Patency-Related Events		*6*	*11*	*2*	*5*	*2*	*1*	***24***
Endoleaks[$$]								
Type 1a	-	-	3	3	-	1	-	7 (7)[#]
Type 1b	-	-	-	1	2	-	-	3 (3)

*Two subjects had unilateral limb stenosis at the 6-month time point and bilateral limb stenosis at a later time point (one at 1 year, one at 2 years); therefore, these subjects are not counted in the total for stenosis of one iliac limb

$$ - Endoleak rows denote new endoleaks identified during the follow-up interval. Total column presents the number of subjects with one or more endoleak (total number of endoleaks).

@@ - Total column reflects the total from the 1-month follow up visit through 5-years.

- *Based on the clinical data presented from the INSPIRATION study including the effectiveness-related observations noted in both the acute and long-term follow-up, please discuss the probable benefits and the probable risks of the INCRAFT device .*
- *Please comment on whether the proposed labeling is acceptable or whether modifications to sections such as the warnings/precautions or follow-up recommendations are recommended to minimize the risks that have been identified during the study.*

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Question #4: Proposed Post-Approval Study (PAS)

The sponsor has proposed to conduct a multi-center, prospective, open label, observational study. The primary objective of this study is to validate the safety and effectiveness of the INCRAFT AAA Stent Graft System in subjects with AAA requiring endovascular repair in routine clinical practice. In addition to long-term follow up of the INSIGHT study subjects (n=150), the study will enroll approximately 150 *de novo* subjects at study sites in the US. Enrolled subjects will be followed at 30 days, 1 year and annually through 5-years post index procedure.

Please comment on whether any additional study objectives, design features, or surveillance are recommended (e.g., modifications to the protocol to identify patients at risk of having the events discussed).

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