CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	103951
Priority or Standard	Standard
Submit Date(s)	9/24/2014
Received Date(s)	9/24/2014
PDUFA Goal Date	7/25/2015
Division / Office	OHOP/DHP
Reviewer Name(s)	Saleh Ayache, MD
Review Completion Date	5/14/2015
Established Name	Darbepoetin alfa
(Proposed) Trade Name	Aranesp®
Therapeutic Class	ESA
Applicant	Amgen
Formulation(s)	IV and SC
Dosing Regimen	Patients with CKD: - 0.45 mcg/kg intravenously or subcutaneously weekly - Not on dialysis may initiated at 0.75 mcg/kg every 2 weeks
Indication(s)	Treatment of anemia with darbepoetin alfa in pediatric patients with chronic kidney disease (CKD) receiving and not receiving dialysis
Intended Population(s)	Pediatric Patients Age <18 years

Template Version: March 6, 2009

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AE	Adverse event
AUC	Area under the curve
BLA	Biologics license application
CI	Confidence interval
CKD	Chronic kidney disease
CSR	Clinical study report
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
ESA	Erythropoiesis-stimulating agent
Hb	Hemoglobin
HD	Hemodialysis
ICH	International Conference on Harmonization
IV	Intravenously
PD	Peritoneal dialysis
PedsQL	Pediatric Quality of Life Inventory
PK	Pharmacokinetic
PMC	Post-marketing commitment
PRCA	Pure red cell aplasia
PSUR	Product Safety Update Report
QW	Once Week
Q2W	Once every two weeks
rHuEPO	Recombinant human EPO
RBC	Red blood cell
ROR	Rate of rise
SC	Subcutaneous
TSAT	Transferrin saturation
USPI	United States prescribing information

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewer recommendation is to grant approval for Prior Approval Labeling Supplement to BLA 103951. I also recommend changes to be made to the Prescribing Information (PI) to add that Aranesp can be used for the initial treatment of anemia in pediatric patients with chronic kidney disease (CKD).

The recommended starting dose for pediatric patients with CKD is:

- 0.45 mcg/kg intravenously or subcutaneously weekly
- Patients with CKD not on dialysis may also be initiated at 0.75 mcg/kg every 2 weeks.

1.2 Risk Benefit Assessment

The results from clinical trials (20050256 and 20070211) indicate that Aranesp was effective in correcting and maintaining hemoglobin in pediatric patients with CKD. There were no new safety signals identified compared to the safety profile that was previously established in adult patients with CKD.

The analysis performed using data from the study 20050256 demonstrated that Aranesp is effective and safe for the correction and maintenance of hemoglobin in pediatric patients with anemia due to CKD. The results of the primary efficacy analysis demonstrated that:

- Hemoglobin concentrations were corrected to ≥ 10 g/dL in 98% of pediatric patients administered darbepoetin alfa QW. The percentage was greater than 0.80, which was statistically significant ($p < 0.001$).
- In subgroup analyses, the correction proportion was also > 0.80, regardless of baseline age, dialysis status, and hemoglobin value.
- In patients who administered darbepoetin alfa Q2W, 84% of them achieved hemoglobin ≥ 10 g/dL during this study. However, this percentage was not statistically significantly greater than 0.80 ($p = 0.293$).
- In subgroup analyses, the correction proportion was also > 0.80 for both age subgroups, patients not receiving dialysis, and patients whose baseline hemoglobin was ≥ 9.0 g/dL.

The results of the safety analysis demonstrated that:

- The safety profiles for the QW and Q2W groups were consistent with the known safety profile for darbepoetin alfa in adults.
- There was no new safety signal identified.
- Adverse event profiles were similar for darbepoetin alfa QW and Q2W dosing, including those for the adverse events of interest for darbepoetin alfa population.
- Less than 10% of patients developed binding anti-erythropoietic protein antibodies during the study. However, there were no patients tested positive for neutralizing antibodies.

- The safety and efficacy profile of Aranesp in pediatric patients with CKD who are less than 1 year of age was consistent with those of one year or older demonstrated by the European (EU) study results.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Aranesp has a REMS named "ESA APPRISE" for restricted distribution to mitigate the risks of mortality, serious cardiovascular reactions, thromboembolic reactions, stroke, and tumor progression in patients with cancer treated with ESA. There is no REMS for the anemia of CKD indication.

1.4 Recommendations for Postmarket Requirements and Commitments

No new PMR or PMC required for this indication.

2 Introduction and Regulatory Background

Chronic kidney disease is characterized by an irreversible deterioration of renal function that gradually progresses to end-stage renal disease (ESRD). Anemia is a universal problem among children with chronic kidney disease (CKD). The lower glomerular filtration rate (GFR) is associated with lower hemoglobin concentration. Anemia in adults is most pronounced when the GFR falls below 60 mL/min per 1.73 m^2. In children, the relationship between GFR and anemia is less clear.

In children, CKD is a serious and life-threatening disease, with a mortality rate in children receiving dialysis of approximately 15 to 115 times that of the general pediatric population in the US.

Anemia of CKD is associated with fatigue, weakness, decreased attentiveness, increased somnolence, and poor exercise tolerance.

Treatment of anemia of CKD in both adults and children has improved dramatically with the advent of regular erythropoietin (EPO) and iron therapy, and it has become possible to avoid routine transfusions to maintain a patient's hemoglobin.

2.1 Product Information

This submission is a Prior Approval Labeling Supplement.

Established Name: Darbepoetin alfa
Proprietary Name: Aranesp
Pharmacologic class: Erythropoietin Stimulating Agent (ESA)
Applicant: Amgen
One Amgen Center Drive

Mail Stop 17-2-C
Thousand Oaks, CA, 19320-1799
Drug Class: Biologics

Applicant's Proposed Indication: Treatment of anemia with darbepoetin alfa in pediatric patients with chronic kidney disease (CKD) receiving and not receiving dialysis.

Applicants Proposed Dosage and Administration:
Recommended starting dose for pediatric patients with CKD:

- 0.45 mcg/kg intravenously or subcutaneously weekly
- patients with CKD not on dialysis may also be initiated at 0.75 mcg/kg every 2 weeks

Darbepoetin alfa is a glycoprotein analog of erythropoietin (EPO). Darbepoetin alfa is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Darbepoetin alfa differs from human recombinant erythropoietin (rHuEPO) in containing of 5 N-linked oligosaccharide chains (instead of 3 chains in the ruHuEPO). However, due to the additional carbohydrate chains, darbepoetin alfa has an approximately 3-fold longer terminal half-life and longer in vivo biological activity than rHuEPO. Aranesp stimulates erythropoiesis by the same mechanism as endogenous erythropoietin.

Aranesp is formulated as a sterile, colorless, preservative-free solution containing polysorbate for intravenous or subcutaneous administration. Each 1 mL contains polysorbate 80 (0.05 mg), sodium chloride (8.18 mg), sodium phosphate dibasic anhydrous (0.66 mg), and sodium phosphate monobasic monohydrate (2.12 mg) in Water for Injection, USP (pH 6.2 ± 0.2).

Darbepoetin alfa is licensed and approved in the US for the treatment of anemia in adult and pediatric patients with chronic kidney disease (CKD), including patients receiving dialysis and patients not receiving dialysis, and for the treatment of anemia in adult patients with non-myeloid malignancies when anemia is due to concomitantly administered chemotherapy.

2.2 Tables of Currently Available Treatments for Proposed Indications

The current United States prescribing information (USPI) contains dosing information on the conversion of pediatric patients from epoetin alfa to darbepoetin alfa, based on results from Study 20000100, an open-label, randomized, non-inferiority study comparing darbepoetin alfa and epoetin alfa for the treatment of anemia in pediatric patients (ages 1-18 years) with Chronic Kidney Disease (CKD) receiving and not receiving dialysis.

Epogen/Procrit (Epoetin alfa) is currently approved for use in pediatric patients for the treatment of anemia due to CKD on dialysis age 1 month and above.

2.3 Availability of Proposed Active Ingredient in the United States

Darbepoetin alfa (Aranesp®) is currently approved and marketed in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

Adverse events of special interest related to darbepoetin alfa have been identified including, hypertension, ischemic heart disease, cardiac failure, cerebrovascular disorders, dialysis vascular access thrombosis, embolic and thrombotic events, convulsions, antibody-mediated pure red cell aplasia (PRCA), hypersensitivity, and malignancies.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Aranesp approval letter (STN 103951/5088) dated December 15, 2005 included the following Postmarketing Commitment (PMC):

> *"To conduct a study, such as a single-arm open-label study or a prospective patient registry, to evaluate the safety and usefulness of Aranesp for initial treatment for the correction of anemia in pediatric chronic renal failure patients. The draft protocol will be submitted to the FDA by June 30, 2006, and the study report will be submitted to the FDA by April 30, 2009."*

To address this commitment, the protocol for Study 20050256, designed as a single-arm open-label study, was submitted on June 22, 2006. On September 18, 2006 the FDA recommended that the Study 20050256 design be changed to that of a double-blind, randomized trial.

On 30 April 2007, Amgen submitted a revised protocol for a randomized two-arm study, response to Agency's comments, and a proposal of the following commitment to reflect the new study design and timeline:

> *"To conduct a randomized, double-blinded, multi-center trial to evaluate the safety and efficacy of Aranesp® for initial treatment for the correction of anemia in pediatric chronic renal failure patients."*

On 30 November 2012, FDA released PMC 5088 made on December 15, 2005 in the approval letter and reissued a new PMC dated June 07, 2007.

On February 13, 2014 the FDA confirmed the fulfilment of PMC 103951/5326-1 based on the submission of the interim clinical study report (CSR) for study 20050256 on January 15, 2013.

A Prior Approval Supplement (PAS) request letter dated February 13, 2014, the FDA requested data sets and a prior approval labeling supplement to be submitted.

On 27 February 2014, the FDA accepted Amgen's proposal to provide the final CSR that includes 13 additional patients and related data in a labeling PAS by September 30, 2014.

On September 24, 2014, Amgen submitted the Prior Approval Labeling Supplement: Pediatric Study 20050256.

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2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the electronic Common Technical Document (eCTD). The overall quality and integrity of the application appear reasonable.

The initial filing review of the submission revealed no potential issues.

3.2 Compliance with Good Clinical Practices

Studies were conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) regulations/guidelines and applicable country regulations.

3.3 Financial Disclosures

Amgen provided financial disclosure forms for all investigators who participated in Study 20050256. These were reviewed and do not appear to have jeopardized the data or their interpretations as provided in the submission. Amgen also stated that no clinical investigators or sub-investigators who participated in Study 20050256 are full or part-time employees of Amgen.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Aranesp is an approved drug in US. No new CMC information was provided in this sBLA submission.

4.2 Clinical Microbiology

N/A

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4.3 Preclinical Pharmacology/Toxicology

No new information was provided.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Aranesp stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. Darbepoetin alfa has an approximately 3-fold longer terminal half-life and longer in vivo biological activity than rHuEPO due to the additional carbohydrate chains. Erythropoiesis-stimulating agents (ESAs) increase hemoglobin concentration and reduce the need for red blood cell (RBC) transfusions.

4.4.2 Pharmacodynamics

Darbepoetin alfa stimulates erythropoiesis via the erythropoietin receptor. The increased sialic acid content of darbepoetin alfa reduces its relative affinity to the erythropoietin receptor compared to rHuEPO. It also causes an increase in relative potency, measured by in vivo response, due to its approximately 3-fold longer terminal half-life ($t_{1/2,z}$). The potency of darbepoetin alfa relative to that of rHuEPO increases as the interval between doses is lengthened. No new pharmacodynamics data are presented in this variation.

