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.

- 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)

- 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.

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,

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.

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.

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

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

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 ($p = 0.293$).

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

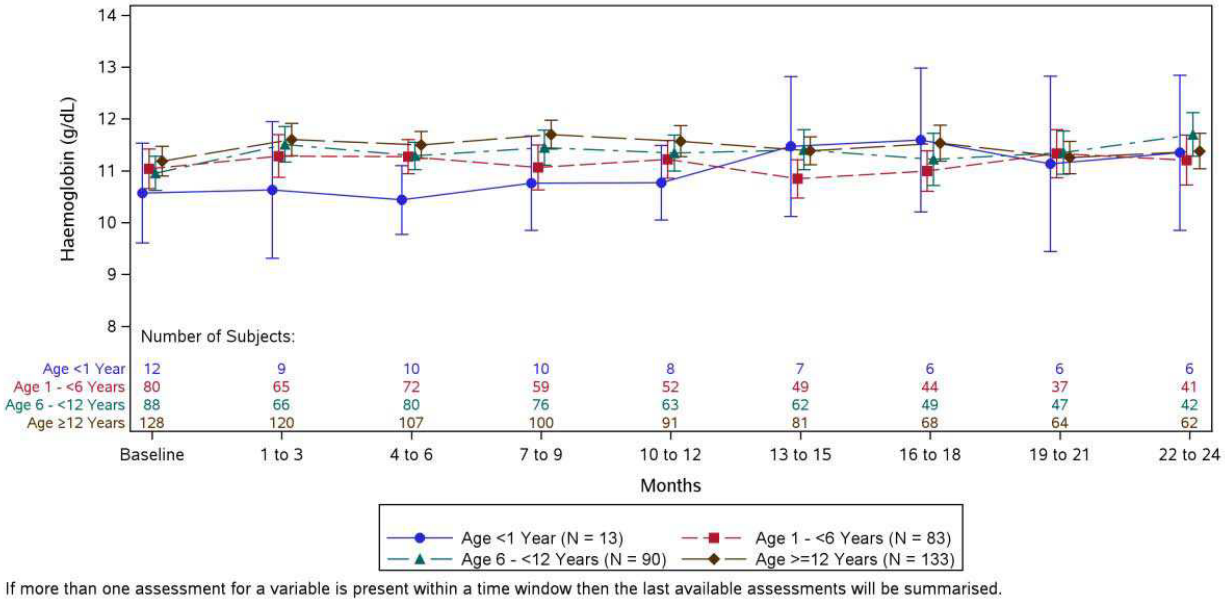
Source: Module 5.3.5.1, Table 3, P 26.

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)

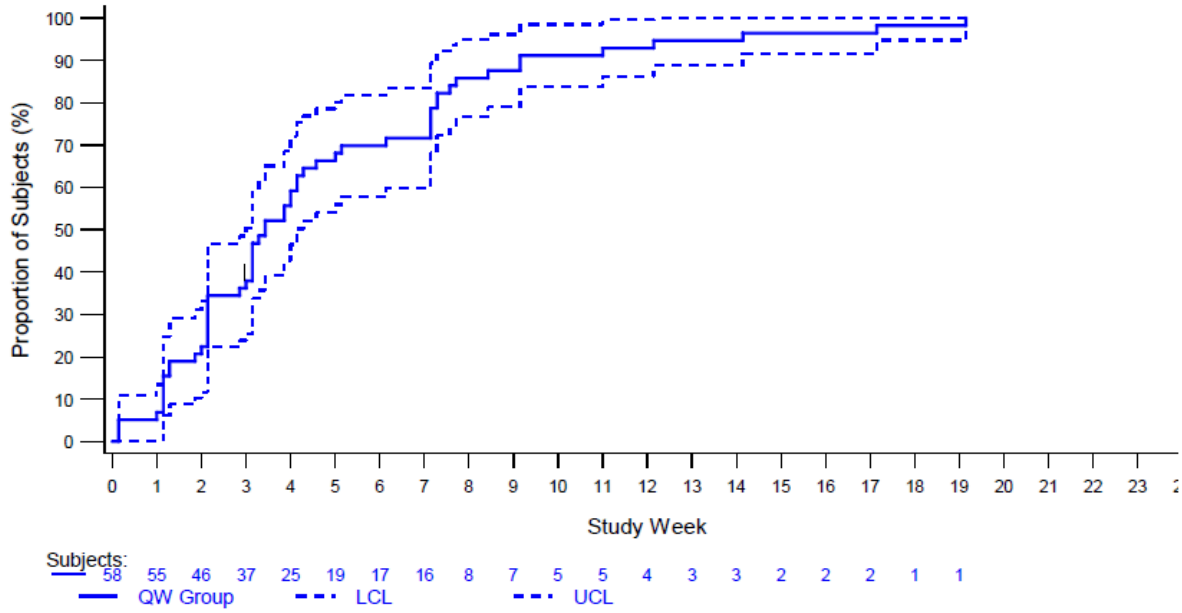
Secondary efficacy endpoints included time to first hemoglobin ≥ 10.0 g/dL, hemoglobin concentrations across time, darbepoetin alfa dose at first value of hemoglobin ≥ 10.0 g/dL and across time, and patient-reported outcome scores (PedsQL) for patients ≥ 2 years of age. The analyses for these endpoints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

