

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021825Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-825/ SE 0056

Drug Name: Deferiprone (Ferriprox)

Indication(s): Treatment of iron overload

Applicant: ApoPharma Inc

Date(s): Letter Date: April 14 2011
Stamp Date: April 14 2011
PDUFA Goal Date:

Review Priority: Standard

Biometrics Division: Division of Biometrics V

Statistical Reviewer: Qing Xu, Ph.D

Concurring Reviewers: Mark Rothmann, Ph.D., Statistical Team Leader
Rajeshwari Sridhara, Ph.D., Director, DBV

Medical Division: Division of Hematology Products

Clinical Team: George Shashaty, M.D., Clinical Reviewer
Kathy M Robie Suh, M.D., Clinical Team Leader

Project Manager: Mara Bauman Miller

Keywords:
Bias, Confidence interval, Covariate, Logistic regression, Meta-analysis, Missing data, Pooling

Table of Contents

LIST OF TABLES.....	3
LIST OF FIGURES.....	3
1. EXECUTIVE SUMMARY	4
2. INTRODUCTION	4
2.1 OVERVIEW.....	4
2.2 DATA SOURCES	5
3. STATISTICAL EVALUATION	5
3.1 DATA AND ANALYSIS QUALITY	5
3.2 EVALUATION OF EFFICACY	6
3.2.1 STUDY OBJECTIVE	6
3.2.2 STUDY DESIGN, ENDPOINTS AND ANALYSIS POPULATION	6
3.2.3 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS	7
3.2.4 <i>Statistical Methodologies</i>	13
3.2.5 <i>Results and Conclusions</i>	14
3.2.5.1 <i>Analysis results for serum ferritin</i>	14
3.2.5.2 <i>Analysis results for Secondary Endpoint: LIC</i>	19
3.2.5.3 <i>Analysis results for Secondary Endpoint: MRI T2*</i>	22
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	23
4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION	23
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS	24
5. SUMMARY AND CONCLUSIONS	25
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE	25
5.2 CONCLUSIONS AND RECOMMENDATIONS	27
SIGNATURES/DISTRIBUTION LIST.....	30

LIST OF TABLES

Table 1	Number of eligible patients by study for serum ferritin-ITT population	7
Table 2	Number of eligible patients by study for liver iron concentration-ITT population	8
Table 3	Number of eligible patients by study for cardiac MRI T2* -ITT population	8
Table 4	Summary of eligible patients between the Agency's results and the sponsor's results	9
Table 5	Reviewer's summary of race by study for serum ferritin (ITT population).....	9
Table 6	Reviewer's summary of demographic for serum ferritin using ITT population	11
Table 7	Reviewer's summary of demographic for serum ferritin, LIC, and MRI T2*.....	11
Table 8	Reviewer's summary of number of subjects and drop out rate over time.....	12
Table 9	Reviewer's summary of success rate by study for serum ferritin (ITT)	15
Table 10	Reviewer's meta-analysis for serum ferritin.....	16
Table 11	Reviewer's summary of descriptive statistics for serum ferritin	17
Table 12	Reviewer's Estimate for covariates using logistic regression for serum ferritin	17
Table 13	Reviewer's summary of mean serum ferritin over time within 24 month	18
Table 14	Reviewer's summary of success rate by study for LIC	19
Table 15	Reviewer's meta-analysis of LIC	20
Table 16	Reviewer's summary of descriptive statistics for LIC.....	20
Table 17	Reviewer's Summary of estimate for covariates using logistic regression for LIC.....	20
Table 18	Reviewer's summary of mean serum ferritin over time within 24 month	21
Table 19	Reviewer's summary of success rate by study for MRI T2*.....	22
Table 20	Reviewer's summary of descriptive statistics for MRI T2*	22
Table 21	Reviewer's Summary of estimate for covariates using logistic regression for MRI T2*	22
Table 22	Reviewer's summary of mean MRI T2* over time within 24 month	23
Table 23	Reviewer's subgroup analysis of gender, race, age and region for serum ferritin	24
Table 24	Reviewer's summary of subgroup analysis for serum ferritin by baseline of serum ferritin and thalassemia	24

LIST OF FIGURES

Figure 1	Reviewer's summary of number of subjects over time	12
Figure 2	Reviewer's summary of drop out rate over time	13
Figure 3	Reviewer's summary of mean serum ferritin over time	18
Figure 4	Reviewer's analysis of mean serum ferritin change over time (study LA-01, LA-16, LA-28).....	19
Figure 5	Reviewer's summary of mean LIC over time	21
Figure 6	Reviewer's summary of mean MRI T2* over time.....	23

1. EXECUTIVE SUMMARY

Deferiprone (Ferriprox) is an orally administered iron chelator that is being developed for the indication of the treatment of patients with transfusional iron overload when current chelation therapy is inadequate. NDA 21825 for Ferriprox (deferiprone) was submitted on January 29, 2009 and a Complete Response letter was sent to the sponsor on November 30, 2009. This resubmission of NDA 21825/SE0056 including study LA36-0310 was designed as an analysis of existing data from studies previously conducted to evaluate the efficacy of Ferriprox. No new data were collected and the original purpose of collecting the data and their application did not change. Efficacy data for study LA 36-0310 were derived from 12 of 17 studies. The primary efficacy endpoint was the change in serum ferritin concentration from baseline within one year of Ferriprox therapy. Ferriprox therapy was considered successful in individual patients who experienced a $\geq 20\%$ decline in serum ferritin concentration within one year of therapy.

The sponsor's efficacy analysis for serum ferritin by pooling 12 studies showed that the overall success rate was 52% with 95% CI of (45%, 58%). As the lower limit of the 95% CI is larger than 20%, the protocol defined endpoint was met for this trial. However, this study has several serious limitations including lack of randomization, lack of control group, high rate of missing data and ignoring the variation between studies by simple pooling, all of which can introduce biases to the primary outcome. Therefore, it is unclear whether the efficacy shown in the study is solely due to the Ferriprox therapy, and the interpretation of these analysis results should be taken cautiously.

The Oncology Drug Advisory Committee (ODAC) Meeting discussed NDA 21825/SE0056 study results on September 14, 2011. For the question:

1. Is there a favorable benefit/risk profile for deferiprone in the treatment of patients in who current chelation therapy is inadequate?
- Committee voted: No 2, Yes 10.

The results for the AC member's questions are given in the Appendix.

2. INTRODUCTION

2.1 Overview

The original NDA 21825 was submitted to the Agency on January 29, 2009. The submission of the NDA included a single randomized controlled trial. The primary endpoint in that trial was the change in cardiac iron as measured by cardiac MRI T2* assessment after one year of treatment with Ferriprox. The comparator drug was deferoxamine, which at the time of the study was the only approved drug for the indication. The agency was concerned that the primary endpoint

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.