4.4.3 Pharmacokinetics

Pharmacokinetic profiles were determined after a single subcutaneous or intravenous dose in pediatric patients with CKD ages 3 to 16 years in Study 980212. Study 980212 was an open-label, single-dose, crossover, pharmacokinetic study in pediatric patients with CKD who were between 3 and 16 years of age that was included in the original marketing authorization application (MAA) in the EU, and the original biologics license application (BLA) in the US. This study provided supporting PK information in the USPI for the conversion of pediatric patients from epoetin alfa to darbepoetin alfa (approved 15 December 2005).

The results showed that following IV administration, an approximate 25% difference between pediatric and adult patients in the area under the curve from time 0 to infinity ($AUC_{[0-\infty]}$). $AUC_{(0-\infty)}$ was similar between adult (311 ng*hr/mL) and pediatric (233 ng*hr/mL) patients with CKD following SC administration. Half-life was also similar between adult (25.3 h for IV and 48.8 h for SC) and pediatric (22.1 for IV and 42.8 h for SC) patients with CKD following both intravenous and subcutaneous administration.

Refer for clinical pharmacology review for further details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1: Summary of Clinical Trials with Darbepoetin Alfa in Pediatric Patients with CKD

Study Number	Study Design	Entry Criteria	Study Objective(s)	Number of Subjects (age range)	Duration of Treatment	Key Results
Completed Studies (continued)						
20070211	A Prospective, Observational Study	Pediatric CKD patients either receiving or not receiving dialysis	Safety, efficacy, and patterns of use of darbepoetin alfa in clinical practice in the EU	321 enrolled 319 received IP (< 1 to 16 years)	Once enrolled, subjects were followed for 2 years.	• No new safety signal was identified in pediatric CKD patients. • Darbepoetin alfa dosing and Hb concentrations remained relatively stable throughout the 2-year study.
20050256	A Multicenter, Double-blind, Randomized Study	Pediatric CKD subjects either receiving or not receiving dialysis	De novo QW and Q2W darbepoetin alfa dosing for the correction of anemia PK in subjects < 6 years of age	116 enrolled 114 received IP (2-18 years)	24 weeks	• Hb concentrations were corrected to ≥ 10 g/dL in > 80% for both QW and Q2W groups, with statistical significance reached for darbepoetin alfa QW. • The adverse event profile for QW and Q2W dosing is consistent with what is expected in this disease population.
(b) (4)						
20090302	Single-arm, open-label study	Pediatric CKD subjects	PK, PD, and safety in infants < 1 year of age	5 planned (b) (4) < 1 year of age	Single dose, then followed for 29 days	• (b) (4)

Source: sBLA 103951, Module, 5.3.5.1, Table, Page

Reviewer comments: The applicant conducted Study 20050256 which was randomized double-blind trial to evaluate the safety and efficacy of Aranesp for the initial correction of hemoglobin levels in pediatric subjects aged 1 to 18 years with CKD either receiving or not receiving dialysis. Also submitted data results from an observational study (20070211) conducted in Europe to assess the long-term safety of darbepoetin alfa therapy for the treatment of anemia in pediatric patients with CKD receiving or not receiving dialysis.

5.2 Review Strategy

This review is focused on safety and efficacy evidence that the applicant provided to support labeling changes to the prescribing information (PI) pertain to the pediatric use of Aranesp. Analysis will be performed using data from Study 20050256 for efficacy and safety profile of Aranesp use in pediatric patients with anemia due to CKD. Data from the observational study 20070211 will be analyzed for the safety of darbepoetin alfa therapy in pediatric patients < 16 years old with CKD.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Clinical Trial 20050256

5.3.1.1 Trial Overview:

Title: 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 Patients With Chronic Kidney Disease Receiving and Not Receiving Dialysis

Study objectives

Primary

- To test if the proportion of patients achieving a hemoglobin value ≥ 10.0 g/dL at any time point after the first dose during the study is greater than 0.8 when administered de novo darbepoetin alfa QW for treatment of anemia in pediatric CKD patients receiving and not receiving dialysis.
- To test if the proportion of patients achieving a hemoglobin value ≥ 10.0 g/dL at any time point after the first dose during the study is greater than 0.8 when administered de novo darbepoetin alfa Q2W for treatment of anemia in pediatric CKD patients receiving and not receiving dialysis

Secondary

- To assess the safety and tolerability of darbepoetin alfa administered QW and Q2W
- To estimate hemoglobin values over the duration of the study in the QW and Q2W groups
- To estimate doses over the duration of the study in the QW and Q2W groups
- To assess the health-related quality of life (HRQOL) in pediatric CKD patients ≥ 2 years old over the duration of the study in the QW and Q2W groups
- To obtain PK data in patients < 6 years of age

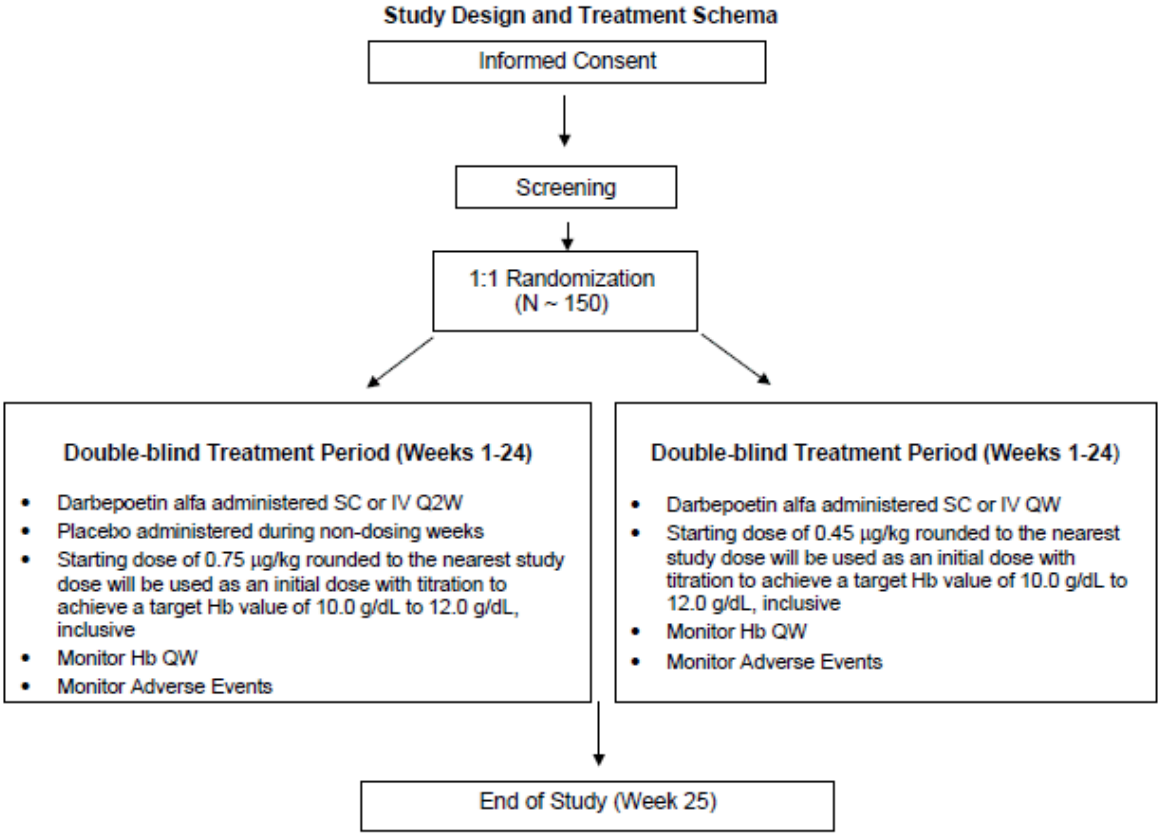
Study Design:

This was a phase 3, multicenter, double-blind, randomized study in pediatric patients 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.

Patients were randomized to the Q2W arm received Q2W injections of placebo during non-dosing weeks to maintain the blind. Darbepoetin alfa was administered intravenously (IV) to patients receiving HD. The initial darbepoetin alfa dose was 0.45 μg/kg or 0.75 μg/kg, rounded to the nearest unit dose, for patients randomized to the QW and Q2W group, respectively. For HD patients, 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. Patients were assessed during the treatment phase and at an

end-of-study visit, which was 1 week after the final dose of Darbepoetin (week 25) or at the time of early study withdrawal.

Figure 1: Study Schema (study 20050256)



Hb = hemoglobin; IV = intravenously; QW = once weekly; Q2W = once every 2 weeks; SC = subcutaneously
Source: sBLA 103951, Module 5.3.5.1, Figure 8-1, Page 26.

Primary Endpoints

- For the QW arm: Achieving a Hb value ≥ 10.0 g/dL at any time point after the first dose without receiving any red blood cell transfusions after randomization and within 90 days prior to the Hb measurement
- For the Q2W arm: Achieving a Hb value ≥ 10.0 g/dL at any time point after the first dose without receiving any red blood cell transfusions after randomization and within 90 days prior to the Hb measurement

Secondary Endpoints

- Hb value at each scheduled time point
- Darbepoetin alfa doses over the duration of the study
- Time to first Hb value ≥ 10.0 g/dL
- Dose at first Hb value ≥ 10.0 g/dL
- Maximum Hb value increase over a 2 week period
- Adverse events, blood pressure, and changes in laboratory parameters during the study

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- Hb rate of rise (ROR) during the study and excursions above 12.0 g/dL, above 13.0 g/dL, and above 14.0 g/dL
- Anti-erythropoietic protein antibodies at each scheduled time point
- Change from baseline at Week 13 and Week 25 in Pediatric Quality of Life Questionnaire (PedsQL) scores for patients ≥ 2 years of age
- PK data in patients < 6 years of age

5.3.1.2 Eligibility Criteria:

Inclusion criteria include

- Ages 1 year through 18 years. Distribution of randomization by age group:
  - approximately 50% randomized 1 year to < 12 years of age
    - 10% randomized 1 year to < 6 years of age
    - 40% randomized 6 years to < 12 years of age
  - approximately 50% randomized 12 years through 18 years of age
- Diagnosis of CKD defined as CKD stage 3 – 5, with an estimated Glomerular Filtration Rate (GFR) < 60 mL/min/1.73 m^2 (Schwartz equation) if not receiving dialysis, or: Receiving dialysis
- Two consecutive screening Hb values drawn at least 5 days apart must be < 10.0 g/dL
- Transferrin saturation (TSAT) ≥ 20%
- Clinically stable, in the judgment of the investigator

Exclusion criteria

- Anticipating or scheduled for a living related-donor kidney transplant
- Prior history (within 6 months prior to randomization) of thromboembolism
- Prior history (within 12 weeks before randomization) of events including:
  - acute myocardial ischemia
  - hospitalization for congestive heart failure
  - myocardial infarction
  - stroke or transient ischemic attack
- Hematologic disease that is likely to affect red blood cell production or turnover (eg, hemolytic anemia, thalassemia, sickle cell disease, myelodysplastic syndromes, hematologic malignancy); myeloma
- Upper or lower GI bleeding within the 6 months prior to randomization
- Use of any erythropoiesis stimulating agent (ESA) within the 8 weeks prior to randomization, and/or, previous use of an ESA for an unapproved indication or administered via an unapproved route at any time prior to randomization
- Uncontrolled hypertension defined as stage 2 hypertension or greater. This is defined as a systolic or diastolic blood pressure value greater than the 99th percentile + 5 mmHg for a patient's age
- Use of any erythropoietic-stimulating agent (ESA) within 8 weeks before randomization, and/or, previous use of an ESA for an unapproved indication or administered via an unapproved route at any time prior to randomization.
- History of non-febrile seizure 4.2.8 Major surgery within 12 weeks prior to randomization (excluding vascular access surgery)

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- Clinical evidence of current malignancy and/or receiving systemic chemotherapy/radiotherapy with the exception of localized basal cell or squamous cell carcinoma of the skin and cervical intraepithelial neoplasia
- RBC transfusions within 1 week prior to randomization
- Androgen therapy within 8 weeks prior to randomization
- Currently receiving antibiotic therapy for systemic infection
- Prior history (within 6 months prior to randomization) of thromboembolism (eg, deep vein thrombosis or pulmonary embolism)
- Peritoneal dialysis patients with an episode of peritonitis within 30 days prior to randomization
- Pregnant or breast-feeding, or planning to become pregnant within 4 weeks after the end of treatment. Females who have reached menarche must have a negative serum pregnancy test.

