



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 MEMO

### CLINICAL STUDIES

<b>sBLA #:</b>	103951
<b>Supplement #:</b>	(b) (4)
<b>Drug Name:</b>	Aranesp® (Darbepoetin alfa)
<b>Indication(s):</b>	Anemia in pediatric subjects
<b>Applicant:</b>	AMGEN
<b>Submitted Date:</b>	24-SEPT-2014
<b>Review Due Date:</b>	20-MAY-2015
<b>PDuFA date:</b>	25-JUNE-2015
<b>Review Priority:</b>	Standard
<b>Biometrics Division:</b>	DB V / CDER
<b>Statistical Reviewer:</b>	Dr. Kallappa M. Koti
<b>Concurring Reviewers:</b>	Dr. Lei Nie, Team Leader Dr. Thomas Gwise, Deputy Director Division of Biometrics V
<b>Medical Division:</b>	DHP
<b>Clinical Team:</b>	Dr. Saleh Ayache Dr. Angelo De Claro, Team Leader
<b>Project Manager:</b>	Ms. Rachel McMullen
<b>Keywords:</b>	Correction proportion, z-test.

## 1 BACKGROUND

This BLA is a Prior Approval Labeling Supplement. In this BLA, recent data are provided from 2 pediatric studies to support updates to the USPI for the initial correction of anemia in pediatrics:

- study 20050256, entitled “A Multicenter, Double-blind, Randomized Study Evaluating De Novo Weekly and once every 2 week Darbepoetin alfa Dosing for the Correction of Anemia in Pediatric Subjects With Chronic Kidney Disease Receiving and Not Receiving Dialysis,”
- study 20070211, entitled “A Prospective Registry Study Observing the safety and Patterns of Use of Darbepoetin Alfa in EU Pediatric Chronic Kidney disease patients Receiving or Not Receiving Dialysis,” is an observational registry that assessed the long-term (2 year) safety of darbepoetin alfa therapy in pediatric subjects < 17 years of age

Study 20070211 was not designed to test a hypothesis, but rather to describe the safety profile of darbepoetin alfa in pediatric CKD patients. This study is not reviewed.

## 2 DESIGN AND CONDUCT OF STUDY 20050256

The study report, the datasets and the labeling package insert were provided in

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Study 20050256 was “A Multicenter, Double-blind, Randomized Study Evaluating De Novo Weekly and Once Every 2 Week Darbepoetin alfa Dosing for the Correction of Anemia in Pediatric Subjects With Chronic Kidney Disease Receiving and Not Receiving Dialysis”.

The primary objectives of study20050256 were:

- To test if the proportion of subjects achieving a hemoglobin value  $\geq 10.0$  g/dL at any time point after the first dose during the study was greater than 0.8 when administered de novo darbepoetin alfa once weekly (QW) for treatment of anemia in pediatric chronic kidney disease (CKD) subjects receiving and not receiving dialysis
- To test if the proportion of subjects achieving a hemoglobin value  $\geq 10.0$  g/dL at any time point after the first dose during the study was greater than 0.8 when administered de novo darbepoetin alfa once every 2 weeks (Q2W) for treatment of anemia in pediatric CKD subjects receiving and not receiving dialysis

This was a multicenter, double-blind, randomized study in pediatric subjects with CKD receiving dialysis (either hemodialysis [HD] or peritoneal dialysis [PD]) or not receiving dialysis who are anemic (hemoglobin < 10.0 g/dL) and not being treated with an ESA. Subjects were randomized

to receive darbepoetin alfa QW or Q2W for 24 weeks. Subjects randomized to the Q2W group received Q2W injections of placebo during non-dosing weeks in order to maintain the blind for treatment group and dose. Darbepoetin alfa was administered by subcutaneous (SC) injection to subjects not receiving dialysis and to subjects receiving PD. Darbepoetin alfa was administered intravenously (IV) to subjects receiving HD. The initial darbepoetin alfa dose was 0.45µg/kg or 0.75µg/kg, rounded to the nearest unit dose, for subjects randomized to the QW and Q2W group, respectively. For HD subjects, initial dose calculations were based on post-dialysis weight. For both treatment groups, subsequent darbepoetin alfa doses were titrated to achieve a target hemoglobin value of 10.0 g/dL to 12.0 g/dL, inclusive. Subjects were assessed during the treatment phase and at an end-of-study visit, which was 1 week after the final dose of investigational product (week 25) or at the time of early study withdrawal.

