CMS National Coverage Analysis Erythropoiesis Stimulating Agents (ESAs) for Treatment of Anemia in Adults with Chronic Kidney Disease (CKD) Including Patients on Dialysis and Patients not on Dialysis (CAG-00413N)

Erythropoiesis Stimulating Agents (ESA) in Anemia Related to Kidney Disease

Clinical White Paper Developed for CMS by
Centocor Ortho Biotech Products, LP

Executive Summary

Erythropoietic stimulating agents [such as PROCRIT® (epoetin alfa) and Aranesp® (darbepoetin alfa)], are safe and effective and have an acceptable risk/benefit profile for the treatment of anemia in patients with chronic kidney disease according to its approved label. Erythropoietic stimulating agents should be initiated at a baseline hemoglobin < 10g/dL and discontinued for hemoglobin levels > 12 g/dL.

Treatment with epoetin alfa, a manufactured form of erythropoietin, has been demonstrated to elevate and maintain hemoglobin levels, decrease the need for red blood cell transfusions, and improve-patient reported outcomes in patients with chronic kidney disease. Many studies have been conducted over the past 20 years evaluating different dosing regimens of epoetin alfa. These studies have demonstrated the efficacy of epoetin alfa in the treatment of anemia in chronic kidney disease.

Erythropoietic stimulating agents are valuable in reducing the need for red blood cell transfusions and are the only viable alternative to transfusions for this patient population. The benefits of reducing transfusions include reduction in hospital visits, avoidance of infectious complications, including the potential for new and emerging pathogens, non-infectious complications, and conservation of the limited national blood supply already constrained with limited marginal capacity, especially at the regional level and during seasonal and holiday periods. Transfusions are also associated with the development of antibodies to the blood panel, resulting in greater difficulty for these patients to match for a renal transplant. Thus, blood transfusions in patients with chronic kidney disease may condemn otherwise suitable transplant candidates to a longer wait for a compatible renal transplant.

In addition to transfusion reduction, epoetin alfa treatment is associated with improvements in patient reported outcomes as demonstrated in a number of clinical trials. Erythropoietic stimulating agents are FDA approved for patients with anemia of chronic kidney disease. Erythropoietic stimulating agents use has been recommended in anemia treatment guidelines of the National Kidney Foundation.

When erythropoietic stimulating agents are used according to product labeling (to initiate and maintain hemoglobin between 10 and 12 g/dL) to correct anemia of chronic kidney disease, there is an increased risk for thromboembolic events and this risk is well described in product labeling. New safety information has emerged from investigational studies, when erythropoietic stimulating agents were used to target hemoglobin >12 g/dL, which showed an increased risk of thromboembolic events, congestive heart failure hospitalizations and death. In collaboration with the FDA, Ortho Biotech and Amgen Inc., another marketer of erythropoietic stimulating agents, updated the erythropoietic stimulating agents labeling safety information to reflect this important safety information. In addition, in light of the data from investigational trials, a joint meeting between the Cardiovascular and Renal Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee convened on Sept. 11, 2007 to re-assess the safety of erythropoietic stimulating agents in patients with chronic kidney disease and to re-evaluate the net clinical benefit of erythropoietic stimulating agents in this setting. At that meeting the Committee provided recommendations to the FDA urging further study of the drugs and potential labeling changes on the use of erythropoietic stimulating agents in chronic kidney disease, the FDA had determined to wait until the results of the TREAT trial (an investigational study of placebo treatment vs. treatment with darbepoetin alfa to a hemoglobin of 13.0 g/dL to help inform next steps. This study was carried out by Amgen and was recently reported in *The New England Journal of Medicine* (Pfeffer et al, 2009).

On March 24, 2010, CMS convened the MedCAC to review the available evidence on the use of erythropoietic stimulating agents[*] to manage anemia in patients who have chronic kidney disease. As noted by CMS in its overview of the MedCAC meeting, anemia is prevalent in patients with kidney disease due to progressive inability of the kidney to produce erythropoietin and is more common as chronic kidney disease progressively worsens. Erythropoietic stimulating agents raise hemoglobin and hematocrit levels in anemic patients who have chronic kidney disease, including both those on dialysis and those who do not require dialysis.