The duration of the study for an individual patient was approximately 25 weeks with up to 2 additional weeks for screening prior to randomization.

Eligible patients were randomly assigned, in a ratio of 1:1, to 1 of the 2 treatment arms. Patients were stratified by age (1 to < 6 years, 6 to < 12 years, and 12 through 18 years) and dialysis status (non-dialysis, or dialysis (HD or PD)). The investigator (or designee) was to contact IVRS to randomize a patient within 14 days after initiating screening procedures.

The distribution of randomization for the study was to target approximately:

- 50% randomized 1 year to < 12 years of age
    - 10% randomized 1 year to < 6 years of age
    - 40% randomized 6 years to < 12 years of age
- 50% randomized 12 years through 18 years of age

5.3.1.3 Treatment:

For patients randomized to the QW arm, the first dose of darbepoetin alfa was 0.45 μg/kg based on the patient's weight (post-dialysis weight for HD patients). For patients randomized to the Q2W arm, the first dose of darbepoetin alfa was 0.75 μg/kg based on the patient's weight (post-dialysis weight for HD patients).

Dosage Adjustments
Throughout the study, the dose of darbepoetin alfa was adjusted as necessary to maintain the patient's Hb value within a target range of 10.0 g/dL to 12.0 g/dL. Dose adjustment was according to the Hb level (Table 2 below).

Dose increases was not allowed more than once every 4 weeks unless it is to resume a previously held dose, which can be done at any time. The first dose increase may not be made until Week 5.

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Table 2: Dose Adjustment Rules (study 20050256)

Hb value (g/dL)	Dose Adjustment
< 10.0	Dose increased to the next higher unit dose[a,b]
Within target (≥ 10.0 and ≤ 12.0)	No dose change
> 12.0 and ≤ 13.0 or Hb ROR ≥ 1.0 g/dL/2 weeks	Dose decreased to the next lower unit dose[c]
1 Hb value > 13.0	Dosing held until the Hb level was < 12.0, then resumed at the next lower unit dose

Hb = hemoglobin; ROR = rate of rise
[a] A dose increase was allowed only once every 4 weeks, unless to resume a previously held dose.
[b] If a subject reached the maximum dose and their Hb value was still below the target range, then the site contacted Amgen to discuss the subject's future dosing with investigational product.
[c] If the subject was already receiving the lowest dose, then the site contacted Amgen to discuss the subject's future dosing with investigational product.
Source: sBLA 103951, Module, 5.3.5.1, Table 8-2, Page 34

Prior and Concomitant Therapy: Throughout the study, investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except ESAs (apart from study medication), androgen therapy, systemic chemotherapy, radiotherapy, or Darbepoetin or devices other than those specified for this study.

Iron was administered according to clinic policy to ensure that patients were iron replete (ie, TSAT ≥ 20%). Red blood cell transfusions and, if clinically indicated for polycythemia, phlebotomy were allowed during the study.

All doses of Darbepoetin (darbepoetin alfa or placebo) were administered at the study center or at home by designated, trained, medical personnel.

Patients could be removed from the study for the following reasons:

- withdrawal of consent,
- administrative decision by the investigator or Amgen,
- pregnancy in female patient or pregnancy in female partner of a male patient if he was unwilling to use a condom during treatment and for 1 month after the end of treatment,
- ineligibility,
- noncompliance,
- lost to follow up,
- significant protocol deviation,
- kidney transplant,
- adverse event,
- death.

5.3.1.4 Study Assessment:

On visit days, all blood samples were obtained before dialysis was initiated (if applicable) and before dosing with Darbepoetin. If the patient was unable to go to the clinic, a designated,

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qualified, trained, nurse/medical assistant/technician went to the patient's home to draw blood samples and perform other protocol-specified procedures. Patients were required to visit the clinic at least once a month.

Table 3: Schedule of Assessments

Tests and Observations	Screening[i]	Treatment Period (Weeks)																							EOS
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Informed consent (assent if applicable)	X																								
Medical history	X																								
Physical examination	X																								X
Weight[e]	X	X		X		X		X		X		X		X		X		X		X		X		X	X
Height, RR, HR, temperature	X																								X
Hb	X[a]	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Resting BP[b]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[c]	X													X												X
TSAT	X													X												X
Chemistry[c]	X													X												X
CRP, IL-6			X[d]											X												X
Serum pregnancy[f]	X																									
PK blood draws[g]			X	X	X																					
Darbepoetin alfa											QW OR Q2W, depending on randomization															
Concomitant medications											Record Continuously[h]															
Blood transfusions														Record Continuously											
HRQOL (PRO) assessment (subj ≥ 2 years)			X[d]											X												X
Anti-erythropoietic protein antibody assay			X[d]																							X
Adverse events											Record Continuously															

BP = blood pressure; CRP = c-reactive protein; EOS = end of study; Hb = hemoglobin; HR = heart rate; HRQOL = health-related quality of life; IL-6 = interleukin 6; PK = pharmacokinetic; QW/Q2W = once weekly/ once every 2 weeks; RR = respiration rate; TSAT = transferrin saturation

[a] Hb: 2 consecutive Hb values drawn at least 7 days apart were < 10.0 g/dL (see Section 8.3)

[b] obtained as part of screening physical exam and measured throughout study; if applicable, collected during the 2nd or 3rd hemodialysis session of the week (except for end of study)

[c] The chemistry profile included urea or blood urea nitrogen, creatinine, potassium, albumin, alanine aminotransferase and aspartate aminotransferase. The hematology panel included red blood cells, Hb, hematocrit, reticulocytes, platelets and white blood cells.

[d] obtained on day 1 before the first dose of investigational product

[e] pre- and post-dialysis for hemodialysis subjects

[f] Serum pregnancy test (or definitive evidence to demonstrate lack of pregnancy) required for all females who reached menarche, unless there was a documented history of amenorrhea

[g] for subjects < 6 years only: drawn at Weeks 1,2, and 3 before the investigational product dose and 2 days after the first investigational product dose

[h] anti-hypertensive medications, iron therapy, vitamin D, phosphate binders, cinacalcet, growth hormone and corticosteroids (corticosteroid use was collected at each visit.)

[i] 14 days before randomization

Source: sBLA submission, Module 5.3.5.1, table 8-3, P. 38.

Efficacy Assessments: Hemoglobin measured weekly by central lab was used to evaluate the efficacy of darbepoetin alfa to achieve and maintain the target (10 to 12 g/dL).

Darbepoetin alfa dose was determined by IVRS from protocol-specified dosing criteria based on hemoglobin level and hemoglobin rate of rise (ROR).

Pharmacokinetic Sample Assessments: For all patients < 6 years of age, serum samples for determination of darbepoetin alfa concentrations were obtained according to the assessment schedule. Serum concentrations of darbepoetin alfa were measured by an enzyme-linked immunosorbent assay (ELISA). The assay was developed and validated at Amgen.

Anti-erythropoietic Protein Antibody Sample Assessments: Serum samples for the assessment of potential anti-erythropoietic protein antibodies were obtained from each patient before the first dose of Darbepoetin on day 1 and at the end of study or early termination

Safety Assessments: Safety was assessed by determining the nature, frequency, severity, relation to treatment, and outcome of all adverse events; changes in laboratory variables (including hemoglobin) and vital signs; requirements for RBC transfusions, and anti-erythropoietic protein antibody formation.

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5.3.1.5 Analysis Plan

The primary endpoint for the QW and Q2W arms was defined as the number of patients who have at least 1 single post dose Hb ≥ 10.0 g/dL during the study (without receiving any red blood cell transfusions after randomization and within 90 days prior to the Hb measurement) divided by the number of patients in the efficacy analysis subset. The first null hypothesis was that 'correction proportion' is less than or equal to 0.8 in the QW arm, and the second null hypothesis is that 'correction proportion' is less than or equal to 0.8 in the Q2W arm. When data from either arm rejected the null hypothesis at significance level 0.025 (1-sided), the study was demonstrating the efficacy of darbepoetin alfa administered in that frequency.

A total of 150 patients was planned to enroll in the trial. Patients were to be randomized in 1:1 and stratified by age (1 to < 6 years, 6 to < 12 years, and 12 through 18 years) and dialysis status (non-dialysis, and dialysis (HD and PD)) to avoid randomizing patients of an age/dialysis stratum to only 1 arm, thus to facilitate sub-group analyses in each arm.

Descriptive statistics were planned to be summarized for all the secondary endpoints by administration group.

Statistics for the secondary safety endpoints (adverse events, Hb-related parameters, blood pressure, laboratory parameters and antibody results) were planned to compose the safety analyses.

A subgroup analysis making assessments for selected endpoints by age group (1 to < 6 years, 1 to < 12 years, 6 to < 12 years, 12 through 18 years) and stage of CKD (CKD not receiving dialysis, HD and PD) was planned to be performed.

The PK data for patients < 6 years of age planned to be combined with PK data obtained in other Amgen pediatric studies using darbepoetin alfa and analyzed using population PK methodology.

Efficacy analyses was based on the data set (efficacy analysis subset) including all patients (both dialysis and non-dialysis patients), who received at least 1 dose of Darbepoetin.

Safety analyses was based on the data set including all patients (both dialysis and non-dialysis patients) receiving at least 1 dose of Darbepoetin (safety analysis subset). Patients were included in the treatment group according to their initially administered treatment frequency.

No interim analyses were planned. However, an unplanned interim analysis was conducted to fulfill regulatory obligations and was included all patients who ended study by 31 July 2012. To protect the blind, data for ongoing patients remained blinded.

5.3.1.6 Protocol Amendment:

The protocol was originally approved on 14 June 2006 and amended on 20 August 2007, 08 November 2007, 26 August 2008, 04 May 2010, 30 January 2012, and 13 September 2012.

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The following is a summary of the major changes for each amendments:

1. Amendment 1: August 20, 2007
    a. The study design was changed from an open-label, single-arm study assessing the safety and efficacy of darbepoetin alfa administered Q2W to a double-blind, randomized, parallel-group study assessing the safety and efficacy of darbepoetin alfa administered QW or Q2W.
        b. The targeted age distribution was revised to enroll a greater percentage of patients < 12 years.
        c. The Hb target range was revised from 11.0 - 13.0 g/dL to 11.0 - 12.0 g/dL.
        d. Collection of samples for pharmacokinetic analyses was added for patients < 6 years old.
        e. The frequency of Hb measurements was changed from biweekly to weekly.
        f. Darbepoetin alfa product used in this study was changed from vials to prefilled syringes.
2. Amendment 2: November 8, 2007
        a. The procedures section was updated to reflect the use of a central laboratory for analyses.
3. Amendment 3: August 26, 2008
        a. Minor updates were made to the eligibility criteria,
        b. Number of blood samples collected were reduced by removing samples required for future analysis, and
        c. Regions outside North America were allowed to participate.
4. Amendment 4: May 4, 2010
        a. The exclusion criteria were revised to allow the use of low dose corticosteroids (such as those used for asthma treatment)
5. Amendment 5: January 30, 2012
        a. The protocol was amended to allow a 5 μg dose so that patients who required treatment with < 10 μg darbepoetin alfa (lowest dose previously specified) could receive Darbepoetin.
        b. Darbepoetin alfa product was changed from prefilled syringes to vials in order to accommodate this dose while retaining the blind.
6. Amendment 6: September 13, 2012
        a. The protocol was amended to include the occurrence of an unplanned interim analysis of data from all patients who ended the study by July 31, 2012 in order to fulfill regulatory requirements.

