CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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
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Medical Division:	Division of Hematology Products
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Project Manager:	Mara Bauman Miller

Keywords:

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

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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 ≥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

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