Panel Question 1

Two radiographic success elements were included in the “absence of major implant or procedure related complications” subcomponent of the primary composite endpoint defined in the IDE protocol. Both the Superion® (88.9%) and X-STOP® (86.1%) cohorts had similar results at 24 months for this subcomponent; in other words, 11.1% of Superion® subjects and 13.9% of X-STOP® subjects experienced a major implant or procedure related complication. However, the majority of failures in the Superion® cohort were due to spinous process fractures (n=31 at any time), while the failures in the X-STOP® cohort were primarily due to migrations (n=16) and dislodgements (n=20). Spinous process fractures (n=17 at any time) also occurred in the X-STOP® group. Please discuss the potential clinical impact of the different types of radiographic failure modes (i.e., spinous process fracture, migration, dislodgement), as well as the appropriateness of comparing them in determining radiographic success, and consequently, overall success.
Panel Question 2

During the course of the clinical study, the patient incidence of spinous process fractures observed in the Superion® and X-STOP® cohorts were 16.3% (31/190) and 8.5% (17/201), respectively. At 24 months, 32.3% (10/31) of the Superion® fractures and 41.2% (7/17) of the X-STOP® fractures exhibited signs of healing as described by the sponsor. In addition, the sponsor provided an analysis of ZCQ, ODI, VAS Leg, and VAS Back scores to support their conclusion that most of the spinous process fractures in both groups were asymptomatic.

a) Please discuss the clinical significance of the observed spinous process fractures, particularly given that interspinous process devices rely upon intact spinous processes to exert their treatment effect.

b) Please discuss the analysis presented to assess the correlation between spinous process fractures and effectiveness (i.e., ZCQ, ODI, VAS Leg, and VAS Back scores) outcomes at 24 months with particular focus on whether the analysis is adequate to determine the clinical significance of the observed spinous process fractures.
Panel Question 2 cont.

c) The diagnosis of spinous process fractures in this clinical trial were made by plain radiographs, and when comparing the treatment groups there was a disproportionate discrepancy between the investigators (Investigational Arm = 13, Control Arm = 10) and core lab (Investigational Arm = 31, Control Arm = 17) in identifying the number of spinous process fractures. Recent literature suggests that spinous process fractures related to interspinous process devices are under-recognized, and recommends the use of CT scans for a more accurate diagnosis (Kim et al., *The Spine Journal*, 2012). Please discuss the utility of CT scans as compared to plain radiographs in the diagnosis and classification of spinous process fractures after treatment with an interspinous process device, as well as in the assessment of bony healing of fractures that are identified. In addition, please discuss the most appropriate time point(s) for conducting these imaging studies.
Panel Question 3

Overall success of the Superion® device as compared to the control device (X-STOP®) was evaluated based on a primary composite endpoint consisting of: clinically significant improvement in 2/3 domains of the Zurich Claudication Questionnaire (ZCQ), no additional surgeries at the index level(s), no major implant or procedure related complications, and no confounding treatments (e.g. epidural injections or rhizotomies). This composite endpoint, as suggested by the FDA during review of the original IDE application, includes effectiveness measurements, safety measurements, and takes into account potential risks. Overall success for the Superion® modified Intent-to-Treat (ITT) cohort (52.7%) as compared to the X-STOP® mITT cohort (50.2%) was demonstrated to be non-inferior at 24 months, per the IDE protocol reviewed and approved by FDA.
Panel Question 3 cont.

a) Considering the patient population defined in P140004, and the intent of the Superion® device, please discuss the adequacy of the primary composite endpoint and the timepoint at which non-inferiority was tested (24 months).

b) Please discuss the overall clinical success rates (in both the Superion® and X-STOP® groups) in the context of expected clinical success rates for commonly used treatments for the patient population defined in this study.
Panel Question 4