6 Review of Efficacy

Efficacy Summary

Study 20050256 was a randomized, double-blind randomized study in pediatric patients with CKD receiving dialysis (HD or PD) or not receiving dialysis who were anemic (hemoglobin < 10.0 g/dL) and not being treated with an ESA. A total of 114 patients age 2 to 18 years were evaluated for the efficacy of darbepoetin alfa administered QW or Q2W for the correction and

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maintenance of hemoglobin concentrations. The efficacy results of this study demonstrate the following:

- Hemoglobin concentrations were corrected to ≥ 10 g/dL in 98% of pediatric patients administered darbepoetin alfa QW. The percentage was greater than 0.80, which was statistically significant ($p < 0.001$).
- In subgroup analyses, the correction proportion was also > 0.80, regardless of baseline age, dialysis status, and hemoglobin value.
- In patients who administered darbepoetin alfa Q2W, 84% of them achieved hemoglobin ≥ 10 g/dL during this study. However, this percentage was not statistically significantly greater than 0.80 ($p = 0.293$).
- In subgroup analyses, the correction proportion was also > 0.80 for both age subgroups, patients not receiving dialysis, and patients whose baseline hemoglobin was ≥ 9.0 g/dL.
- Hemoglobin concentrations were maintained across the study period with both darbepoetin alfa QW and Q2W, with weight-adjusted doses generally decreasing over the study period for both treatment groups.

6.1 Indication

The proposed indication: Aranesp is indicted for the initiation of treatment of anemia in pediatric patients with chronic kidney disease (CKD) receiving and not receiving dialysis.

6.1.1 Methods

6.1.1.1 Clinical Trial 20050256

Title: 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 Patients With Chronic Kidney Disease Receiving and Not Receiving Dialysis.

This trial was a phase 3, multicenter, double-blind, randomized study in pediatric patients with CKD receiving dialysis (HD or PD) or not receiving dialysis who were anemic (hemoglobin < 10.0 g/dL) and not being treated with an ESA.

A total of 116 patients were randomized to receive darbepoetin alfa QW (n=59) or Q2W (n=57) for 24 weeks. Patients 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 IV to patients receiving HD and SC to patients not receiving dialysis and to patients receiving PD. darbepoetin alfa was administered in prefilled syringes at the following unit doses: 10, 20, 30, 40, 50, 60, 80, 100, 150, 200 or 300 µg. In protocol amendment 5, darbepoetin alfa drug product (and placebo) was changed to a single-use vial (in 5 concentration strengths of 25, 100, 200, 300, and 500 µg/mL) in order to provide the added dose of 5 µg. The initial darbepoetin alfa dose was 0.45 µg/kg (QW group) or 0.75 µg/kg (Q2Wgroup), rounded to the nearest unit dose. For both treatment groups, subsequent darbepoetin alfa doses were titrated

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to achieve a target hemoglobin value of 10.0 g/dL to 12.0 g/dL. Patients were assessed throughout the treatment period and at an end-of-study visit, which was 1 week after the final dose of Darbepoetin (week 25) or at the time of early study withdrawal.

6.1.2 Demographics

Clinical Trial 20050256

Most of the patients were male (60% in QW and 59% in Q2W). Patients were grouped in 3 cohorts. Age group 1 to < 6 years cohort, only 3 patients (2 in QW and 1 in QW) out of the planned 25, enrolled in the trial. From the planned 50 patients in age group 6 to <12 cohort, a total of 37 (19 in QW and 18 in Q2W) were enrolled. However, 74/75 patients (37 in each arm) in age group 12-18 years of age were enrolled in the trial. The majority of patients ~50% were white, followed by Hispanic or Latino ~ 40% than black 8%. Approximately, 60% of the patients were not on dialysis.

The median baseline hemoglobin level was 8.68 (6.4, 9.9) g/dL in the QW group and 8.85 (6.1, 9.9) g/dL in the Q2W group. The percentage of patients with baseline hemoglobin values < 9.0 g/dL was higher in the QW group than that in the Q2W group (62% vs. 55%).

The mean baseline eGFR for patients not receiving dialysis at baseline was similar between the two groups (24.8 for the QW and 24.5 mL/min/1.73 m^2 in the Q2W groups).

Summary of baseline characteristic for efficacy analysis set presented in Table 4.

Table 4: Baseline Demographics (Efficacy Analysis Set)

	Darbepoetin alfa		
	QW (N=58)	**Q2W (N=56)**	**Total (N=114)**
Sex, n (%)			
Male	35 (60)	35 (59)	70 (60)
Female	23 (40)	23 (41)	46 (40)
Age group in years, n (%)			
Age group 1- < 6	2 (3)	1 (2)	3 (3)
Age group 6- <12	19 (33)	18 (32)	37 (32)
Age group 12- 18	37 (64)	37 (66)	74 (65)
Median age (Min, Max), years	13 (2, 18)	13.5 (5, 18)	13 (2, 18)
Race, n (%)			
White	30 (52)	30 (54)	60 (53)
Black or African American	4 (7)	5 (9)	9 (8)
Hispanic or Latino	23 (40)	20 (36)	43 (38)

Other	1 (2)	1 (2)	2 (2)
Dialysis Status, n (%)			
Not Receiving Dialysis	33 (57)	33 (59)	66 (58)
Receiving Dialysis	25 (43)	23 (41)	48 (42)
Hemodialysis	25 (43)	14 (25)	29 (25)
Peritoneal Dialysis	10 (17)	9 (16)	19 (17)
Hemoglobin (g/dL)			
Mean (SD)	8.59 (0.84)	8.73 (0.84)	8.66 (0.84)
Median (Min, Max)	8.68 (6.4, 6.9)	8.85 (6.1, 9.9)	8.8 (6.1, 9.9)
Hemoglobin at baseline, n (%)			
< 9.0 g/dL	36 (62)	31 (55)	67 (59)
≥ 9.0 g/dL	22 (38)	25 (45)	47 (41)
Baseline eGFR (ml/min/1.73m^2)	n= 32	n= 33	n= 65
Mean (SD)	24.8 (13.7)	24.5 (11.2)	24.6 (12.4)
Median (Min, Max)	20 (7, 64)	23 (10, 49)	21 (7, 64)

Source: sBLA submission, Module 5.3.5.1, Tables 9-3 & 9-4, page 61& 63.

Reviewer comments: The demographic and baseline characteristics were comparable between the two groups in sex, age group, race, dialysis status, median and mean hemoglobin and baseline eGFR.

6.1.3 Patient Disposition

A total of 116 patients were enrolled in the study. Of these patients, 59 and 57 were randomized to receive darbepoetin alfa QW and Q2W, respectively. One hundred and fourteen patients (58 QW, 56 Q2W) received at least 1 dose of Darbepoetin and were included in the efficacy and safety analysis sets. The first patient was enrolled into the study on September 16, 2008 and the last patient was enrolled on December 2, 2013. The last patient ended treatment with Darbepoetin on February 24, 2014 and completed the study on March 3, 2014.

In the QW group, 45 (76%) patients completed treatment with IP, and 48 (81%) patients completed the study. One patient did not receive IP because study ineligibility was determined after randomization, and 3 patients in this group discontinued treatment, but completed all other study procedures.

In the Q2W group, 45 (79%) patients completed treatment with IP, and completed the study. Consent was withdrawn for 1 patient before IP was administered.

Table 5: Patient Disposition

Number of patients Randomized	Darbepoetin alfa		
	QW (N = 59)	Q2W (N = 57)	Total (N = 116)
Never received Darbepoetin, n (%)	1 (2)	1 (2)	2 (2)
Received Darbepoetin	58 (98)	56 (98)	114 (98)
Completed Darbepoetin	45 (76)	45 (79)	90 (77.6)
Discontinued Darbepoetin	13 (22)	11 (19)	24 (21)
Completed study	48 (81)	45 (79)	93 (80)
Discontinued study	11 (19)	12 (21)	23 (20)

Source: Module 5.3.5.1, Tables

Reviewer comments: The rate of patients who completed the trial was similar between the two groups.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was defined as the proportion of patients who have at least 1 postdose hemoglobin ≥ 10.0 g/dL during the study (without receiving any red blood cell transfusion after randomization and within 90 days prior to the hemoglobin measurement). The primary efficacy endpoint will be considered statistically significant if 80% or greater of the patients achieved the hemoglobin level of 10 g/dL or above during the trial.
Secondary efficacy endpoints included time to first hemoglobin ≥ 10.0 g/dL, hemoglobin concentrations across time, darbepoetin alfa dose at first value of hemoglobin ≥ 10.0 g/dL and across time.

Secondary safety endpoints included the incidence of treatment-emergent adverse events, hemoglobin-related analyses, vital signs, laboratory parameters, and anti-erythropoietic protein antibodies. An additional secondary endpoint was to determine darbepoetin alfa serum concentrations for patients < 6 years of age.

Efficacy and safety analyses included all patients who received ≥ 1 dose of Darbepoetin.

Efficacy Results:
Hemoglobin concentrations were corrected to ≥ 10 g/dL in 98% of pediatric patients who received darbepoetin alfa QW. This proportion was significantly greater than 0.80 ($p < 0.001$). However, 84% of patients in the Q2W achieved hemoglobin ≥ 10 g/dL during this study. The percentage was not statistically significantly greater than 0.80 ($p = 0.293$).

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Table 6: Patients Achieving Hemoglobin ≥ 10.0 g/dL, (Study 20050256)

	QW (n=58)	Q2W (n=56)
Proportion of patients achieving Hb ≥ 10 g/dL, (95% CI)	0.98 (0.91, 1.0)	0.84 (0.72, 0.92)
One sided p-value	<0.001	0.29
Proportion of patients on dialysis achieving Hb ≥ 10 g/dL, (95% CI)	0.96 (0.80, 0.99)	0.72 (0.51, 0.88)
One sided p-value	0.023	0.780
Proportion of patients not on dialysis achieving Hb ≥ 10 g/dL, (95% CI)	1.0 (0.89, 1.0)	0.94 (0.79, 0.99)
One sided p-value	< 0.001	0.037

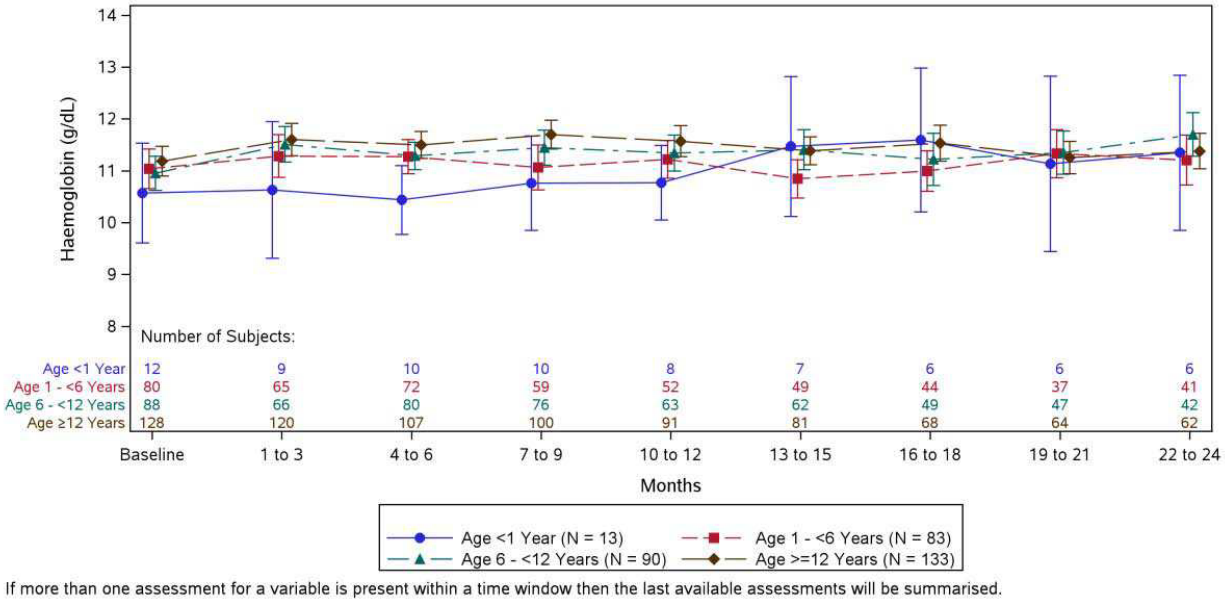
Source: Module 5.3.5.1, Table 3, P 26.

