U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	N20-905/SE012
Drug Name:	AVARA™ (leflunomide 20 mg)
Indication(s):	Rheumatoid Arthritis
Applicant:	Aventis Pharmaceuticals, Inc.
Date(s):	Received: October 1, 2003
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	Suktae Choi, Ph.D.
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Keywords: Active Control/Superiority, Clinical Studies, Confidence Interval

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1.1 Conclusions and Recommendations

This NDA supplement failed to establish the efficacy of leflunomide comparing to methotrexate in treatment of JRA. The efficacy results demonstrated statistical superiority of methodtrexate for DOI 30% responder rate which is one of two co-primary efficacy variables. The other co-primary efficacy variable, % Improvement Index, showed in favor of methotrexate but the difference was not statistically significant.

1.2 Brief Overview of Clinical Studies

This submission is being made to supplement the current approved NDA with pediatric data pertaining to the clinical utility of leflunomide in juvenile reheumatiod arthritis. The sponsor submitted three studies (1037, 3503, and 3504) under the pediatric program. Study 1037 was an open-label, non-controlled, five-centers, Phase IB study over a 6 month treatment period with up to a 24-month extension phase. Study 3503 was a randomized, double blind, parallel group 16-week treatment trial comparing leflunomide to methotrexate, in pediatric subjects with polyarticular course JRA who were DMARD-therapy naïve. This study was originally planned 240 subjects (120 per treatment group) for a non-inferiority design, but amended to 94 (47 per group) because of the difficulty of recruitment. Study 3504 was an eight month extension of study 3503 and still ongoing. This review will focus only on study 3503.

In study 3503, following efficacy variables were observed at screening, baseline, week 4, 8, 12, and 16: Percent Improvement Index and JRA DOI $\geq$ 30% responder status using the 6 core set measures of the JRA Definition of Improvement. Additional response assessments were time to response, DOI $\geq$ 30%, $\geq$ 50%, and $\geq$ 70% responder-at-endpoint rates, AUC, physician's global assessment, subject/parent global assessment, number of active joints, number of joints with limitation of motion plus pain and/or tenderness, functional assessment (CHAQ), ESR, CRP, and pain score.

1.3 Statistical Issues and Findings

- Methotrexate performed statistically better than leflunomide as measured by the JRA DOI $\geq$ 30% responder rate. The rate in the methotrexate group was 89.4% vs. 68.1 % in the leflunomide group. P-value is 0.0091 and 95% Confidence Interval of the difference is (-37.3%, -5.3%).

- The percent Improvement Index demonstrated no significant difference between treatment groups at week 16, LS Mean improvement was –44.41% (SE4.51) in the leflunomide group and –52.87% (SE4.39) in the methotrexate group.

- JRA DOI ≥ 30% responder rate was requested to add as a primary efficacy variable by agency, because this variable is one of the most commonly used efficacy variable. In fact, percent Improvement Index is rarely used as a primary efficacy variable.

- Secondary analyses showed similar results with primary analyses. All the secondary efficacy variables at week 16 showed in favor of methotrexate compared with leflunomide except CHAQ, and some of them showed significant differences. At week 4, 8, 12, and 16, majority of them showed in favor of methotrexate.

- Since both primary efficacy variables showed in favor of methotrexate, and one of them showed significant difference, we cannot conclude that the efficacy of leflunomide is as good as the efficacy of methotrexate in this study.

2. INTRODUCTION

2.1 Overview

This submission is being made to supplement the current approved NDA with pediatric data pertaining to the clinical utility of leflunomide in juvenile reheumatiod arthritis. The sponsor submitted three studies (1037, 3503, and 3504) under the pediatric program. Study 1037 was an open-label, non-controlled, five-centers, Phase IB study over a 6 month treatment period with up to a 24-month extension phase. Study 3503 was a randomized, double blind, parallel group 16-week treatment trial comparing leflunomide to methotrexate, in pediatric subjects with polyarticular course JRA who were DMARD-therapy naïve. This study was originally planned 240 subjects (120 per treatment group) for a non-inferiority design, but amended to 94 (47 per group) because of the difficulty of recruitment. Study 3504 was an eight month extension of study 3503 and still ongoing. This review will focus only on study 3503.

2.2 Data Sources

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

The study was a multinational, multicenter, two arms, double-blind, double-dummy, randomized, parallel, and active controlled study. Duration was 16 weeks. Among 103 patients screened, 94 were randomized (47 per each group). Patients were between the ages of 3-17 years. Visits were at week 4, 8, 12 and 16.

Dosage schedule

Randomized to leflunomide: each subject received a leflunomide loading dose ranging from one 100 mg tablet /day for 1 day to one 100 mg tablet /day for 3 consecutive days, depending on body weight. Thereafter, subjects received a maintenance dose of 10 mg every other day, 10 mg daily, or two-10 mg tablets daily (20 mg daily), depending on weight. Detail of dosage schedule is summarized in Table 1 of appendix. Subjects also received methotrexate placebo tablets weekly based on body weight.
Randomized to methotrexate: each subject received methotrexate 2.5 mg tablets weekly, based on body weight, for a dose of 0.5 mg/kg/wk to a maximum of 25 mg/wk. If the calculated methotrexate dose was not a multiple of 2.5 mg, the subject was dosed at the closest whole number of methotrexate tablets. Subjects also received leflunomide placebo.

For those children who were unable to swallow a tablet, tablets were permitted to be crushed and mixed in applesauce or jam.

