
FDA DRAFT PANEL QUESTIONS

As indicated in the summary memo, the agency has identified a number of areas of concern where they would like your input. In general terms, these questions are related to the following:

- the manufacturing of the recombinant human protein;
- the immune response to the recombinant protein;
- the definitions of overall success, clinical success and radiographic success; and
- the clinical performance, *i.e.*, effectiveness and safety, of the combination product.

1. Irradiation sterilization

The combination product is provided sterile after exposure to relatively high levels of gamma irradiation, *i.e.*, 24.5-31.5kGy. Based on the sponsor's data, this induces numerous changes in the recombinant protein, including oxidation, aggregation and truncation. These changes to the protein likely contribute to the observed high incidence of anti-OP-1 antibodies in subjects receiving the product (94% of investigational subjects), including the development of antibodies that neutralize OP-1 activity (26% of investigational subjects).

Please comment on the potential for changes in the recombinant protein, including oxidation, aggregation and truncation, to have an impact on the following:

- a. the stability or potency of the recombinant protein component of the combination product;
- b. the biological activity of OP-1 Putty; and
- c. the immunological response to the combination product, and clinical effects that ensue from such responses.

2. Definitions of overall success and statistical analyses

Several definitions of overall success were proposed and evaluated by the sponsor during the course of the PMA review. Three of these definitions involved data from the pivotal study and a fourth definition was designed specifically for the data from the extension study. With the exception of the definition from the extension study, all evaluations were based on data collected at 24 months post-op.

Along with the revised definitions, the sponsor also made three major modifications to the statistical analysis plan (SAP) prior to database lock. The first was a modification to the intent-to-treat population (now referred to as mITT), which included all treated subjects with at least one post-treatment follow-up visit. The second was a modification to the fixed non-inferiority margin. The third was a modification to the imputation method. In each case, the agency expressed concerns with the clinical and statistical implications of the revised definitions.

According to the original protocol-defined SAP, the pivotal study showed that OP-1 Putty treatment is significantly inferior to the autograft control treatment in terms of the primary endpoint, *i.e.*, subject overall success at 24 months (which includes the radiographic data). According to the late-stage revised SAP, the non-inferiority claim was still not supportable. After acknowledging the problems associated with the *post hoc* analysis of the overall clinical success, the sponsor designed and conducted the extension study with the primary endpoint being re-defined again, *i.e.*, the 24 month clinical outcome data combined with the new 36+ month CT scan/re-operation data. Based on the unadjusted $p = 0.025$ of their mITT analysis (non-inferiority margin = 0.14, multiple imputation for approximately 30% missing data), the sponsor concluded that the non-inferiority had been demonstrated by the extension study results.

Please comment on:

- a. the clinical soundness of the various definitions of overall success; and
- b. the statistical soundness of the sponsor's claim of non-inferiority.

3. Clinical performance - effectiveness

Please comment on the clinical effectiveness of the combination product. In addition, please include in your discussion the potential necessity for performing a human dosing study to assess the correlation between the reported effectiveness and selection of the correct dose of the recombinant protein component of the combination product.

4. Clinical performance - safety

Please comment on the safety of the combination product. Please include in your discussion on the potential for clinical concerns associated with the immune response to the recombinant protein including any that potentially could affect either maternal and child health.