Hemoglobin Concentration Over Time

The mean hemoglobin concentration was 11.1 g/dL at baseline. Mean hemoglobin for all patients remained consistent throughout the duration of the study, ranging between 11.3 and 11.5 g/dL. The majority (95.0%) of patients had at least 1 hemoglobin value between 10 and 12 g/dL (inclusive) at some time during the study.

The mean hemoglobin assessed by age subgroup remained constant (Figure 2). Mean hemoglobin levels ranged between 10.9 g/dL and 11.5 g/dL for patients receiving dialysis at baseline and between 11.2 g/dL and 11.7 g/dL for patients not receiving dialysis at baseline.

Figure 2: Mean (95% CI) Hemoglobin Level by 3-Monthly Intervals and Baseline Age Group



Source: sBLA submission, Module 2.5, Figure 4, P.32

6.1.5 Analysis of Secondary Endpoints(s)

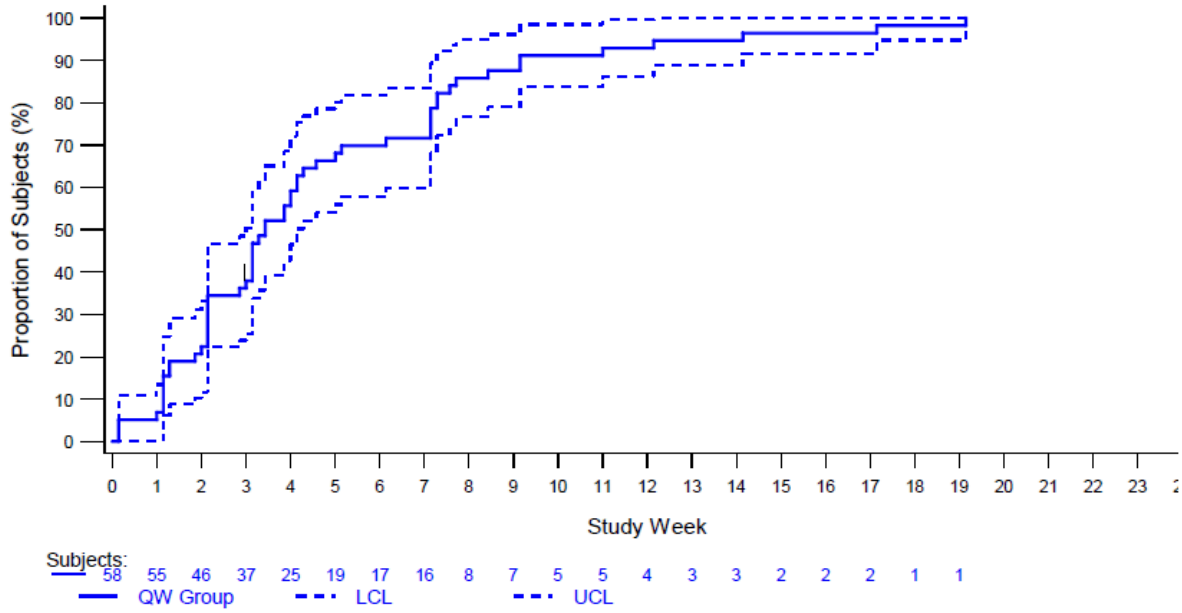
Secondary efficacy endpoints included time to first hemoglobin ≥ 10.0 g/dL, hemoglobin concentrations across time, darbepoetin alfa dose at first value of hemoglobin ≥ 10.0 g/dL and across time, and patient-reported outcome scores (PedsQL) for patients ≥ 2 years of age. The analyses for these endpoints were descriptive.

Time to First Hemoglobin Value ≥ 10.0 g/dL

The median time to achieve the first hemoglobin ≥ 10.0 g/dL was 24 (15, 50) days for the QW group and 22 (14, 41) days for the Q2W group.

The Kaplan-Meier percentage of patients in the QW group to achieved hemoglobin ≥ 10.0 g/dL increased steadily to 0.88 at week 9, with all patients achieving the endpoint by week 20 (Figure 3). However, the Kaplan-Meier percentage of patients in Q2W group who achieved hemoglobin ≥ 10.0 g/dL increased steadily to 0.89 at week 13, with achieving the endpoint by week 22 (Figure 4).

Figure 3: Kaplan-Meier Plot of Time to Achieve Hemoglobin ≥ 10.0 g/dL in QW Group (Efficacy Analysis Set)



LCL = lower 95% confidence interval; QW = once every 2 weeks; UCL = upper 95% confidence interval.
Source: sBLA submission, Module 5.3.5.1, Figure 10-1, P.69.

Figure 4: Kaplan-Meier Plot of Time to Achieve Hemoglobin ≥ 10.0 g/dL in Q2W Group (Efficacy Analysis Set)

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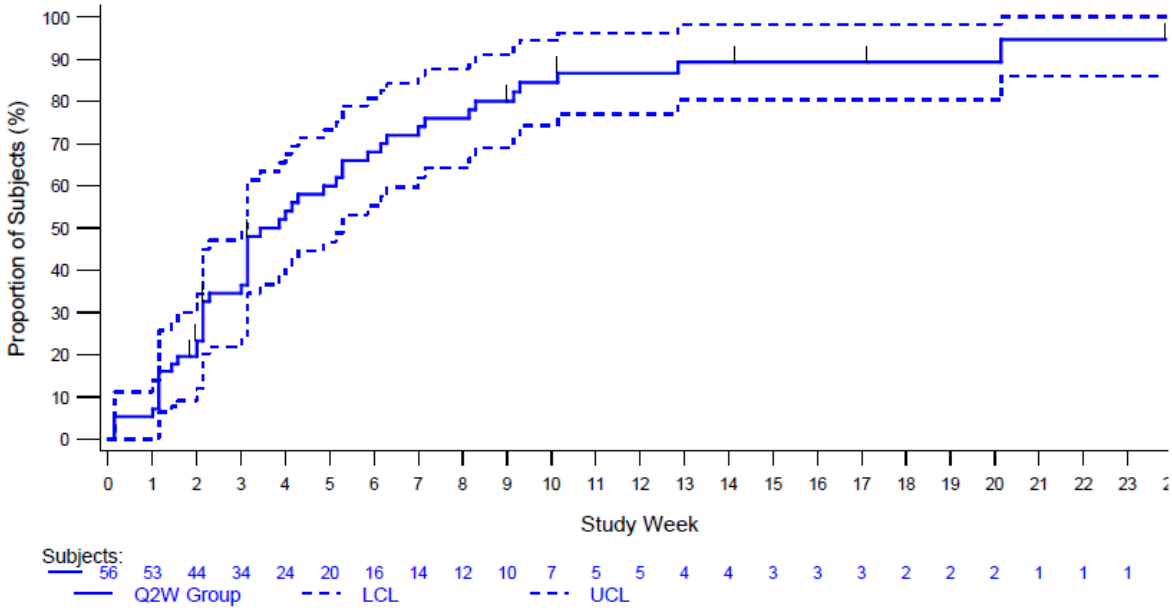

LCL = lower 95% confidence interval; Q2W = once every 2 weeks; UCL = upper 95% confidence interval.
Source: sBLA submission, Module 5.3.5.1, Figure 10-2, P.70.

Hemoglobin Value at Each Scheduled Time Point

The mean hemoglobin for the QW group increased from 8.6 (0.84) g/dL at baseline to 11.3 (1.33) g/dL at week 10 and remained relatively stable through week 25. The mean hemoglobin for the Q2W group increased from 8.7 (0.84) g/dL at baseline to 10.9 (1.38) g/dL at week 12 and then remained relatively stable through the end of the study.

The mean change in hemoglobin from baseline generally increased from week 1 to week 13 and then remained between approximately 2.5 and 2.8 g/dL through the end of the study for the QW group. The mean change in hemoglobin from baseline generally increased from week 1 to week 12 and then remained between approximately 1.6 and 2.0 g/dL through the end of the study for the Q2W group.

Dose at First Hemoglobin Value ≥ 10.0 g/dL

At the time hemoglobin ≥ 10.0 g/dL was first achieved, the mean weight-adjusted dose was 0.48 (0.24) µg/kg weekly for the QW group and 0.76 (0.21) µg/kg biweekly for the Q2W group.

Darbepoetin alfa Doses Over the Duration of the Study

The mean weight-adjusted dose of darbepoetin alfa for patients in QW group decreased from an initial weekly dose of 0.45 (0.07) µg/kg to 0.21 (0.27) µg/kg at week 14, and then remained between 0.29 (0.34) and 0.41 (0.63) µg/kg for the remainder of the treatment period.
The mean (SD) weight-adjusted dose of darbepoetin alfa for patients in Q2W group decreased from an initial biweekly dose of 0.73 (0.13) µg/kg to 0.45 (0.30) µg/kg at week 19 and then remained stable for the remainder of the treatment period.

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6.1.6 Other Endpoints

RBC Transfusion: A total of nine patients, 4 (7%) in the QW group and 5 (9%) in the Q2W group received at least one RBC transfusions during the study. Most of these patients received the transfusions over 1 day (3 QW, 4 Q2W). The mean volume infused was 543 (333.0) mL for the patients in the QW group and 430 (220.8) mL for the patients in the Q2W group. The mean weight-adjusted volume infused was 11.6 (7.56) mL/kg for the patients in the QW group and 11.6 (4.46) mL/kg for the patients in the Q2W group.

6.1.7 Subpopulations

The point estimate of the correction proportion in patients administered darbepoetin QW based on baseline age, dialysis status, and hemoglobin value was > 0.80. The point estimate of the correction proportion in patients administered darbepoetin Q2W was also > 0.80 for both age subgroups, patients not receiving dialysis, and patients whose baseline hemoglobin was ≥ 9.0 g/dL.

