5.3.4 Extension Study

Overview of Extension Study 06-UPLF-01

Protocol 06-UPLF-01 (also called the "extension study" or "follow-up study") was designed as a prospective collection of longer-term data on the patient population from pivotal study S01-01US (IDE G990028), and was conducted to expand the information regarding efficacy, particularly with regard to radiographic assessment of fusion, as well as the longer-term safety of OP-1 Putty in uninstrumented PLF as compared to autograft.

As described in section 1.2.1, it was discovered during the data analyses for pivotal study S01-01US that the plain film technique used to assess fusion at 24 months was inadequate for assessing the medial bone formation associated with OP-1 Putty. Medial bone formation is not easily detected on plain films because the lumbar vertebrae are retroperitoneal structures such that overlying abdominal organs, bowel, bowel contents, and bowel gas can easily obscure bone formation. In addition, the medial location of the OP-1 Putty-directed bone formation may be obscured by the lateral border of the vertebral body. CT scans had not been collected at 24 months in the pivotal study. Therefore, protocol 06-UPLF-01 prospectively collected follow-up CT scans on as many patients as possible in both arms of the pivotal uninstrumented PLF trial (S01-01US). The mean length of follow-up post-study procedure for the entire population was 4.4 years (range 3.7 to 5.5 years).

In addition to undergoing a CT scan, all patients enrolled in this study were brought back for re-assessments of all clinical parameters including ODI assessments, neurological testing, surgical retreatment assessment (i.e., revision, removal, supplemental fixation or reoperation intended to promote fusion) at the original treated level, as well as flexion and extension plain films for evaluation of angulation and translation at the same time point as the CT scans. Stryker Biotech also obtained serum for assessment of OP-1 immunogenicity at the follow-up visit in patients who had been antibody positive at their last recorded visit for S01-01US. The safety data gathered in pivotal study S01-01US was further supported by longer-term safety data at 36+ months, which included occurrence of new serious adverse events since last study visit, new medical history and physical findings since last study visit, and review of adverse events that had been ongoing at the close of pivotal study S01-01US. Collection of the same clinical and radiographic data as pivotal study S01-01US, with the addition of a CT scan, permits the data from extension study 06-UPLF-01 to be analyzed in a manner consistent with the Statistical Analysis Plan for pivotal study S01-01US.

CT scans taken at the 36+ month interval in the extension study were assessed for the presence of bone using a prospective, multi-reviewer, blinded radiographic assessment protocol designed to minimize bias. Flexion/extension films were taken at the 36+ month interval to allow measurement of angulation and translation at the same time point. Great care was taken to standardize the prospective CT scan including the imaging algorithm and a standard imaging protocol. The 36+ month radiographic data was read by 3 spine surgeons not previously involved with the pivotal study: 2 primary readers, and 1 adjudicating reader. If the primary readers were not in agreement regarding radiographic success or failure, then the adjudicating review was

used, and success or failure with regard to radiographic parameters was determined by the majority of readers. The 9 month CT scans from the original pivotal study were re-examined using the same prospective, multi-reviewer, blinded radiographic assessment protocol applied to the 36+ month scans. Stryker Biotech requested that the 9 month CT's reread by the blinded radiographic assessors even though it was never intended that the 9 month CT scans should serve to provide primary effectiveness information. First, it is important to remember that the 9 month CT scans were of variable quality since they were not collected under a standardized, optimized imaging protocol. Second, the 9-month postoperative period is not optimal for assessing peak bone formation in OP-1 Putty patients, and may therefore underestimate the degree of bone formation in this group. In contrast, it may overestimate the rate of bone formation in the autograft group because it is difficult to distinguish whether visible bone is residual graft material or de-novo bone (whereas all visible bone in the OP-1 Putty group is de-novo bone, since the product itself is not radiopaque). Despite these limitations, an analysis of the CT scan data at 9 months and at 36+ months allows an assessment as to whether the majority of patients in both groups showed evidence of bone formation at 9 months and at 36+ months. This finding, along with assessments of angulation and translation at 24 and 36+ months, would help to demonstrates both the consistency and the durability of effect on presence of bone through 36+ months.

In this extension study, Overall Success remains the primary efficacy endpoint, and is a composite of the same five outcome variables that comprised the Overall Success definition pre-specified in the original PMA submission.