Published in final edited form as:

Curr Med Res Opin. 2009 January ; 25(1): 123–131. doi:10.1185/03007990802594818.

Anemia treatment with Q2W darbepoetin alfa in patients with chronic kidney disease naïve to erythropoiesis-stimulating agents*

M. R. Silver^a, R. Geronemus^b, M. Krause^c, C. Y. Chen^d, R. Kewalramani^d, and C. Stehman-Breen^d

^aCase Western Reserve University School of Medicine at MetroHealth Medical Center, Cleveland, OH, USA

^bSouth Florida Nephrology Associates, Lauderdale Lakes, FL, USA

^cUniversity of Arkansas for Medical Sciences, Little Rock, AR, USA

^dAmgen Inc., Thousand Oaks, CA, USA

Abstract

Objective—To evaluate the efficacy and safety of darbepoetin alfa dosed every-other-week (Q2W) to treat anemia in subjects with chronic kidney disease (CKD), not receiving dialysis, who were naïve to erythropoiesis-stimulating agent (ESA) therapy.

Research design and methods—This was an open-label, multicenter, single-arm study enrolling ESA-naïve CKD subjects with baseline hemoglobin (Hb) < 11.0 g/dL. Q2W darbepoetin alfa treatment was initiated at a dose of 0.75 µg/kg and titrated to achieve and maintain Hb levels at 11.0–13.0 g/dL. Treatment was administered from week 1 to week 19.

Main outcome measures—The primary endpoint was the proportion of subjects who achieved Hb ≥ 11 g/dL at any study visit, except in week 1. Hb levels, darbepoetin alfa dose, and safety were also assessed.

Results—Of the 128 subjects who received at least one dose of darbepoetin alfa and of the subjects who completed the study, 118 (92%) and 112 (97%), respectively, achieved a Hb ≥ 11 g/dL in a median time of 5 weeks. Median darbepoetin alfa dose at week 1 and at the time of achieving a Hb ≥ 11 g/dL were 60 and 80 µg, respectively. Darbepoetin alfa was well-tolerated, and short-term adverse events were consistent with those expected in CKD subjects.

*The data in this paper were previously presented as the abstract, Silver MR, Agarwal AK, Walczyk MH, *et al.* Every-other-week (Q2W) Aranesp[®] (Darbepoetin alfa) dosing in patients with chronic kidney disease (CKD) not receiving dialysis. The American Society of Nephrology Renal Week 2005. November 8–13, 2005, Philadelphia, PA, USA

© 2009 Informa UK Ltd.

Address for correspondence: Catherine Stehman-Breen, MD, One Amgen Center Dr., MS 38-2-C, Thousand Oaks, CA 91320 USA. Tel.: +1 805 447 7791; Fax: +1 805 480 9075; cstehman@amgen.com.

The following investigators (listed alphabetically) enrolled patients for this study:

Abu-Hamdan D, Detroit, MI; Agarwal AK, Columbus OH; Albarracin C, Corpus Christi, TX; Anger M, Thornton, CO; Cheriyan R, Fairfax, VA; Coplin RE, Birmingham, AL; Dewberry FL, Clearwater, FL; Dy G, Mansfield, PA; Fadda G, San Diego, CA; Fitz-Patrick D, Honolulu, HI; Flick R, Mesa, AZ; Geronemus R, Lauderdale Lakes, FL; Hamilton M, Ft. Lauderdale, FL; Handelsman S, Atlanta, GA; Hertel J, Augusta, GA; Hura C, San Antonio, TX; Iranmanesh A, Salem, VA; Jackson TL, Beaver, PA; Jones ER, Philadelphia, PA; Kapatkin K, Brandon, FL; Kipnes MS, San Antonio, TX; Kopyt N, Allentown, PA; Krause M, Little Rock, AR; Leiserowitz M, Las Vegas, NV; Liljenquist J, Idaho Falls, ID; Ling BN, Asheville, NC; Mayeda SO, Orange, CA; Navarro JO, Tampa, FL; Ogundipe A, Marietta, GA; Pride ET, North Charleston, SC; Reed JE, Columbus, MS; Silver MR, Cleveland, OH; Walczyk M, Portland, OR; Weinberg MS, Providence, RI; Weissman PN, Miami, FL; Zeig S, Pembroke Pines, FL.