Table 7: Patients Achieving Hemoglobin ≥ 10.0 g/dL Overall and by Subgroup (Study 20050256, Efficacy Analysis Set)

	QW (n = 58)		Q2W (n = 56)	
Analysis set	Proportion (exact 95% CI)	One-sided p-value[a]	Proportion (exact 95% CI)	One-sided p-value[a]
All subjects	0.983 (0.908, 1.000)	< 0.001	0.839 (0.717, 0.924)	0.293
Baseline subgroups				
Age				
< 12 years	0.952 (0.762, 0.999)	0.058	0.895 (0.669, 0.987)	0.237
≥ 12 years	1.000 (0.905, 1.000)	< 0.001	0.811 (0.648, 0.920)	0.533
Dialysis status				
Not receiving	1.000 (0.891, 1.000)	< 0.001	0.935 (0.786, 0.992)	0.037
Receiving	0.962 (0.804, 0.999)	0.023	0.720 (0.506, 0.879)	0.780
Hb category				
< 9.0 g/dL	0.972 (0.855, 0.999)	0.003	0.742 (0.554, 0.881)	0.730
≥ 9.0 g/dL	1.000 (0.846, 1.000)	0.007	0.960 (0.796, 0.999)	0.027

CI = confidence Interval; Hb = hemoglobin; QW = once every week; Q2W = once every 2 weeks.
N = Number of subjects in the efficacy analysis set
Achieving Hb value ≥ 10.0 g/dL at any time-point during the study (excluding the Hb measurement on study day 1) without receiving any RBC transfusion after randomization and within 90 days prior to the achievement, and within 7 days of the last IP administration of dose ≥ 0.
[a] Proportion of correction compared to 0.8 using the exact method.

Source: Applicant sBLA submission, Module 2.5, Table 3, P.26.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The initial doses of darbepoetin alfa were selected based on results from a previous pediatric study (Study 20000100), which indicated that darbepoetin alfa doses are similar in adults and

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children, as well as additional pharmacokinetic/pharmacodynamic data that suggested that these doses were appropriate in pediatric patients.

The SC route of administration was chosen for patients not receiving dialysis or receiving PD and the IV route was chosen for patients receiving HD because they are the most commonly used routes of administration in these patient populations.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The analysis of mean hemoglobin over time of the study showed that the mean hemoglobin concentration for the QW group increased from 8.6 (0.84) g/dL at baseline to 11.3 (1.33) g/dL at week 10 and remained relatively stable (ranging from 10.9 [1.10] to 11.7 [1.19] g/dL) through week 25 in spite of that the dose of Aranesp decreased from an initial dose of 0.45 µg/kg to 0.21 (0.27) µg/kg at week 14.

Also, the mean hemoglobin concentration for the Q2W group increased from 8.7 (0.84) g/dL at baseline to 10.9 (1.38) g/dL at week 12 and then remained relatively stable between 10.4 (0.97) and 11.1 (1.00) g/dL through the end of the study, in spite of that the dose of Aranesp decreased from an initial (biweekly) dose of 0.73 (0.13) µg/kg to 0.45 (0.30) µg/kg at week 19.

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy analysis performed.

7 Review of Safety

Safety Summary

The review of safety profile of darbepoetin alfa for the proposed indication of the treatment of anemia due to chronic kidney disease (CKD) in pediatric patients on dialysis and patients not on dialysis were consistent with that has been established in adults. The safety findings are the follows:

- The most frequently reported adverse events were hypertension (26% QW, 23% Q2W), vomiting (19% QW, 16% Q2W), upper respiratory infection (18% QW, 32% Q2W), pyrexia (10% QW, 20% Q2W), headache (10% QW, 18% Q2W), abdominal pain (12% QW, 11% Q2W), and cough (12% QW, 7% Q2W).
- The most frequently reported adverse events of interest were hypertension and hypersensitivity (9% QW, 13% Q2W).
- The safety profiles for the QW and Q2W groups were consistent with the known safety profile for darbepoetin alfa in adults.
- There was no new safety signal identified.
- Adverse event profiles were similar for darbepoetin alfa QW and Q2W dosing, including those for the adverse events of interest for darbepoetin alfa population.

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- Less than 10% of patients developed binding anti-erythropoietic protein antibodies during the study. However, there were no patients tested positive for neutralizing antibodies.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This main safety data derived from study 20050256, which includes safety assessments of 114 pediatric patients with CKD (58 QW, 56 Q2W) who received ≥ 1 dose of Darbepoetin in the randomized, double-blind. Supportive safety data came from the observational study 20070211, which includes safety assessments of 319 pediatric.

Study 20050256, was a randomized, double-blind trial that provided safety data for de novo QW and Q2W darbepoetin alfa dosing for the correction of anemia in pediatric patients ages 1 to 18 years with CKD either receiving or not receiving dialysis.

Study 20070211, was an observational safety study that provided long-term safety data for darbepoetin alfa treatment of anemia in pediatric patients ages < 1 to 16 years with CKD in clinical practice.

7.1.2 Categorization of Adverse Events

Safety was assessed by determining the nature, frequency, severity, relation to treatment, and outcome of all adverse events; changes in laboratory variables (including hemoglobin) and vital signs; requirements for RBC transfusions, and anti-erythropoietic protein antibody formation. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from the 2 clinical trials (Studies 20000100 and 20050256) conducted in pediatric patients were pooled to provide an integrated safety profile for pediatric patients. The safety data was compared to that in the adults.

The results showed a lower overall incidence of treatment-emergent adverse events was observed in pediatric patients (86.2%) compared to adult patients (95.8%) with CKD. Table 8 summarized TEAEs occurred in ≥ 10% of patients in pooled pediatric and adult studies.

Table 8: Incidence of Treatment-emergent Adverse Events by Preferred Term in ≥ 10% Patients in Pooled Pediatric and Pooled Adult Studies Receiving Darbepoetin alfa (Safety Analysis Set)

Preferred Term	**Pooled Pediatric[a] (N = 195)**	**Pooled Adult[b] (N = 766)**
Number Of Subjects Reporting Events, n (%)	168 (86.2)	734 (95.8)
Pyrexia	32 (16.4)	71 (9.3)
Headache	31 (15.9)	149 (19.5)
Hypertension	30 (15.4)	224 (29.2)
Vomiting	28 (14.4)	136 (17.8)
Nasopharyngitis	21 (10.8)	94 (12.3)
Cough	19 (9.7)	95 (12.4)
Hypotension	17 (8.7)	156 (20.4)
Upper Respiratory Tract Infection	16 (8.2)	54 (7.0)
Abdominal Pain	15 (7.7)	71 (9.3)
Medical Device Complication	15 (7.7)	88 (11.5)
Injection Site Pain	14 (7.2)	34 (4.4)
Diarrhea	13 (6.7)	163 (21.3)
Muscle Spasms	13 (6.7)	202 (26.4)
Nausea	13 (6.7)	139 (18.1)
Fatigue	11 (5.6)	105 (13.7)
Dizziness	10 (5.1)	96 (12.5)
Pain In Extremity	7 (3.6)	99 (12.9)
Procedural Hypotension	6 (3.1)	83 (10.8)
Dyspnea	5 (2.6)	132 (17.2)
Edema Peripheral	4 (2.1)	110 (14.4)

[a] includes Studies 20050256 and 20000100
[b] includes Studies 970200, 970235, 980117, 980202, and 980211
Source: sBLA 103951, Integrated Summary of Safety (ISS), Table 14-6.1.1

Reviewer comments: The rate of adverse events was generally lower in the pediatric patients compared to that in adults.

7.2 Adequacy of Safety Assessments

The data submitted to this sBLA is adequate to perform the safety review.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Study 20050256:

Treatment duration was similar between the two arms. The median time of exposure to darbepoetin alfa was 24.1 (2.1 to 25.1) weeks for the QW group and 24.5 (2.0 to 25.1) weeks for

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the Q2W group. The median (range) time on study was 24.1 (2.1 to 31.6) weeks for the QW group and 24.1 (2.1 to 25.7) weeks for the Q2W group.

The mean initial weight-adjusted dose was 0.45 (0.073) µg/kg for the QW group and 0.73 (0.125) µg/kg for the Q2W group. The mean weekly weight-adjusted dose was 14.7 µg/kg for the QW group and 15 µg/kg for the Q2W group.

Table 9: Duration of Darbepoetin Alfa Exposure during the Study (Safety Analysis Set)

	Darbepoetin alfa	
	QW (N=58)	Q2W (N=56)
Median (range) Time of exposure, weeks	24.1 (2, 25)	24.5 (2, 25)
Median (range) Time on study, weeks	24.1 (2, 32)	24.1 (2, 26)
Mean (SD) initial weight-adjusted dose, µg/kg	0.45 (0.07)	0.73 (0.13)
Mean (SD) weekly dose of drug, µg/kg	14.7 (10.3)	15.1 (8.8)

Source: sBLA submission, Module 5.3.5.1, Table 14-5.1, P 297.

7.2.2 Explorations for Dose Response

No dose response study was conducted in pediatric patients with anemia due to CKD. The initial QW starting dose (0.45 µg/kg, rounded to the nearest unit dose) was consistent with that specified in the darbepoetin alfa product label for anemia correction in patients with CKD at the time of study initiation. The initial Q2W starting dose (0.75 µg/kg, rounded to the nearest unit dose) was consistent with that used in 2 clinical studies for correction of anemia in adult patients with CKD (Studies 990151 and 20030237); this dose was subsequently included in the darbepoetin alfa product label.

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

The effect of the drug was monitored by weekly measurement of hemoglobin level. The dose of Aranesp was adjusted based on the hemoglobin value. Transferrin saturation (TSAT) was determined at the start of the study and during the study treatment period. In order to support the erythropoietic response to darbepoetin alfa, supplemental iron therapy was to be administered to ensure that the subjects were iron replete (ie, TSAT ≥ 20%) throughout the study.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to Section 12 (CLINICAL PHARMACOLOGY) of Aranesp label.

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7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The safety profile of Aranesp is comparable to that described the Epogen/Procrit PI.

7.3 Major Safety Results

7.3.1 Deaths

No patients died during study 20050256.

7.3.2 Nonfatal Serious Adverse Events

Study 20050256

A total of 68 serious treatment-emergent adverse events were reported in 30 patients (16 (28%) in the QW group and 14 (25%) in the Q2W group) during the study. The most common serious adverse events were hypertension (2% of patients in QW and 5% of patients in Q2W), hyperkalemia (5% in QW and 0% in Q2W), and abdominal pain (3% in QW and 2% in Q2W).

Table 10 summarized the incidence of serious adverse events by arm in study 20050256.

Table 10: Serious Adverse Events by Preferred Term Reported by ≥ 2 Patients

	Darbepoetin alfa		
	QW (N=58)	Q2W (N=56)	Total (N=114)
Hypertension, n (%)	1 (1.7)	3 (5.4)	4 (3.5)
Hyperkalemia, n (%)	3 (5.2)	0 (0)	3 (2.6)
Abdominal pain, n (%)	2 (3.4)	1 (1.8)	3 (2.6)
Headache, n (%)	2 (3.4)	0 (0)	2 (1.8)
Hypotension, n (%)	0 (0)	2 (3.6)	2 (1.8)
Peritonitis, n (%)	0 (0)	2 (3.6)	2 (1.8)
Renal failure or impairment, n (%)	3 (5.2)	2 (3.6)	2 (1.8)

Source: sBLA submission, Module 5.3.5.1, Table 12-4, P 90.

The majority of serious TEAEs were reported in ≥ 12 years age group (21 patients in age group≥ 12 years vs. 9 patients in age group <12 years).

Table 11 summarized the incidence of serious by age group in study 20050256.

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Table 11: Incidence of Serious Adverse Events by Age group

	Darbepoetin alfa			
	QW Age <12 years (N=21)	Q2W Age <12 years (N=19)	QW Age ≥12 years (N=37)	Q2W Age ≥12 years (N=37)
Patients with SAEs, n (%)	5 (24)	4 (21)	11 (30)	10 (27)
Hypertension, n (%)	2 (10)	1 (5)	1 (3)	2 (5)
Hyperkalemia, n (%)	2 (10)	0 (0)	1 (3)	0 (0)
Abdominal pain, n (%)	0 (0)	2 (10)	0	1 (3)
Headache, n (%)	1 (5)	0 (0)	1 (3)	0 (0)
Hypotension, n (%)	0 (0)	0 (0)	0 (0)	2 (0)
Peritonitis, n (%)	0 (0)	0 (0)	0 (0)	2 (5)
Renal impairment or Failure, n (%)	0 (0)	1 (5)	3 (8)	1 (3)

Source: sBLA submission, Module 5.3.5.1, Table 14-6.5.2, P 387.