[*] FDA-approved ESAs include epoetin alfa and darbepoetin alfa. Epoetin alfa is manufactured by Amgen. Under a licensing agreement, epoetin alfa is marketed as Epogeen by Amgen for use in dialysis patients. It is marketed as PROCRIT by Centocor Ortho Biotech Products / Johnson & Johnson for use in nondialysis patients, including those with CKD. Darbepoetin alfa is manufactured and marketed by Amgen as Aranesp for use in dialysis patients and nondialysis patients, including those with CKD.

In recent years, the results of several clinical trials published in the peer-reviewed medical literature raised concerns about the safety of erythropoietic stimulating agents, especially when they are used to increase hemoglobin and hematocrit beyond the levels specified in the FDA approved label. In response to these safety concerns, the FDA revised the labels of the erythropoietic stimulating agents and issued letters to physicians regarding their concerns about the potential risks of erythropoietic stimulating agents.

Centocor Ortho Biotech Products, LP developed and submitted a white paper to assist the MedCAC in its review of erythropoietic stimulating agents for this indication and includes a summary of the published clinical evidence related to the benefits and risks of erythropoietic stimulating agents for the treatment of anemia in patients who have chronic kidney disease. It also includes an overview of four recent company-sponsored studies on the use of erythropoietic stimulating agents in this patient population. Two of these studies are published; one is in press and the manuscript for the last study is in preparation (1-3). These data demonstrate that when used according to the current prescribing information for patients with the anemia of chronic renal failure, epoetin alfa is effective in raising hemoglobin levels and maintaining hemoglobin levels within the target labeled range of 10-12 g/dL. Moreover, these studies show that when used in this setting, transfusion rates are low and untoward events are predictable. Studies targeting hemoglobin levels of 13 g/dL or greater were associated with an increased risk of adverse outcomes, including death. The current labels have recently been updated to reflect these findings.

The White Paper is organized into 4 major sections:

1. *Introduction*
2. *Patient Benefits of Hemoglobin Maintenance, Transfusion Reduction and Improved Patient Reported Outcomes*
3. *Safety of Erythropoietic stimulating agents in the Treatment of Anemia in Patients with Chronic Kidney Disease*
4. *References*
5. *Appendix Tables*

1. *Introduction*

The kidney is the major site of human erythropoietin production. Erythropoietin is secreted when the kidney senses tissue hypoxia and circulating erythropoietin stimulates the bone marrow to produce red blood cells. As kidney function declines, erythropoietin production declines, leading to progressive anemia. In the absence of sufficient erythropoietin, severe anemia ensues.

Other than red blood cell transfusion, treatment for the anemia of chronic kidney disease (CKD) includes recombinant human epoetin alfa or darbepoetin alfa. Without these drugs, many patients with CKD would require regular blood transfusions for the rest of their lives to maintain hemoglobin (Hb) at concentrations necessary to maintain normal tissue oxygenation. Anemia, or low Hb concentration, causes weakness, fatigue, and lightheadedness. Severe anemia is also associated with cardiovascular abnormalities, such as congestive heart failure, left ventricular hypertrophy, postural hypotension that can predispose to syncope. Patients with severe coronary artery disease may suffer from angina attacks and even myocardial infarction in the face of severe anemia.

Over the past 20 years, the safety and efficacy of erythropoietic stimulating agents (ESAs) were evaluated in multiple randomized and non-randomized trials in patients with anemia of CKD. The data demonstrate that ESAs used according to labeled guidance are safe and effective for decreasing the need for red blood cell transfusions and have an acceptable risk/benefit profile for patients with anemia of CKD. ESAs are the only treatment studied for chronic use as alternatives to red blood cell transfusions for this patient population. They have proven value in reducing the need for transfusions and improving patient reported outcomes (PROs).