Conclusions—This study demonstrates that *de novo* Q2W darbepoetin alfa was effective in correcting and maintaining Hb levels in ESA-naïve subjects with CKD who were not receiving dialysis. Study limitations, including lack of a control arm for the study and multiple race information for subjects, must be considered in interpreting the results.

Keywords

Anemia; Chronic kidney disease; Darbepoetin alfa; Erythropoietin; Extended dosing

Introduction

Chronic kidney disease (CKD) is often associated with anemia. Anemia develops secondary to CKD as the diseased kidneys lose their ability to produce erythropoietin, which is required to stimulate the bone marrow to produce mature red blood cells¹. The decline in hemoglobin (Hb) level may start early in CKD, and progresses as renal function and erythropoietin production decline^{2,3}. Anemia associated with CKD is a risk factor for impaired physical capacity and reduced quality of life, and may contribute to the increased morbidity and mortality seen in CKD^{4–11}.

Guidelines are in place for the treatment of anemia in patients with CKD. The current National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines for managing CKD-related anemia with erythropoiesis-stimulating agents (ESAs) recommend a Hb target in the range of 11.0–12.0 g/dL. The recent update also includes a guideline that the target Hb should not exceed 13.0 g/dL¹². Recent studies have questioned the benefits of treating to high Hb levels^{13,14}, however, evidence supporting improved patient outcomes with ESA therapy, when used according to the label, is clearly documented^{15–22}. ESAs, therefore, provide a means to effectively treat anemia in CKD patients.

Darbepoetin alfa (Aranesp*) is an ESA approved for the treatment of anemia in chronic kidney failure. In the US, the initiation dosing frequency approved by the Food and Drug Administration is weekly (QW) or every other week (Q2W) when patients are naïve to previous ESA therapy. Data from clinical studies have shown that appropriate target Hb levels can be achieved and/or maintained when darbepoetin alfa is administered Q2W^{23–25}. The purpose of the current study was to add to the safety and efficacy data on *de novo* Q2W administration of subcutaneous (SC) darbepoetin alfa in achieving and maintaining target Hb levels in patients with CKD who were not receiving dialysis.

Patients and methods

Study subjects

Subjects were eligible for inclusion in the study if they were ≥ 18 years of age with a diagnosis of CKD, but not receiving or scheduled to receive dialysis. They were required to have an estimated glomerular filtration rate (eGFR) ≥ 15 mL/min/1.73m² and ≤ 60 mL/min/1.73m², using the Modification of Diet in Renal Disease (MDRD) equation^{26,27}; mean Hb level < 11.0 g/dL, based on two screening visits at least 3 days apart; normal serum vitamin B₁₂ and folate levels; and transferrin saturation (TSAT) levels $\geq 15.0\%$. Subjects were excluded from the study if they had received ESA therapy within 12 weeks before enrollment or received, or were scheduled to receive, a kidney transplant. Additionally, subjects with uncontrolled hypertension (diastolic blood pressure > 110 mmHg or systolic

* Aranesp, Amgen Inc., Thousand Oaks, CA, USA

blood pressure > 180 mmHg during screening), cardiovascular disease (acute myocardial infarction or hospitalization for chronic heart failure within 12 weeks before enrollment), and intact parathyroid hormone level > 1500 pg/mL were not enrolled. Subjects who had undergone major surgery within 12 weeks before enrollment (excluding vascular access surgery), had systemic infection or hematologic disease, and/or had received red blood cell (RBC) transfusions within 8 weeks before enrollment were also excluded from the study.

Study design and intervention

This was a 21-week, open-label, multicenter, single-arm study conducted in the United States. The study consisted of an initial 2-week screening period followed by Q2W darbepoetin alfa treatment from week 1 to week 19. The study design is shown in Figure 1.

Darbepoetin alfa treatment was initiated at 0.75 µg/kg, rounded to the nearest unit dose (20, 30, 40, 50, 60, 80, 100, 150, 200, or 300 µg). The starting dose was based on the recommended dose in the US label for darbepoetin alfa (0.45 µg/kg administered QW). However, rather than doubling the dose (i.e., 0.90 µg/kg) for Q2W administration, a more conservative approach was chosen when initiating treatment for subjects in this study. Following treatment initiation, darbepoetin alfa doses were adjusted to achieve and maintain target Hb levels in the range of 11.0 to 13.0 g/dL, inclusive, which was a range similar to previously reported ESA trials^{24,25} and was consistent with clinical practice at the time the study was designed.