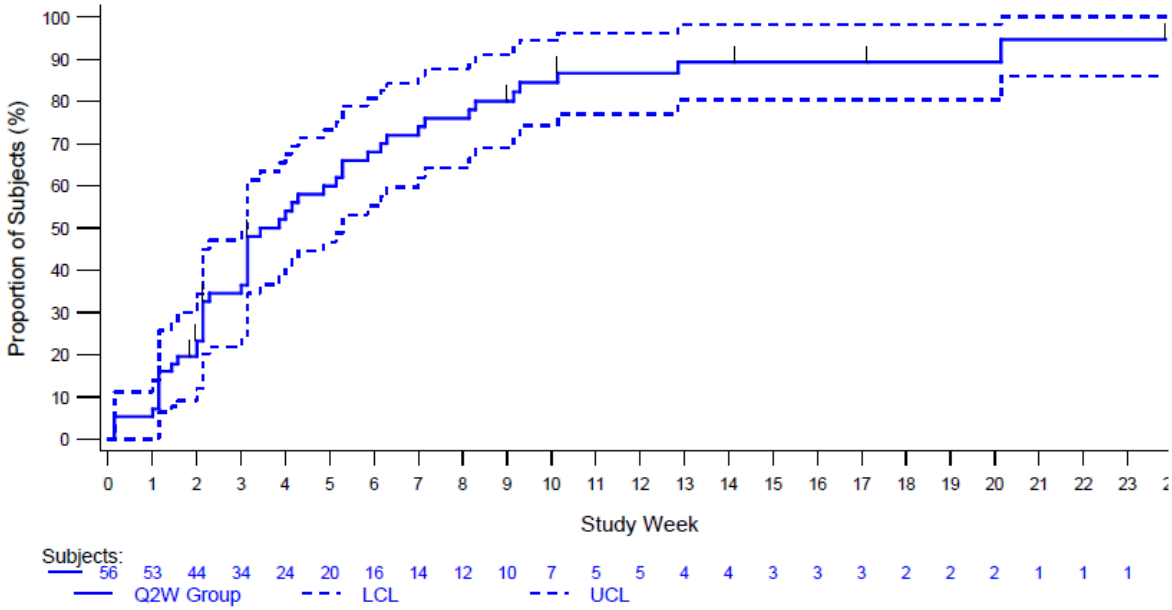
The Kaplan-Meier percentage of patients in the QW group to achieved hemoglobin ≥ 10.0 g/dL increased steadily to 0.88 at week 9, with all patients achieving the endpoint by week 20 (Figure 3). However, the Kaplan-Meier percentage of patients in Q2W group who achieved hemoglobin ≥ 10.0 g/dL increased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



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.

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