Reviewer comments: The rate of SAEs was similar across age groups.

7.3.3 Dropouts and/or Discontinuations

Thirteen patients (19%) in the darbepoetin alfa QW group had withdrawn from Darbepoetin. The most frequently cited reasons for withdrawal were renal transplant (6 (10%) patients). Eleven patients (19%) in the QW group withdrew from the study, including 1 patient who did not receive Darbepoetin. Eleven patients (22%) in the darbepoetin alfa Q2W group withdrew from Darbepoetin.

Table 12: Study Completion and Discontinuation (all randomized patients)

	Darbepoetin alfa		
	QW (N=59)	Q2W (N=57)	Total (N=116)
Never received Darbepoetin, n (%)	1 (1.7)	1 (1.8)	2 (1.7)
Received Darbepoetin, n (%)	58 (98.3)	56 (98.2)	114 (98.3)
Completed Darbepoetin, n (%)	45 (76.3)	45 (78.9)	90 (77.6)
Discontinued Darbepoetin, n (%)	13 (22.0)	11 (19.3)	24 (20.7)
Due to Adverse events, n (%)	0 (0)	3 (5.3)	3 (2.6)
Ineligibility determined, n (%)	0 (0)	1 (1.8)	2 (1.8)
Noncompliance, n (%)	1 (1.7)	2 (3.6)	2 (1.8)
Consent withdrawn, n (%)	1 (1.7)	2 (3.5)	3 (2.6)
Administrative decision, n (%)	2 (3.4)	0 (0)	2 (1.7)
Kidney Transplant, n (%)	6 (10.2)	4 (7.0)	10 (8.6)
Other, n (%)	3 (5.1)	1 (1.8)	4 (3.4)

Source: sBLA submission, Module 5.3.5.1, Table 14-1.2, P 109.

Reviewer comments: The rate of patients who discontinue treatment was comparable between the QW and Q2W groups.

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7.3.4 Significant Adverse Events

Adverse events that occurred during the study are summarized in Table 13.

Table 13: Summary of Adverse Events (Safety Analysis Set)

	Darbepoetin alfa		
	QW (N=58)	Q2W (N=56)	Total (N=114)
All treatment emergent adverse events, n (%)	48 (82.8)	50 (89.3)	98 (86.0)
Serious adverse events, n (%)	16 (27.6)	14 (25.0)	30 (26.3)
Leading to discontinuation of Darbepoetin, n (%)	0 (0.0)	2 (3.6)	2 (1.8)
Leading to discontinuation from study, n (%)	0 (0.0)	2 (3.6)	2 (1.8)
Events of interest, n (%)	18 (31.0)	20 (35.7)	38 (33.3)
Treatment-related TEAE, n (%)	14 (24.1)	16 (28.6)	30 (26.3)
Serious adverse events, n (%)	1 (1.7)	2 (3.6)	3 (2.6)
Leading to discontinuation of Darbepoetin, n (%)	0 (0.0)	2 (3.6)	2 (1.8)
Leading to discontinuation from study, n (%)	0 (0.0)	2 (3.6)	2 (1.8)
Events of interest, n (%)	6 (10.3)	9 (16.1)	15 (13.2)

Source: sBLA submission, Module 5.3.5.1, Table 12-1, P84.

Reviewer comments: The rates of TEAEs and events of special interest were comparable between the two groups.

7.3.5 Submission Specific Primary Safety Concerns

Clinically significant adverse events of interest (hypertension, ischemic heart disease, cardiac failure, cerebrovascular disorders, embolic and thrombotic events, convulsions, lack of efficacy-effect, and malignancies) were reported in 18 (31%) of patients in the Darbepoetin alfa QW group and in 20 (36%) patients in the darbepoetin alfa Q2W group. The incidence of treatment-related adverse events of interest was reported in 6 (10%) patients in the QW group and in 9 (16%) patients in the Q2W groups.

Table 14: Incidence of Adverse Events of Interest (Safety Analysis Set)

	Darbepoetin alfa	
	QW (N=58)	Q2W (N=56)
Patients reporting TEAEs of special interest, n (%)	18 (31)	20 (36)
Hypertension	15 (26)	13 (23)
Hypersensitivity	5 (9)	7 (13)
Cardiac failure	1 (2)	1 (2)
Malignancies	0 (0)	1 (2)
Dialysis vascular access thrombosis	0 (0)	1 (2)

Embolic and thrombotic events	0 (0)	1 (2)
Lack of efficacy-effect	1 (2)	0 (0)
Ischemic heart disease	0 (0)	0 (0)
Cerebrovascular disorders	0 (0)	0 (0)
Convulsions	0 (0)	0 (0)
Antibody-mediated pure red cell aplasia	0 (0)	0 (0)

Source: sBLA submission, Module 5.3.5.1, Table 12-5, P 93.

Reviewer comments: The rate of adverse events of special interest was comparable between the two groups.

7.4 Supportive Safety Results

Study 20070211
Study 20070211 was a prospective multi-center, multi-national EU observational registry study designed to provide long-term safety data on darbepoetin alfa for the treatment for anemia in pediatric patients with CKD receiving and not receiving dialysis, including a minimum of 30 subjects younger than 6 years of age at the time of enrollment.
The registry was observational in nature, with no additional diagnostic or monitoring procedures applied to participating subjects. Eligible subjects were ≤ 16 years of age, diagnosed with CKD, and receiving darbepoetin alfa for the treatment of anemia. Data were collected at study entry, and then at 3-month intervals; the information was obtained at subjects' routine medical visits as per normal care. Subjects were observed for up to 2 years or until renal transplantation, permanent cessation of darbepoetin alfa treatment, enrollment into an interventional study, or withdrawal of informed consent.

The primary endpoints for this study were the occurrence of serious adverse drug reactions, serious adverse events, and events of medical interest (predefined for this study as thromboembolic or cardiovascular events, seizures, severe hypertension, pure red cell aplasia [PRCA], and hypersensitivity reactions). Secondary endpoints included the dose of darbepoetin alfa over time, hemoglobin over time, as well as selected laboratory values that may be related to hemoglobin over time, and non-serious adverse reactions.

A total of 321 subjects were enrolled from 37 centers in 13 European countries, 319 of whom were included in the full analysis set population. One hundred forty-five (45.2%) subjects in the full analysis set completed the 2-year follow-up period.

The mean (range) age was 9.1 (<1 to 16) years. The majority of subjects were male (55.5%) and White (85.9%). At baseline, the mean (SD) hemoglobin concentration was 11.1 (1.6) g/dL. At study entry, 158 (49.5%) subjects were receiving dialysis (hemodialysis, 74 subjects; peritoneal dialysis, 84 subjects). At enrollment, 299 (93.7%) subjects were being treated with darbepoetin alfa, with a mean dose of 75.72 μg/month.

By age subgroup, there were 13 (4.1%) subjects under 1 year of age, 83 (26.0%) subjects 1-< 6 years of age, 90 (28.2%) subjects 6-<12 years of age, and 133 (41.7%) subjects ≥12 years of age.

The mean hemoglobin concentration was 11.1 g/dL at baseline. Mean hemoglobin for all subjects remained consistent throughout the duration of the study, ranging between 11.3 and 11.5 g/dL.

Safety results:
There were 6 (2%) subjects with fatal outcome with no cases was considered to be related to darbepoetin alfa by the investigator. Three of the events with fatal outcomes (pulmonary edema, severe hypertension, gastrointestinal necrosis) were reported in the < 1 year age subgroup, and 1 event was reported in each of the other age subgroups (mitochondrial disease, 1 to < 6 year group; sepsis, 6 to< 12 year group; pulmonary edema, ≥ 12 year group). Four subjects experiencing an event with a fatal outcome were receiving dialysis; 2 were not receiving dialysis. There were a total of 434 serious adverse events were reported by 162 subjects during the study. The most common SAEs reported in the study were peritonitis (32 [10.1%] patients, gastroenteritis (19 [6.0%] patients), and hypertension (13 [4.1%] patients). The rates of SAEs were similar between all age subgroups.

The most common special interest AEs were severe hypertension (reported in 13% of patients) followed by seizures (reported in 7% of patients) followed by thromboembolic (reported in 4% of patients) and hypersensitivity reaction (reported in 1% of patients). No events of PRCA were reported.

Summary of adverse reactions presented in Table 15.

Table 15: Summary of Adverse Drug Reactions, Serious Adverse Events, and Events of Medical Interest For All Subjects and by Baseline Age Group (Study 20070211, Full Analysis Set)

	All Subjects (N = 319) n (%)	Age < 1 y (N = 13) n (%)	Age 1 - < 6 y (N = 83) n (%)	Age 6 - < 12 y (N = 90) n (%)	Age ≥ 12 y (N = 133) n (%)
Serious Adverse Events	162 (50.8)	7 (53.8)	51 (61.4)	39 (43.3)	65 (48.9)
Fatal Adverse Events	6 (1.9)	3 (23.1)	1 (1.2)	1 (1.1)	1 (0.8)
Adverse Drug Reactions	8 (2.5)	0 (0.0)	1 (1.2)	4 (4.4)	3 (2.3)
Serious Adverse Drug Reactions	4 (1.3)	0 (0.0)	0 (0.0)	2 (2.2)	2 (1.5)
Events of Medical Interest	39 (12.2)	2 (15.4)	12 (14.5)	13 (14.4)	12 (9.0)
Adverse Events Leading to Withdrawal	2 (0.6)	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)

Note: Percentages based on N.
Includes all events starting between study day 1 and end of study.
Adverse drug reactions are events deemed related to treatment with darbepoetin alfa by the investigator.
Events of Medical Interest were defined in the protocol (thromboembolic event, seizures, severe hypertension, cardiovascular events, pure red cell aplasia [PRCA], hypersensitivity reactions).

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Reviewer comment: the safety assessments from 319 pediatric patients in the observational safety study 20070211 suggested that the rate of serious adverse events and the special interest adverse events are consistent with the safety profile of Aranesp in adult patients with CKD as been described in the label.

7.4.1 Common Adverse Events

The majority of patients in both treatment groups reported ≥ 1 adverse event during the study, regardless of baseline age, dialysis status, race, or sex. A total of 48 patients (83%) in the QW group and 50 patients (89%) in the Q2W group reported at least 1 adverse event during this study. The most common adverse events in either treatment group was vomiting which reported in 11 (19%) patients in QW group, (16%) 9 patients in Q2W. Hypertension was reported in 10 (17%) patients in the QW and 9 (16%) patients in the Q2W group. Pyrexia occurred in 6 (10%) patients in the QW and in 11 (20%) patients in the Q2W. Headache was reported in 6 (10%) patients in the QW and in 10 (18%) patients in the Q2W group. Abdominal pain was reported in 7 (12%) patients in the QW and in 6 (11%) patients in the Q2W group.

Table 16 Summarized the incidence of all adverse event occur in ≥ 5% of patients.