Darbepoetin alfa dose adjustments were based on the Hb rate of rise and the most recent Hb measurement. The dose was reduced to the next lower unit dose if the Hb rate of rise in a 2-week period exceeded 1.0 g/dL. If Hb level was < 11.0 g/dL, the dose was increased to the next higher dose. If Hb was > 13.0 g/dL and ≤ 14.0 g/dL, the dose was decreased to the next lower dose. If Hb was > 14.0 g/dL, dosing was withheld until Hb decreased to < 13.0 g/dL and then resumed at the next lower dose. Dose adjustments were permitted no more frequently than every 4 weeks.

Oral and intravenous (IV) iron therapies were encouraged according to clinic policy to ensure that subjects were iron replete (TSAT ≥ 19.5%). If a subject entered the study with TSAT ≥ 15% and < 19.5%, IV or oral iron therapy was recommended to correct TSAT to ≥ 19.5%.

Hb level, vital signs, adverse events (AEs), and concomitant medications were evaluated at baseline, at the time of each administration of darbepoetin alfa, and at the end-of-study visit (week 21). The doses of darbepoetin alfa were recorded at the time of each administration. Hematology (other than Hb level), serum chemistry, and TSAT were assessed at baseline, week 7, and the end-of-study visit (week 21 or early termination). All clinical laboratory assessments were performed at a central laboratory (ICON Laboratories Inc, Farmingdale, New York, USA). Antierythropoietin antibody bioassays (MDS Pharma Services, Saint-Laurent [Montreal], Quebec, Canada) were performed before the start of darbepoetin alfa therapy and at the end-of-study visit.

The study was conducted in accordance with applicable United States Food and Drug Administration and International Conference on Harmonization Good Clinical Practice regulations/guidelines. All subjects gave written informed consent and the study was approved by institutional review boards at participating centers. The study is registered on ClinicalTrials.gov under the registry number NCT00112008.

Endpoints

The primary efficacy endpoint was the proportion of subjects achieving a Hb ≥ 11 g/dL. Secondary endpoints were Hb levels and darbepoetin alfa dose over the duration of the study. Safety endpoints included the frequency and relationship to treatment of AEs, and changes in laboratory parameters and blood pressure.

Statistical analysis

A target sample size of 100 was determined based on having a half-width of 8% for the two-sided 95% confidence interval (CI) of the proportion of subjects achieving a Hb ≥ 11.0 g/dL, assuming that an estimated 80% of subjects would achieve a Hb ≥ 11.0 g/dL. Efficacy analyses were performed on efficacy analysis set, which is defined as subjects who received at least one dose of darbepoetin alfa and had a baseline Hb < 11.0 g/dL. The proportion of subjects who achieved a Hb ≥ 11 g/dL was calculated as the number of subjects who had received at least one dose of darbepoetin alfa, had a baseline Hb < 11.0 g/dL, and had achieved a Hb ≥ 11.0 g/dL, divided by the total number of subjects in efficacy analysis set. A similar proportion was calculated for subjects who completed the study. Safety analyses were performed on subjects who received at least one dose of darbepoetin alfa. Safety analyses included the incidence of AEs tabulated according to system organ class. Only AEs occurring with a $\geq 5\%$ frequency are reported here. Exploratory analysis was also done for subjects with Hb > 13 g/dL and > 14 g/dL at any time during the study. SAS version 8.2 (SAS Institute Inc, Cary, NC, USA) was used for statistical analysis.

Descriptive statistics included mean, standard deviation (SD), and quartiles (25th [Q1] and 75th [Q3] percentiles) for continuous variables, and count and percent for categorical variables. Two-sided 95% CIs were calculated for the primary endpoint. Hodges–Lehmann's distribution-free 95% CIs²⁸ were calculated for median darbepoetin alfa doses.

Results

Subject characteristics

A total of 128 subjects recruited from 36 centers across the United States were enrolled in the study and included in the efficacy and safety analyses (first subject was enrolled May 2004 and last subject completed the study November 2004). All (100%) subjects received at least one dose of darbepoetin alfa, 117 (91%) completed all planned darbepoetin alfa treatments, and 115 (90%) completed all study assessments (Table 1). Thirteen subjects discontinued participation in the study; of these, 11 subjects discontinued participation during the treatment period and 2 subjects completed treatment but discontinued during the follow-up period. Reasons for discontinuation from the study were AEs other than death ($n = 3$; one subject due to hyperglycemia, one subject due to cerebrovascular accident, and one subject due to hypertension), death ($n = 3$), initiation of dialysis ($n = 3$), noncompliance ($n = 2$), lost to follow-up ($n = 1$), or other reasons ($n = 1$).

