

## **Draft FDA Panel Questions: PMA 100006**

### Indications for Use

1. In the clinical study for Augment™, the patient population included various diagnostic groups (i.e. osteoarthritis, rheumatoid arthritis, and traumatic arthritis) for the Augment treatment group and the autologous bone graft control group. The patient population was also heterogeneous with respect to specific joint(s) fused (ankle, subtalar, calcaneocuboid, etc.), total number of screws utilized in the procedure, and estimated amounts of graft material used. (Details of observation are provided in Tables 19-21 of FDA's executive summary.)
  - a. Please comment and provide feedback on the appropriateness of the sponsor's proposed indications for use:

“The intended use of Augment™ rhPDGF-BB Bone Graft is indicated for use as an alternative to autograft in hindfoot and ankle fusion procedures that require supplemental graft material, including tibiotalar, tibiocalcaneal, talonavicular, and calcaneocuboid fusions.”
  - b. Is it appropriate to pool the patient population with respect to diagnostic groups, joint(s) to be fused, number of screws utilized, and amounts of graft materials used to determine safety and effectiveness?

### Study Endpoints

2. Taking into consideration the response to question #1, please comment and provide feedback on the appropriateness of the sponsor's primary/secondary study endpoints in consideration of the following points:

The single primary endpoint of successful fusion defined as computed tomography (CT) evidence of greater than 50% osseous bridging and involving a “full complement of joints”.

- a. There was no predefined secondary composite clinical endpoint that included pain and function of the treated joint. Instead the sponsor used pain at the graft donor site in the control group.
- b. The sponsor's CT radiographic method of analysis did not include validation information with respect to traditional radiographic methods.

### Statistical Analysis

3. Please comment on the appropriateness of the statistical analyses for each of the following points:

- a. The mITT (Modified Intent to Treat) analysis was not identified in the IDE as the primary analysis dataset for the Pre-Market Application. Rather it was the ITT (Intent to Treat) analysis that had been identified in the IDE.
- b. Statistical significance was attained only in the mITT analysis population and not in the ITT analysis population.
- c. While the results were statistically supportive for non-inferiority at 24 months in the mITT analysis population, statistical significance was not retained at 36 months.
- d. The results of the tipping point sensitivity analysis suggest that the results are extremely sensitive to the potential impact of missing data.
- e. FDA has concerns that the patient accounting table provided by the sponsor is inaccurate.

#### Adverse Events

4. Please discuss any potential concerns with adverse events, rates, and/or reporting, including the following:
  - a. The seven subgroup analyses of adverse events categorized by the sponsor. FDA and the study's DSMB have previously expressed concern that only certain adverse events were being documented with this method.
  - b. The sponsor defined "Therapeutic Failures" to capture safety events not related to delayed or non-union and its substitution for a complete categorization of secondary surgeries.

#### Carcinogenicity/Tumor Promotion Potential

5. Please discuss the potential need for additional pre-clinical and/or clinical testing to evaluate this combination product with regard to carcinogenicity, and its potential effect on undetected transformed cells in the patient's body, i.e., tumor promotion. Please be as specific as possible on the type of testing needed. Please consider the following:
  - a. The sponsor has evaluated the product via an *in vitro* mutagenicity assessment and has conducted a one year, femur-onlay evaluation of the device for its carcinogenic potential. The assessments were negative for any indication of carcinogenicity.
  - b. There is a potential for implanted or injected cytokines to promote or stimulate transformed cell growth, i.e., cancers not detected or diagnosed a priori to the device usage. There may be a risk for tumor promotion with use of the device.

This concern is based on epidemiologic findings regarding rhPDGF-BB used for the treatment of venous stasis ulcers. These findings and concerns for rhPDGF-BB led to an FDA public health advisory.

- c. FDA has asked this sponsor to conduct a more standard drug type of tumor promotion assessment, i.e., the Rat Liver Foci Bioassay, where foci of altered hepatocytes (FAH) or preneoplastic lesions due to chemical carcinogenesis are assessed with respect to whether rhPDGF-BB can promote their growth and development. Do you believe this assessment should be completed prior to marketing the product?

#### Reproductive Toxicology/Teratogenicity

6. Please discuss the potential need for additional pre-clinical and/or clinical testing to evaluate this combination product with regard to reproductive toxicology/teratogenic potential. Please be as specific as possible on the type of testing needed. Please consider the following:
  - a. The sponsor has conducted a standard reproductive toxicology assessment to investigate the potential of rhPDGF-BB to influence reproduction and reproduction outcomes, e.g., fetal growth and development. The study found changes in rates of ossification of certain bones in the fetus, i.e., the sponsor does acknowledge that the changes in ossification parameters, i.e., indication of a minor transitory change in the rate of ossification, were likely attributable to rhPDGF-BB.
  - b. The sponsor is in the process of conducting a 2<sup>nd</sup> reproductive toxicology evaluation which will investigate the effect of anti-rhPDGF-BB antibodies on developing fetuses. These results are not available at this time. This experimental paradigm investigates the consequences of “knocking-out” PDGF-BB during embryonic development, i.e., interference with the protein’s normal roles in embryonic tissue growth and development as could occur in a pregnant woman exposed to the implanted product.

#### Immunologic Concerns

7. Please discuss the potential need for additional pre-clinical and/or clinical testing to evaluate this combination product with regard to its’ potential ability to elicit an immune response. Please be as specific as possible on the type of testing needed. Please consider the following:
  - a. There were differences noted in antibody events in patients treated with Augment<sup>™</sup>, as compared to the controls. An acceptable neutralizing assay has not yet been performed and therefore the incidence of neutralizing antibody formation is unknown. Accordingly, there is a concern that antibody formation could interfere with normal PDGF-BB signalling.

- b. Antibodies elicited to rhPDGF-BB could cross react with endogenous PDGF-BB and cause an autoimmune syndrome.

#### Post Approval Study

8. If the device is deemed approvable by FDA, the sponsor has provided a post approval study to continue following the IDE patients for 5 years. FDA is concerned that the proposed plan lacks critical key components of a PAS, including specific study hypothesis, the target study population, justification of the study powder, and comprehensive endpoints for the evaluation of safety and effectiveness in the post-market setting. In your discussion please address the following:
  - a. Whether a PAS is needed if the device is found to be approvable?
  - b. If a PAS is recommended, whether the proposed safety endpoints are adequate to assess the long-term safety? If not, please recommend the major safety endpoints.
  - c. If a PAS is recommended, what are the long-term effectiveness endpoints you would recommend?
  - d. If a PAS is recommended, what type of study design you would recommend to evaluate the study questions?

#### Premarket Voting Questions

9. Is there a reasonable assurance that Augment™ Bone Graft is safe for the indication for use as an alternative to autograft in hindfoot and ankle fusion procedures that require supplemental graft material, including tibiotalar, tibiocalcaneal, talonavicular and calcaneocuboid fusions?
10. Is there a reasonable assurance that Augment™ Bone Graft is effective for the indication for use as an alternative to autograft in hindfoot and ankle fusion procedures that require supplemental graft material, including tibiotalar, tibiocalcaneal, talonavicular and calcaneocuboid fusions?
11. Is there a reasonable assurance that Augment™ Bone Graft has a reasonable benefit/risk ratio for its indication for use as an alternative to autograft in hindfoot and ankle fusion procedures that require supplemental graft material, including tibiotalar, tibiocalcaneal, talonavicular and calcaneocuboid fusions?