Table 16: Adverse Events in ≥ 5% Patients by Treatment Group (Safety Analysis Set)

	Darbepoetin alfa	
	QW (N=58)	**Q2W (N=56)**
Patients with at least 1 TEAE, n (%)	**48 (83)**	**50 (89)**
Vomiting	11 (19)	9 (16)
Hypertension	15 (26)	13 (23)
Upper respiratory tract infection	9 (18)	18 (32)
Pyrexia	6 (10)	11 (20)
Headache	6 (10)	10 (18)
Abdominal pain & Abdominal pain upper	10 (17)	8 (14)
Cough	7 (12)	4 (7)
Nausea	5 (9)	4 (7)
Constipation	4 (7)	4 (7)
Catheter site infection	4 (7)	3 (5)
Diarrhea	3 (5)	4 (7)
Fatigue	5 (9)	2 (4)
Hypotension	5 (9)	8 (14)

Muscle Spasms	5 (9)	2 (4)
Dizziness	3 (5)	3 (5)
Medical device complication	2 (3)	4 (7)
Anemia	3 (5)	2 (4)
Back pain	2 (4)	3 (5)
Injection site pain	3 (5)	2 (4)
Nasal congestion	4 (7)	1 (1.8)
Oropharyngeal pain	2 (3)	3 (5)
Pain in extremity	4 (7)	1 (1.8)
Pruritus	4 (7)	1 (1.8)
Catheter site pain	3 (5)	1 (2)
Contusion	1 (2)	3 (5)
Ear infection	4 (7)	0 (0.0)
Hyperkalemia	4 (7)	0 (0.0)
Peritonitis	0 (0.0)	4 (7)
Rash	3 (5)	1 (2)
Urinary Tract Infection	4 (7)	0 (0.0)
Local Swelling	3 (5)	0 (0.0)
Patients with at least 1 TEAE related, n (%)	**14 (24)**	**16 (29)**
Hypertension	5 (8)	6 (12)
Injection Site Pain	4 (6)	2 (4)
Iron deficiency	2 (3)	2 (4)
Headache	2 (3)	1 (2)
Injection Site reaction	2 (3)	2 (4)
Arthralgia	0 (0.0)	2 (4)
Urticaria	0 (0.0)	2 (4)

Source: sBLA submission, Module 5.3.5.1, Table 12-2, P87.

The overall incidences were 19 (91%) patients in QW and 18 (95%) patients Q2W for age 1 to < 12 years and 29 patients (78%) QW and 32 patients (87%) Q2W for age 12 to 18 years.

Reviewer comments: The rate of TEAEs was comparable between the two groups.

7.4.2 Laboratory Findings

Transferrin Saturation (TSAT)
At baseline, mean TSAT was 33% (12.8%) and 35% (13.3%) for the QW and Q2W groups, respectively. The mean (SD) change from baseline in TSAT was between -9% (16.9%) and 1.3% (15.6%) for the QW group and between -3% (20.8%) and 3% (23.0%) for the Q2W group during the treatment period (visits with n > 3 per group).

Hematology and Serum Chemistry
The rates of shifts ≥ 2 from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), eGFR, potassium, and white blood cell counts were low within each treatment group. One patient in Q2W experienced a grade 3 ALT. No patients reported grade 3 or 4 ALT, AST, or white blood cell values during the treatment period in either treatment groups.

Four subjects (7%) in each treatment group decreased from grade 2 eGFR at baseline to grade 3 during the treatment period. No subject in either treatment group had a grade 4 eGFR value during the study.

Three subjects (5%) in the QW group and 5 subjects (9%) in the Q2W group increased from a grade 0 potassium value at baseline to grade 2 during the treatment period. Four subjects (7%) in the QW group increased from grade 0 (3) or 2 (1) to grade 3 and 2 subjects (4%) in the Q2W group increased from grade 0 (1) or 2 (1) to grade 3. One subject (2%) in each treatment group increased from grade 0 to grade 4.

7.4.3 Vital Signs

Blood Pressure (BP)
Mean systolic blood pressure (BP) was 116 (15.3) mmHg at baseline and between 112 (16.2) and 119 (19.7) mmHg during the treatment period for the QW group. Mean systolic BP was 119 (14.0) mmHg at baseline and between 114 (12.6) and 121 (12.9) mmHg during the treatment period for the Q2W group. Mean change from baseline in systolic blood pressure was between –2.4 (17.2) and 3.4 (16.0) mmHg for the QW group and between -4.0 (13.0) and 1.2 (11.5) mmHg for the Q2W group.

Mean diastolic BP was 68 (12.8) mmHg at baseline and between 69 (13.7) and 73 (13.9) mmHg during the treatment period for the QW group. Mean diastolic BP was 70 (12.1) mmHg at baseline and between 68 (11.3) and 73 (11.1) mmHg during the treatment period for the Q2W group. Mean change from baseline in diastolic BP was between 1.2 (10.4) and 5.0 (13.8) mmHg for the QW group and between -2.0 (14.0) and 3.1 (10.8) mmHg for the Q2W group.

Increased blood pressure (hypertension) was reported as an adverse event in 15 subjects (26%) and 13 subjects (23%) in the QW and Q2W groups, respectively.

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7.4.4 Electrocardiograms (ECGs)

An abnormality in ECG was reported in one patient in the QW group. The subject was an 8 year old Hispanic male. Medical history included an end stage renal disease, interstitial nephritis, nephrotic syndrome, proteinuria, hyperkalemia, hypocalcemia, focal segmental sclerosis and allergies to clindamycin, azithromycin, amoxicillin and Keflex (ceftriaxone). Prior to initiation of the investigational product, he was hospitalized with left-sided chest pain while lying down at home. Electrocardiogram showed a prolonged QTc interval (corrected 0.545 sec) and chest X-ray revealed cardiomegaly. His laboratory test results revealed hemoglobin 7.3, calcium was 4.9, potassium 6.2, blood urea nitrogen 95, creatinine 11.3, bicarbonate 35, chloride 88, hematocrit 22, and white blood cell (WBC) count 15.11 with 81% neutrophils. He was treated appropriately and his chest pain was resolved.

Reviewer comments: The case of ECG abnormality is not drug-related since occurred prior to initiation of treatment with Aranesp.

7.4.5 Special Safety Studies/Clinical Trials

The adverse events of interest were discussed in details (see 7.3.5).

7.4.6 Immunogenicity

Screening for seroreactivity was performed on patient samples collected at baseline and the end-of-study visit. No neutralizing antibody formation due to darbepoetin alfa administration was observed, and no cases of antibody-mediated PRCA were reported.

Thirteen events of pure red cell aplasia were spontaneously reported in pediatric patients during the post-marketing experience with Aranesp; only 1 event was confirmed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Refer to Section 7.3 and 7.4 for comparison of safety profiles for the QW and Q2W dosing regimens.

7.5.2 Time Dependency for Adverse Events

Analysis of time dependency of adverse events was not performed due to the small size of the pediatric safety database.

7.5.3 Drug-Demographic Interactions

The effect of baseline demographic on safety in pediatric subjects was evaluated for age (< 6 years, 6 to 12 years, and ≥ 12 years), dialysis status, gender (male, female), and race (White, Black/African American, Other) using the integrated pediatric safety data. Adverse event profiles for the integrated pediatric patients were generally similar, regardless of baseline age, dialysis status, race, or gender.

7.5.4 Drug-Disease Interactions

There were 33 patients from each group (QW and Q2W) not on dialysis and a total of 48 patients (25 in QW and 23 in Q2W) on dialysis. The rate of TEAEs was 89% (n=59) in patients not on dialysis compared to 81% (n=39) in patients on dialysis. In general the incidences of adverse events were similar between patients on dialysis or not on dialysis except for tachycardia and vascular access thrombosis which were reported only in patients on dialysis.

7.5.5 Drug-Drug Interactions

Drug interactions between darbepoetin alfa and other drugs have not been fully evaluated. The potential for interaction with drugs that are bound by RBCs is unknown.

7.6 Additional Safety Evaluations

No additional safety evaluation was performed.

7.6.1 Human Carcinogenicity

Refer to Section 13.1 of the US prescribing information.

7.6.2 Human Reproduction and Pregnancy Data

Refer to Section 13.3 of the US prescribing information.

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessment of Aranesp effects on growth was was performed. The assessment of the effects of Aranesp on growth and development would be confounded by the underlying disease for Aranesp treatment, i.e., chronic kidney disease or chemotherapy for cancer.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The maximum amount of darbepoetin alfa that can be safely administered in single or multiple doses to either pediatric or adult patients has not been determined. The therapeutic margin of darbepoetin alfa is wide. Even at high serum levels, no symptoms of overdose have been

observed to date in adult patients. Doses over 3.0 µg/kg/wk for up to 28 weeks have been administered to adult patients with CKD without any direct toxic effects. Doses up to 8.0 µg/kg QW and 15.0 µg/kg every 3 weeks have been administered to adult patients with cancer for up to 12 to 16 weeks. Maximum doses administered in the pediatric trials were lower than those studied in adults.

Misuse of darbepoetin alfa by healthy persons may lead to an excessive increase in red cell volume, which may be associated with life-threatening complications of the cardiovascular system.

No withdrawal or rebound effects were observed with darbepoetin alfa during the study period in either of the studies.

7.7 Additional Submissions / Safety Issues

No new safety issues were identified.

8 Postmarket Experience

Amgen global safety database for spontaneous adverse events reported in pediatric patients < 18 years of age treated with Aranesp® (darbepoetin alfa) from May 16, 2001 through June 12, 2014 revealed the following:

- A total of 158 pediatric patients reported 386 adverse events during the post-marketing experience with Aranesp. There were 278 serious and 108 non-serious per regulatory reporting criteria.
- A total of 133 events were reported from US sources and 253 from sources outside of the US.
- Adverse events were observed more frequently in male than female pediatric patients (71 male vs. 63 female).
- The ages ranged from 20 days to 17 years; age was not provided for 75 patients.
- The most commonly reported events were therapeutic response decreased (n = 50), followed by injection site pain (n = 28). There were 8 cases of hypertension, 7 cases of pyrexia, 6 cases of death and 5 cases of convulsion.

For further details about postmarketing experience of the use of Aranesp in pediatric patients with CKD, refer to the review completed by Dr. Lynda McCulley from the Division of Pharmacovigilance (DPV)/Office of Surveillance and Epidemiology (OSE) dated February 25, 2015.

Reviewer comments: The postmarketing reported adverse events were consistent with the known Aranesp safety profile described in the label. No new safety signal identified.

9 Appendices

9.1 Literature Review/References

Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D, Burgess E, Jindal K, Barrett B, Singer J, Djurdjev O. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. Am J Kidney Dis. 1999 Jul;34:125–134.

Morris KP, Skinner JR, Hunter S, Coulthard MG. Cardiovascular abnormalities in end stage renal failure: the effect of anemia or uremia? Arch Dis Child 1994 Aug;71:119–122.
Susan M. Koshy, Denis F. Geary. Anemia in children with chronic kidney disease; Pediatr Nephrol. 2008 February; 23(2): 209–219. Published online 2007 January 24. doi: 10.1007/s00467-006-0381-2

9.2 Labeling Recommendations

We recommend the following changes to the current USPI pertaining to pediatric use of Aranesp for the treatment of anemia associated with CKD:

1. Add study description and indication of Aranesp use for initial treatment of anemia in pediatric patients in Section 8.4
2. The recommended starting dose for pediatric patients with CKD is 0.45 mcg/kg intravenously or subcutaneously weekly. However, patients with CKD not on dialysis may also be initiated at staring dose of 0.75 mcg/kg every 2 weeks.
3. Dose adjustment rules should be mirror of that in adults and based on hemoglobin level.
4. [redacted] (b) (4) is based on the results from 13 patients age less than 1 year participated in the EU registry study.

9.3 Advisory Committee Meeting

This application was not taken for an Advisory Committee Meeting because the application did not raise significant public health questions on the use of Aranesp in pediatric patients with anemia due to CKD.

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/s/

SALEH AYACHE
05/15/2015

ROMEO A DE CLARO
05/15/2015