Subject demographics and baseline characteristics are shown in Table 2. The majority of subjects were female (57%) and white (59%). Mean (SD) age was 66.8 (13.7) years. Mean (SD) eGFR, Hb, and TSAT levels were 32.1 (12.2) mL/min/1.73m², 10.0 (0.6) g/dL, and 23.6% (6.4%), respectively. The mean (SD) time since the onset of CKD was 29.2 (40.1) months. The most common cause of CKD was diabetes mellitus (52%), followed by hypertension (29%). At study entry, 98%, 73%, 38%, and 16% of subjects had histories of hypertension, diabetes, coronary artery disease, and myocardial infarction, respectively.

Achievement and maintenance of target Hb level

The target Hb level was achieved by 92% (95% CI: 86%, 96%) of subjects who received at least one dose of darbepoetin alfa, and 97% (95% CI: 93%, 99%) of subjects who completed the study (Table 3).

The median (Q1, Q3) time to achieve a Hb $\geq$ 11 g/dL was 5 (3, 8) weeks. Mean (SD) Hb levels increased steadily during the first 14 weeks, from a baseline of 10.0 (0.6) g/dL to 12.5 (1.2) g/dL, and remained stable for the remainder of the study (Figure 2). In the first 4 weeks of therapy, Hb levels increased by a mean (SD) of 1.0 (0.8) g/dL.

A total of 57 (45%) and 28 (22%) subjects had at least one Hb measurement of > 13.0 g/dL or at least one Hb measurement > 14 g/dL, respectively, at any time during the study. For subjects who had a Hb > 13.0 g/dL or Hb > 14 g/dL, the median (Q1, Q3) time for Hb levels to return to ≤ 13 g/dL were 6 (2, 10) and 8 (5, 8) weeks, respectively.

Darbepoetin alfa dose levels

The median (Q1, Q3) starting Q2W darbepoetin alfa dose was 60.0 (50.0, 80.0) μ g, and the median last dose on study (week 19) was 65.0 (30.0, 100.0) μ g (Figure 3). The median (Q1, Q3) Q2W dose was 80.0 (60.0, 100.0) μ g at the time of achieving the primary Hb endpoint (Hb ≥ 11.0 g/dL) and 64.0 (47.0, 95.0) μ g over the course of the study.

Iron parameters and RBC transfusions

Nine (7%) subjects received intravenous iron and 78 (61%) subjects received oral iron during the study. Mean (SD) TSAT levels at baseline, weeks 7 and 21 were 23.6 (6.4)%, 19.6 (6.4)%, and 27.3 (13.8)%, respectively. Mean TSAT level was $\geq 20\%$ throughout the course of the study, which is the minimum level recommended in the NKF-K/DOQI guidelines to achieve and maintain a Hb level of 11–12 g/dL with ESA treatment²⁹. Six subjects (5%) received one RBC transfusion and only one subject received ≥ 3 RBC transfusions.

Adverse events

Safety was assessed for subjects who received at least one dose of darbepoetin alfa. AEs reported irrespective of relationship to study treatment were mostly mild to moderate in severity and typical of the CKD nondialysis population (Table 4).

One or more AEs were reported in 97 (76%) subjects. The most common AEs were peripheral edema (9%), headache (8%), diarrhea (7%), and hypertension (7%). Treatment-related AEs (as determined by each study site investigator) were reported for 11 subjects (9%), but none was considered by the study investigators to be serious or life-threatening. Nontreatment-related serious AEs were reported for 26 subjects (20%). Of special interest, hypertension (worsening or exacerbated hypertension) was reported in 9 (7%) subjects. In each case, the local principal investigator judged the event as not treatment related. Three subjects (2%) discontinued the study because of AEs; one with hyperglycemia, one with cerebrovascular accident, and one with hypertension. Four subjects (3%) died during the study; two due to myocardial infarction (one death occurred within 30 days of the last dose of darbepoetin alfa), one due to acute renal failure, and one had an unspecified cause of death. None of the events leading to discontinuation or death were considered to be treatment related.

Exploratory analysis of subjects who had at least one Hb measurement of > 13 g/dL or one Hb measurement of > 14 g/dL indicated that 41 (72%) and 19 (68%), respectively, reported

at least one AE (Table 5). In general, the types and frequency of AEs in these subjects were similar to the AEs in subjects who never had a Hb measurement > 13 g/dL or > 14 g/dL.