In May of 2008, the Agency approved the Superion® IDE clinical trial using a PMA approved device (X-STOP®) as the control. Subsequently, as described above, overall success for the Superion® as compared to the X-STOP® was demonstrated to be non-inferior at 24 months. The Agency is aware of literature which has been published on interspinous process spacer devices including randomized, controlled, clinical trials (Moojen, *BMJ*, 2013; Moojen, *European Spine Journal*, 2015; Strömqvist, *Spine*, 2013), which suggest that decompression alone (the “gold standard” to treat lumbar spinal stenosis) results in comparable effectiveness outcomes compared to treatment with an interspinous process device alone, although use of an interspinous process device is associated with a higher reoperation rate. In addition, the Agency is aware of recent literature that suggests patients with degenerative spondylolisthesis should be considered as a distinct sub-population of spinal stenosis patients (Pearson, *Spine*, 2010), and the use of interspinous process devices to treat patients with degenerative spondylolisthesis is controversial (Kabir, *Spine*, 2010). Please comment on whether the literature referenced above is a fair representation of your current understanding of treatments available for this patient population and whether or not the findings are relevant to the device under discussion today. If so, please discuss the impact, if any, of this literature on the interpretation of the results of the Superion® study (e.g., study design, study endpoints, determination of benefit risk, device labeling, etc.). Please note that your feedback may also be useful to the clinical trial design of future interspinous process spacers.
Reminder

• The discussion of a PAS prior to FDA determination of product approvability should not be interpreted to mean FDA is suggesting that the product is safe and effective.

• The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for product approval.

• The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk/benefit balance.
Panel Question 5

If the Superion® device is deemed approvable by the FDA, the sponsor has proposed a post approval study to continue following the IDE subjects for up to 5 years, as well as an additional “actual conditions of use” post approval study which would enroll new subjects. Please discuss the adequacy of the sponsor’s proposed post approval study plans for the evaluation of the safety and effectiveness of the Superion® device in the post-market setting. In your discussion, please specifically address the following:
**Panel Question 5**

a) The proposed new cohort post approval study is powered to demonstrate that Superion® performance is not clinically inferior in the new Superion® cohort as compared to the pivotal IDE Superion® cohort based on a comparison of the primary endpoint at 24 months. The proposed secondary objective of the new cohort study is to compare clinical outcomes in subjects implanted with the Superion® device to clinical outcomes in subjects treated with surgical decompression at 24 months post operatively. Please discuss the clinical importance of these two objectives, and discuss the most clinically relevant primary objective of the new cohort post approval study.
Panel Question 5

b) Within the current outline for the long term follow-up of the IDE cohort, it is unclear whether CT scans will be done to evaluate spinous process fractures in the Superion® and X-STOP® groups. In addition, the proposed new cohort post approval study states that CT scans will be done at 24 months only in symptomatic Superion® subjects. Please discuss the role of CT scans in evaluating subjects (in both the Superion® and X-STOP® treatment groups) for spinous process fractures in order to assess the long term safety profile of the Superion® device. Please specifically discuss the most appropriate timepoints for CT evaluation in order to identify all spinous process fractures, as well as whether there should be different algorithms in symptomatic and asymptomatic subjects. If different algorithms are recommended, please discuss the specific criteria that should be used to define “symptomatic” subjects.
Panel Voting Question 1

The VertiFlex® Superion® InterSpinous Spacer (ISS) is indicated for those patients with impaired physical function who experience relief in flexion from symptoms of leg/buttock/groin pain, numbness, and/or cramping, with or without back pain. Is there a reasonable assurance that the VertiFlex® Superion® ISS is safe for the indication for use as treatment for pain, numbness, and/or cramping in the legs (neurogenic intermittent claudication) secondary to a diagnosis of moderate lumbar spinal stenosis, with or without Grade 1 spondylolisthesis?
Panel Voting Question 2

The VertiFlex® Superion® ISS is indicated for those patients with impaired physical function who experience relief in flexion from symptoms of leg/buttock/groin pain, numbness, and/or cramping, with or without back pain. Is there a reasonable assurance that the VertiFlex® Superion® ISS is effective for use in patients who meet the criteria specified in the proposed indications?
Panel Voting Question 3

The VertiFlex® Superion® ISS is indicated for those patients with impaired physical function who experience relief in flexion from symptoms of leg/buttock/groin pain, numbness, and/or cramping, with or without back pain. Do the probable benefits of the VertiFlex® Superion® ISS outweigh the probable risks for use in patients who meet the criteria specified in the proposed indications?