CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Division of Biostatistics (HFM-215)

Statistical Review

FDA NUMBER: 99-1490

TASK TYPE: BLA

SPONSOR: *Amgen Inc.*

SUBJECT: *Statistical analytic plan for additional ACR data to support the BLA for Anakinra (r-IL-1ra) in the treatment of rheumatoid arthritis*

DATE: 12/13/2000

FROM: *Bo-guang A. Zhen, Ph.D.*

THROUGH: *G. Gupta, Ph.D., Chief, Therapeutics Evaluation Branch*
Division of Biostatistics

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BACKGROUND

Results from the two pivotal trials with ACR20 as the primary endpoint have been submitted under BLA (99-1490, Amgen). After completing the review on this BLA, it was found that these trials do not demonstrate sufficient evidence of efficacy in terms of the clinical endpoint as measured by ACR20. In order to support the current finding in the BLA, we requested the sponsor to provide additional ACR data in the ongoing trial in which the ACR20 is not the primary endpoint (the radiographic endpoint as measured by the total modified sharp score (TMSC) is the pre-specified primary endpoint).

The ongoing trial (Protocol 990145) was designed to provide confirmatory evidence that Anakinra plus MTX is superior to MTX alone in reducing disease progression as measured by TMSC in order to support an indication that is different from the one under the current BLA. All subjects who were randomized on or before May 18, 2000 will be included in the interim analysis (this leads to a total of 506 subjects, approximately 50% of the planned sample size). Only efficacy data on signs and symptoms (ACR response) and serious infection data will be

provided at the interim analysis. No radiographic data will be included in the interim analysis. In order to preserve the integrity of the study and the analysis of the primary endpoint at the study's conclusion, Amgen has developed a plan to control unnecessary unblinding of the individual treatment assignments. The most important endpoint at the interim analysis is the proportion of subjects who achieve an ACR20 response at week 24. Analysis of the ACR composite scores will use a nonresponder imputation for subjects whose ACR composite can not be established at a particular time-point due to missing data, incomplete assessments, or an increase of DMARDs or corticosteroids from baseline while on study. A sensitivity analysis will be performed using the subset of completer.

For the statistical analytic plan, Amgen asked for our concurrence on a variety of issues. A teleconference was held to discuss questions regarding unblinding of the study data and maintaining the integrity of the data on November 21, 2000. During the teleconference, we informed the sponsor that the unblinding proposal is adequate to maintain the integrity of the study. An adjustment of the alpha level for the radiographic endpoint would not be required at the end of the study. However, we raised the concern that the sponsor may want to re-test the ACR endpoint at the end of the ongoing trial if a negative result is observed at the interim analysis. Therefore, we have delivered the message to the sponsor that adjustment of type I error rate was required if they planned to re-test the ACR endpoint. The following are the additional comments on the analytic plan.

COMMENTS:

1. **The primary analysis method on the ACR endpoints**: The sponsor proposed to analyze the proportions of ACR20, ACR50 and ACR70 at week 24 using a logistic regression model adjusted for center. In order to ensure estimability of the model, centers without an ACR responder (or non-responder) will be pooled based on a cluster analysis using subject's baseline covariates prior to the blind break.

   Pooling some centers together based on the outcome data may leave a room for subjective data manipulation. Therefore, it is recommended that Cochran Mantel Haenszel (CMH) method be used to compare proportions between the Anakinra and placebo groups as the primary analysis method. The advantage of using CMH is its applicability for small number of observations in each stratum so that it is not necessary to pool some centers together. The logistic regression model may be considered as the secondary analysis method. Please comment.

2. **Sensitivity analysis in the interim analysis**: A worst case analysis should be considered as one of the sensitivity analyses for ACR20, i.e.: all patients with missing data in the treatment arm would be treated as nonresponders while all patients in the placebo arm would be considered as responders.

3. **Safety data for the interim analysis**: The sponsor stated that the only safety data submitted for the interim analysis will be the aggregate serious infectious data. The sponsor should provide all safety data available for subjects used for the interim analysis.

Tony and Shyam:

Please comment on the attached review. I would like to have your concurrence with my review on the analytic plan before I deliver it to the team.

APPEARS THIS WAY
ON ORIGINAL