There were no clinically relevant changes in mean laboratory values (hematology and serum chemistry) or mean vital signs (blood pressure) over the course of the study. All bioassay tests for neutralizing antibodies to darbepoetin alfa were negative.

Discussion

The results of this multicenter study indicate that 92% of subjects who received at least one dose of darbepoetin alfa and 97% of subjects who completed the study achieved a Hb level of ≥ 11 g/dL in a median time frame of 5 weeks. These results further confirm the observations made in previous studies demonstrating that Hb levels can be corrected and maintained in ESA-naïve patients who are treated with darbepoetin alfa on a Q2W schedule^{23–25}. Suranyi *et al.*²⁴ and Toto *et al.*²⁵ reported that of the subjects who completed the respective studies, 97% and 96%, respectively, achieved the primary efficacy endpoint (Hb level of 11.0–13.0 g/dL for Suranyi *et al.* and ≥ 11.0 g/dL for Toto *et al.*).

Subjects in this study were successfully initiated on Q2W dosing at 0.75 μ g/kg similar to what has been shown in the two *de novo* Q2W darbepoetin alfa studies mentioned^{24,25}. The median time to response reported here was also consistent with that reported in Suranyi *et al.*²⁴. However, in this study, the median and the mean darbepoetin alfa doses (80.0 μ g and 84.2 μ g Q2W, respectively) at time of response were higher than those reported in Suranyi *et al.* (median Q2W dose of 60 μ g to achieve a hemoglobin response of 11.0–13.0 g/dL) and Toto *et al.* (mean Q2W dose of 63.6 μ g at the time the Hb level was ≥ 11 g/dL). Some differences exist between these studies including mean weight (73.8 kg in Suranyi *et al.*, 81.0 kg in Toto *et al.*, and 83.7 kg for the present study), mean baseline TSAT levels (mean [SD] 31.4 [2.2]% for Suranyi *et al.*, 28.0 [21.2]% for Toto *et al.*, and 23.6 [6.4]% for the present study), and dosing rules (dose increase or decrease was based on two consecutive Hb values in both Suranyi *et al.* and Toto *et al.*, but was based on the most recent Hb measurement in the current study). The differences in dose may be as a result of one or a combination of these differences. Subjects with higher TSAT levels may respond to lower doses of darbepoetin alfa. While these studies were not designed to test that observation, this would be consistent with NKF-K/DOQI guidelines.

The results of this study indicate that darbepoetin alfa was well-tolerated with an AE profile consistent with previous studies^{23–25}; the most common AEs were peripheral edema, headache, diarrhea, and hypertension. None of the serious, fatal, or life-threatening AEs reported in this study were considered related to darbepoetin alfa treatment as determined by the investigator.

In this study, subjects were treated to maintain their Hb levels between 11.0 and 13.0 g/dL and treatment adjustments were made when Hb levels were < 11.0 or > 13.0 g/dL (treatment was withheld only if Hb was > 14.0 g/dL). The results indicate that 45% and 22% of subjects had at least one Hb measurement of > 13 g/dL or one Hb measurement > 14 g/dL, respectively, during the study. Further exploratory analysis summarizing the AEs in subjects with Hb > 13 g/dL or > 14 g/dL indicate that the AEs were similar in incidence and severity to subjects who achieved Hb < 13 g/dL. These results must be interpreted with caution, however, since the study was not designed to assess Hb variability or the outcomes associated with a Hb level outside the range specified by the study. The results are based on post-hoc analyses on a small patient population so their interpretation is limited.

The results of two recent clinical trials, CREATE¹³ and CHOIR¹⁴, demonstrate the need to approach anemia management with care; however, there is considerable evidence supporting

the benefits of anemia correction with ESAs when used according to the label in CKD patients^{15–22}. Benefits demonstrated when treating CKD patients with ESAs according to the label guidelines have included slowing the progression of CKD^{15,16}, improving quality-of-life measures^{17–20}, and improving cardiac performance^{21,22}. Despite this, studies indicate that anemia in the CKD population is not commonly treated in accordance with current guidelines^{30,31}. The United States Renal Data System reports that 45% of incident end-stage renal disease (ESRD) patients start dialysis with a Hb level less than 10 g/dL³⁰. Initiating and maintaining Hb levels with less frequent dosing, such as using Q2W darbepoetin alfa, may offer a more convenient dosing schedule for physicians and patients and provide opportunities for improving anemia management in CKD patients not receiving dialysis.