Efficacy data

Primary efficacy variables:
1. JRA DOI $\geq$ 30% responder rate at week 16
2. Percent Improvement Index at week 16

Percent Improvement Index is defined as follow:
- This variable is based on the JRA DOI's 6 core set measures.
- For each subject, the % Improvement Index was the mean of the 6 core set percent changes from baseline.
  The percent change from baseline to end of treatment was calculated as follows:

(value at end of treatment – value at baseline)/value at baseline x 100

- In the event that the mean percent change was positive (worsened), then the % Improvement Index for that subject was set to zero.

Secondary efficacy variables:

1. JRA DOI $\geq$ 50% and $\geq$ 70% responder rates
2. JRA DOI $\geq$ 30%, $\geq$ 50%, and $\geq$ 70% responder-at-endpoint rates (this variable considers non-completers as not responders)
3. AUC of DOI $\geq$ 30%, $\geq$ 50%, and $\geq$ 70% responses: Months of response
4. Time to JRA DOI 30% response
5. Physician global assessment of disease activity
6. Patient/parent global assessment of disease activity
7. Number of active joints
8. Joints with limited range of motion
9. CHAQ disability index
10. Erythrocyte sedimentation rate (ESR)
11. Pain score
12. C-reactive protein (CRP)

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

As shown in Table 2 and Table 3 of appendix, two treatment groups are similar in disposition and in key demographic characteristics. Primary disease were compared between two treatment groups at baseline by sponsor, and the variables were JRA type at onset, JRA duration, Active joint count, Limited ROM joint count, MD global assessment score, Patient global assessment, Disability index, ESR, CRP, and Pain score, but none of them showed significant difference.

3.1.3 Statistical Methodologies

The following inferential null hypothesis was tested:

H_0: no treatment difference between leflunomide and methotrexate for JRA DOI 30% Responder rate at endpoint (or mean % Improvement Index).

H_1: treatment difference between leflunomide and methotrexate for JRA DOI 30% Responder rate at endpoint (or mean % Improvement Index).

The null hypothesis H_0 will be tested against the alternative H_1 two-sided with α=0.05. Since both comparisons have to show significant difference, multiple comparison adjustment is not necessary.

For the analysis for JRA DOI 30% Responder at Endpoint, the difference of responder rates of treatment groups was supposed to be compared using the normal approximation in

statistical analysis plan (Appendix B of sponsor's NDA submission). However, in the sponsor's NDA final report, CMH method was used to calculate p-values, which was not specified in the statistical analysis plan. The p-values using the protocol specified method were calculated by this reviewer and replaced with CMH p-values in this review, because the primary analysis must be the one specified in the protocol.

For the analysis of % Improvement Index, ANOVA was used on the mean % Improvement Index with treatment and country as fixed effects. This was specified in the statistical analysis plan.

For secondary analyses, 95% CI of responder rate difference between treatment groups using normal approximation was used for binary variables (p-values are correspondent to this CI), and ANCOVA with factors of treatment and baseline was used for changes from baseline continuous variables.

ITT was used in efficacy analyses for primary population, and LOCF was used as an imputation method for early dropout for all the efficacy analysis as specified in the protocol.

3.1.4 Results and Conclusions

- Methotrexate performed statistically better than leflunomide as measured by the JRA DOI $\geq$ 30% responder rate. The rate in the methotrexate group was 89.4% vs. 68.1 % in the leflunomide group. P-value is 0.0091 and 95% Confidence Interval of the difference is (-37.3%, -5.3%). The comparison results during the study period are summarized in Table 4 and Figure 1.

- The percent Improvement Index demonstrated no significant difference between treatment groups at week 16, LS Mean improvement was –44.41% (SE4.51) in the leflunomide group and –52.87% (SE4.39) in the methotrexate group. The comparison results during the study period are summarized in Table 5 and Figure 2.

- JRA DOI $\geq$ 30% responder rate was requested to add as a primary efficacy variable by agency, because this variable is one of the most commonly used efficacy variable. In fact, percent Improvement Index is rarely used as a primary efficacy variable.

- Secondary analyses showed similar with primary analysis results. All the secondary efficacy variables at week 16 showed in favor of methotrexate compared with leflunomide except CHAQ, and some of them showed significant differences. At week 4, 8, 12, and 16, majority of them showed in favor of methotrexate. Details of secondary analysis results are summarized in Table 6 to Table 17 of appendix.

- Since both primary efficacy variables showed in favor of methotrexate, and one of them showed significant difference, we cannot conclude that the efficacy of leflunomide is as good as the efficacy of methotrexate in this study.

3.2 Evaluation of Safety

Safety data were not reviewed.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Subgroup analysis results for gender and age are summarized in Table 18 and Table 19 for JRA DOI 30% and percent Improvement Index, respectively. Race was not included because most of RA patients are white. Since these subgroup analyses were not planned in the protocol, CMH method is acceptable for analysis of DOI 30%. As shown, there is no significant interaction between subgroup and treatment group.

4.2 Other Special/Subgroup Populations

Subgroup analysis result for Body weight is summarized in . As shown, there is no significant interaction between subgroup and treatment group.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

- Methotrexate performed statistically better than leflunomide as measured by the JRA DOI ≥ 30% responder rate. The rate in the methotrexate group was 89.4% vs. 68.1 % in the leflunomide group. P-value is 0.0091 and 95% Confidence Interval of the difference is (-37.3%, -5.3%).

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This NDA supplement failed to establish the efficacy of leflunomide comparing to methotrexate in treatment of JRA. The efficacy results demonstrated statistical superiority of methotrexate for DOI 30% responder rate which is one of two co-primary efficacy variables. The other co-primary efficacy variable, % Improvement Index, showed in favor of methotrexate but the difference was not statistically significant.

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