Correction proportion (p)- the proportion of subjects who have at least 1 single post dose Hb  $\geq$  10.0 g/dL during the study (without receiving any red blood transfusion after randomization and within 90 days prior to the Hb measurement) was the primary efficacy endpoint. Two hypotheses were tested:

Null hypothesis I:  $p \leq 0.8$  in QW group; Alternative hypothesis I:  $p > 0.8$  in QW group (1-sided)  
Null hypothesis II:  $p \leq 0.8$  in Q2W group; Alternative hypothesis II:  $p > 0.8$  in Q2W group (1-sided)

Assuming the correction proportion under the alternative is 0.92, with type I error of 0.025 (1-sided), 70 subjects are needed to achieve 80% power to reject the null hypothesis. Assuming 5% of the subjects withdraw from the study before receiving their first darbepoetin alfa dose, the total sample size for the study was approximately 150.

Dosing time point in Study 20050256: The planned darbepoetin alfa administration weeks for Q2W were 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23. Subjects in the QW arm were darbepoetin alfa administered every week during the 24 weeks of treatment.

In Study 20050256, baseline hemoglobin was below 10 g/dL for all subjects in both arms.

### **3 PRIMARY EFFICACY RESULTS FROM STUDY 20050256:**

- In this study, hemoglobin concentrations were corrected to  $\geq 10$  g/dL in 57/58 (98%) of pediatric subjects administered darbepoetin alfa QW, which was statistically significantly greater than 0.8 (p-value  $< 0.0003$ ). Of subjects administered darbepoetin alfa Q2W, 47/56 (84%) of subjects achieved hemoglobin  $\geq 10$  g/dL during this study; this proportion was not statistically significantly greater than 0.8 (p = 0.2311).
- In the QW arm, there were a total of 21 pediatric subjects who were younger than 12 years of age, and the remaining 37 pediatric subjects were at least 12 years of age. Of the 21 subjects who were younger than 12 years, 20 (95%) subjects achieved hemoglobin  $\geq 10$  g/dL during this study. All of the 37 (100%) elder pediatric subjects, achieved hemoglobin  $\geq 10$  g/dL during this study.

- In the Q2W arm, 19 pediatric subjects were < 12 years of age, and 37 pediatric subjects were at least 12 years of age. Of the 19 subjects who were younger than 12 years, 17 (89%) subjects achieved hemoglobin  $\geq 10$  g/dL during this study. Thirty of the 37 (81%) elder pediatric subjects, achieved hemoglobin  $\geq 10$  g/dL during this study.
- In the QW arm, 15 subjects received hemodialysis; 10 received peritoneal dialysis, and 33 subjects did not receive dialysis. All 15 (100%) hemodialysis subjects achieved hemoglobin  $\geq 10$  g/dL during this study. Nine of 10 (i.e. 90%) of peritoneal dialysis subjects achieved hemoglobin  $\geq 10$  g/dL during this study. All 33 (100%) subjects who did not receive dialysis achieved hemoglobin  $\geq 10$  g/dL during this study.
- In the Q2W arm, 14 subjects received hemodialysis; 9 received peritoneal dialysis, and 33 subjects did not receive dialysis. Of the 14 hemodialysis subjects, 10 (71%) subjects achieved hemoglobin  $\geq 10$  g/dL during this study. Seven of 9 (i.e. 78%) of peritoneal dialysis subjects achieved hemoglobin  $\geq 10$  g/dL during this study. Thirty (91%) of the 33 subjects who did not receive dialysis achieved hemoglobin  $\geq 10$  g/dL during this study.

#### **4 CONCLUSION AND RECOMMENDATION**

- This reviewer concurs with the Sponsor's stated primary efficacy results from Study 20050256.
- The following labeling statement may be approved: "Study N8 was a double-blind, randomized, controlled study in 114 pediatric patients from 1 to 18 years of age receiving darbepoetin alfa. In this study, pediatric patients with CKD receiving or not receiving dialysis who were anemic (hemoglobin [Hb] < 10.0 g/dL) and not being treated with an erythropoiesis stimulating agent (ESA) (b) (4) darbepoetin alfa weekly or once every 2 weeks for the correction of anemia. (b) (4)"

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05/18/2015

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