Other limitations of this study and the results must be acknowledged. These include limitations inherent to open-label, single-arm studies where no comparison is made to a control group. Also, race assignment in this study was mutually exclusive. The lack of multiple race information for subjects who could be identified with more than one race is a study limitation. Additionally, this study assessed efficacy over a 6-month period only, which is a short time period considering that CKD is a chronic disease. A study designed to examine long-term efficacy and safety outcomes of Q2W darbepoetin alfa administered to patients previously naïve to ESA treatment might support the observations seen in this study.

Conclusion

This study demonstrates that ESA-naïve CKD subjects (not receiving dialysis) who received Q2W darbepoetin alfa successfully achieved and maintained target Hb levels, confirming previous findings of *de novo* Q2W darbepoetin alfa treatment. Furthermore, the safety profile of this study did not suggest safety concerns specifically associated with *de novo* Q2W darbepoetin alfa in CKD patients who were not receiving dialysis. Initiating anemia treatment and maintaining Hb levels with less dosing frequency (i.e., Q2W administration of darbepoetin alfa) as shown here, provides an added option for patient convenience.

Acknowledgments

Declaration of interest: This study (Aranesp 20030237) was supported by Amgen Inc., Thousand Oaks, CA, USA. M. R. S. has received consultation fees from Amgen Inc and Shire Pharmaceuticals, and speaker honoraria from Amgen Inc. R. G. serves on the Speaker's Bureau for Amgen Inc and Watson Pharmaceuticals. C. Y. C., R. K., and C. S-B. are employees of Amgen Inc. Some patients for this study were enrolled through the Veterans Administration Medical Center (Salem VA Medical Center, Salem, VA, USA and John D. Dingell VA Medical Center, Detroit, MI, USA). For M.R.S., this clinical trial was conducted through the General Clinical Research Center supported by the National Center for Research Resources, a component of the National Institutes of Health (Grant Number M01 RR000080). The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official view of the NCRR or NIH. The authors acknowledge Yeshi Mikyas, PhD, Amgen Inc., and Mandy Wyles, on behalf of Amgen Inc., for assistance in writing this manuscript. Trial registration of the 20030237 protocol: <http://www.clinicaltrials.gov/ct2/show/NCT00112008?term=20030237&rank=1>

References

1. Eckardt KU. Pathophysiology of renal anemia. Clin Nephrol. 2000; 53:S2–S8. [PubMed: 10746799]
2. Erslev AJ, Besarab A. Erythropoietin in the pathogenesis and treatment of the anemia of chronic renal failure. Kidney Int. 1997; 51:622–630. [PubMed: 9067892]
3. Kazmi WH, Kausz AT, Khan S, et al. Anemia: an early complication of chronic renal insufficiency. Am J Kidney Dis. 2001; 38:803–812. [PubMed: 11576884]

4. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol.* 2001; 38:955–962. [PubMed: 11583864]
5. Astor BC, Coresh J, Heiss G, et al. Kidney function and anemia as risk factors for coronary heart disease and mortality: the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J.* 2006; 151:492–500. [PubMed: 16442920]
6. Gerson A, Hwang W, Fiorenza J, et al. Anemia and health-related quality of life in adolescents with chronic kidney disease. *Am J Kidney Dis.* 2004; 44:1017–1023. [PubMed: 15558522]
7. Goicoechea M, de Vinuesa SG, Gomez-Campdera F, et al. Predictive cardiovascular risk factors in patients with chronic kidney disease (CKD). *Kidney Int Suppl.* 2005; 67 Suppl 93:S35–S38. [PubMed: 15613066]
8. Jurkovitz CT, Abramson JL, Vaccarino LV, et al. Association of high serum creatinine and anemia increases the risk of coronary events: results from the prospective community-based atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol.* 2003; 14:2919–2925. [PubMed: 14569102]
9. Levin A, Thompson CR, Ethier J, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis.* 1999; 34:125–134. [PubMed: 10401026]
10. Odden MC, Whooley MA, Shlipak MG. Association of chronic kidney disease and anemia with physical capacity: the heart and soul study. *J Am Soc Nephrol.* 2004; 15:2908–2915. [PubMed: 15504944]
11. Perlman RL, Kiser M, Finkelstein F, et al. The longitudinal chronic kidney disease study: a prospective cohort study of predialysis renal failure. *Semin Dial.* 2003; 16:418–423. [PubMed: 14629599]
12. National Kidney Foundation. K/DOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. *Am J Kidney Dis.* 2007; 50:471–530. [PubMed: 17720528]
13. Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med.* 2006; 355:2071–2084. [PubMed: 17108342]
14. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med.* 2006; 355:2085–2098. [PubMed: 17108343]
15. Gouva C, Nikolopoulos P, Ioannidis JP, et al. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. *Kidney Int.* 2004; 66:753–760. [PubMed: 15253730]
16. Jungers P, Choukroun G, Oualim Z, et al. Beneficial influence of recombinant human erythropoietin therapy on the rate of progression of chronic renal failure in predialysis patients. *Nephrol Dial Transplant.* 2001; 16:307–312. [PubMed: 11158405]
17. Abu-Alfa AK, Sloan L, Charytan C, et al. The association of darbepoetin alfa with hemoglobin and health-related quality of life in patients with chronic kidney disease not receiving dialysis. *Curr Med Res Opin.* 2008; 24:1091–1100. [PubMed: 18328118]
18. Alexander M, Kewalramani R, Agodoa I, et al. Association of anemia correction with health related quality of life in patients not on dialysis. *Curr Med Res Opin.* 2007; 23:2997–3008. [PubMed: 17958944]
19. Revicki DA, Brown RE, Feeny DH, et al. Health-related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. *Am J Kidney Dis.* 1995; 25:548–554. [PubMed: 7702049]
20. Rossert J, Levin A, Roger SD, et al. Effect of early correction of anemia on the progression of CKD. *Am J Kidney Dis.* 2006; 47:738–750. [PubMed: 16632012]
21. Pappas KD, Gouva CD, Katopodis KP, et al. Correction of Anemia with Erythropoietin in Chronic Kidney Disease (stage 3 or 4): Effects on Cardiac Performance. *Cardiovascular drugs and therapy/ sponsored by the International Society of Cardiovascular Pharmacotherapy.* 2008; 22:37–44. [PubMed: 18095148]
22. Levin A, Djurdjev O, Thompson C, et al. Canadian randomized trial of hemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. *Am J Kidney Dis.* 2005; 46:799–811. [PubMed: 16253719]

23. Hertel JE, Locay HR, Scarlata DS, et al. Darbepoetin alfa administration to achieve and maintain target hemoglobin levels for 1 year in patients with chronic kidney disease. *Mayo Clin Proc.* 2006; 81:1188–1194. [PubMed: 16970215]
24. Suranyi MG, Lindberg JS, Navarro J, et al. Treatment of anemia with darbepoetin alfa administered *de novo* once every other week in chronic kidney disease. *Am J Nephrol.* 2003; 23:106–111. [PubMed: 12481149]
25. Toto RD, Pichette V, Navarro J, et al. Darbepoetin alfa effectively treats anemia in patients with chronic kidney disease with *de novo* every-other-week administration. *Am J Nephrol.* 2004; 24:453–460. [PubMed: 15331889]
26. Levey AS, Greene T, Kusek JW, et al. A simplified equation to predict glomerular filtration rate from serum creatinine [abstract]. *J Am Soc Nephrol.* 2000; 11 0828.
27. Manjunath G, Sarnak MJ, Levey AS. Prediction equations to estimate glomerular filtration rate: an update. *Curr Opin Nephrol Hypertens.* 2001; 10:785–792. [PubMed: 11706306]
28. Hollander, M.; Wolfe, DA. *Nonparametric Statistical Methods.* New York, NY: John Wiley; 1973.
29. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for anemia of chronic kidney disease: update 2000. *Am J Kidney Dis.* 2001; 37:S182–S238. [PubMed: 11229970]
30. U.S. Renal Data System. *USRDS 2007 Annual Data Report: Atlas of End-Stage Renal Disease in the United States.* Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2007.
31. Obrador GT, Pereira BJ. Anaemia of chronic kidney disease: an under-recognized and under-treated problem. *Nephrol Dial Transplant.* 2002; 17 Suppl 11:44–46. [PubMed: 12386258]

ESA = erythropoiesis-stimulating agent, SC = subcutaneous, Q2W = every other week

Figure 1.
Study design

N = number of subjects who had a hemoglobin measurement during the study week, BL = baseline

Figure 2.
Mean (SD) Hb level over time

N = number of subjects who received a dose of darbepoetin alfa during the study week

Figure 3.
Darbepoetin alfa dose across dosing time points

Table 1

Subject disposition

	Darbepoetin alfa <i>n</i> (%)
Subjects enrolled	128
Subjects who received darbepoetin alfa	128 (100)
Subjects who completed darbepoetin alfa treatment	117 (91)
Subjects who completed study	115 (90)
Subjects who discontinued study	13 (10)
AEs	3 (2)
Death	3 (2)
Initiation of dialysis	3 (2)
Noncompliance	2 (2)
Lost to follow-up	1 (1)
Other	1 (1)

Table 2

Subject demographics and baseline characteristics

	<i>N</i> = 128
Sex, <i>n</i> (%)	
Female	73 (57)
Male	55 (43)
Race, <i>n</i> (%)	
White or Caucasian	75 (59)
Black or African-American	40 (31)
Hispanic or Latino	10 (8)
Asian	3 (2)
Age (years)	
Mean (SD)	66.8 (13.7)
Weight (kg)	
<i>n</i>	127
Mean (SD)	83.7 (21.5)
eGFR (mL/min/1.73m ²)*	
<i>n</i>	127
Mean (SD)	32.1 (12.2)
Hb (g/dL)	
<i>n</i>	128
Mean (SD)	10.0 (0.6)
TSAT (%)	
<i>n</i>	128
Mean (SD)	23.6 (6.4)
Primary cause of CKD, <i>n</i> (%)	
Diabetes	66 (52)
Hypertension	37 (29)
Glomerulonephritis	2 (2)
Polycystic kidney disease	2 (2)
Other	19 (15)
Unknown	2 (2)
Time since the onset of CKD, months	
Mean (SD)	29.2 (40.1)

* Measurements must have been made during the 14 days immediately before enrollment to be included

Table 3

Hemoglobin results

	<i>N</i> = 128
Subjects who received at least one dose of darbepoetin alfa, <i>n</i>	128
Subjects who achieved Hb $\geq$ 11 g/dL	118
Proportion (95% CI)	92% (86%, 96%)
Subjects who completed the study, <i>n</i>	115
Subjects who achieved Hb $\geq$ 11 g/dL	112
Proportion (95% CI)	97% (93%, 99%)
Time to achieve a Hb $\geq$ 11 g/dL, weeks	
Median (Q1, Q3)	5 (3, 8)

Table 4

Adverse events

	<i>N</i> = 128
All AEs, <i>n</i> (%)	97 (76)
Life-threatening AEs	1 (1)
Serious AEs	26 (20)
Treatment-related AEs [*] , <i>n</i> (%)	11 (9)
Life-threatening treatment-related AEs	0 (0)
Serious treatment-related AEs	0 (0)
AEs leading to withdrawal, <i>n</i> (%)	3 (2)
Death on study ^{†,‡} , <i>n</i> (%)	4 (3)
AEs with ≥ 5% occurrence, <i>n</i> (%)	
Peripheral edema	11 (9)
Headache	10 (8)
Diarrhea	9 (7)
Hypertension	9 (7)
Arthralgia	7 (5)
Asthenia	7 (5)
Fatigue	7 (5)
Nausea	7 (5)
Urinary tract infection	7 (5)
Vomiting	7 (5)
Back pain	6 (5)
Depression	6 (5)
Hypotension	6 (5)

* Treatment relatedness was as determined by each study site investigator

[†] Includes deaths occurring within 30 days of last dose of darbepoetin alfa

[‡] Deaths were not considered treatment-related by investigators

Table 5

Adverse events in subjects with hemoglobin level > 13.0 g/dL or > 14 g/dL

	Subjects with			
	At least one Hb > 13 g/dL (n = 57)	All Hb ≤ 13 g/dL (n = 71)	At least one Hb > 14 g/dL (n = 28)	All Hb ≤ 14 g/dL (n = 100)
All AEs, n (%)	41 (72)	56 (79)	19 (68)	78 (78)
Serious AEs	8 (14)	18 (25)	3 (11)	23 (23)
Treatment-related AEs *	7 (12)	4 (6)	5 (18)	6 (6)
Treatment-related serious AEs *	0 (0)	0 (0)	0 (0)	0 (0)
AEs leading to withdrawal	2 (4)	1 (1)	1 (4)	2 (2)
Deaths on study	1 (2)	3 (4)	0 (0)	4 (4)

* AEs related to treatment are attributed at the discretion of the investigator administering the treatment