The benefits of reducing chronic transfusions include reduction in hospital visits; avoidance of infectious complications, including potential new and emerging pathogens; avoidance of non-infectious complications; avoidance of iron overload; and conservation of the limited national blood supply. The latter benefit is especially meaningful as the national blood supply is already constrained with limited marginal capacity, especially at the regional level and during seasonal and holiday periods. Finally, and perhaps of greatest importance, in patients with CKD who may receive a renal transplant it is particularly important to avoid blood transfusions to avoid the risk

of the development of antibodies to human leukocyte antigens, which could disqualify patients from receiving a transplant.

The following review will describe those trials that evaluated the clinical benefit of ESAs in patients with anemia of CKD, both on dialysis and not on dialysis, to represent the data available for the spectrum of disease for which ESAs are approved in the CKD setting. We present the original registration trials, studies that led to the recent safety additions to the epoetin alfa label and four recent company-sponsored trials that studied patients treated to the current labeled target Hb. In addition, data from other company sponsored trials as well as the published literature that demonstrated benefits in patient reported outcomes are referenced.

2. *Patient Benefits of Hemoglobin Maintenance, Transfusion Reduction and Improved Patient Reported Outcomes*

Epoetin alfa and darbepoetin alfa were developed and approved as chronic, supportive therapies to elevate and maintain Hb concentrations and reduce the need for transfusions in patients with CKD. The original pivotal trials used to gain regulatory approval (registration studies) for epoetin alfa measured Hb response, transfusion reduction, and reduction of iron overload as the principal clinical efficacy endpoints. Based upon results from clinical trials and two decades of clinical experience, ESAs provide clear clinical benefit in CKD patients with regard to Hb maintenance, transfusion reduction and improvements in physician-assessed and PRO as described in Section 3.

Hemoglobin is Maintained With Use of ESA's

The ability to maintain Hb concentrations with ESA treatment in patients with CKD was demonstrated in the original registration trials and supported in clinical practice over the last 20 years. We describe four recent company-sponsored studies to provide additional data that demonstrate that Hb is well maintained with the use of epoetin alfa in patients with anemia of CKD. These studies used dosing algorithms designed to achieve target Hb levels between 10-12g/dL. Protocol-specified dose adjustments were designed to follow the dosage and administration section in the epoetin alfa package insert. The primary endpoint in these studies was Hb response to epoetin alfa when administered in less frequent dosing intervals (extended

dosing). The starting dose for each of the extended dosing arms was based on the average weekly dose for a 70 kg patient of 50IU/kg thrice weekly (TIW). A brief description of the trial design for each of these trials is presented below followed by the data to show that these regimens were effective in maintaining Hb in the target range of 10-12 g/dL.

The first company-sponsored study, EPO-AKD-3001, was a randomized open- label, multicenter, 44-week initiation/maintenance treatment study of epoetin alfa comparing two extended dosing regimens, once weekly (QW) and every two weeks (Q2W), with the approved TIW dosing regimen for initiation and maintenance treatment in anemic subjects with CKD.

Eligible subjects (n=375) were randomized (1:1:1) to receive epoetin alfa at an initial dose of 50 IU/kg s.c. TIW (the currently approved dose), 10,000 IU s.c. QW, or 20,000 IU s.c. Q2W. After 22 weeks of treatment, subjects who were receiving TIW treatment were switched to QW treatment; no other changes to dosing interval were permitted. The maximum protocol specified epoetin alfa doses were 150 IU/kg TIW, 20,000 IU QW, and 40,000 IU Q2W. The mean weekly dose for each group over the course of the treatment was 5039 IU for the TIW group, 5034 IU for the QW group and 6662 IU for the Q2W group.

Mean achieved Hb concentrations after the first 22 weeks of the trial (Fig. 1, the initiation period) and through the full 44 weeks (Fig. 2, the maintenance period) are depicted below.

Figure 1 Plot of the Mean Hemoglobin over the First 22 Weeks of Treatment – Study AKD-3001.

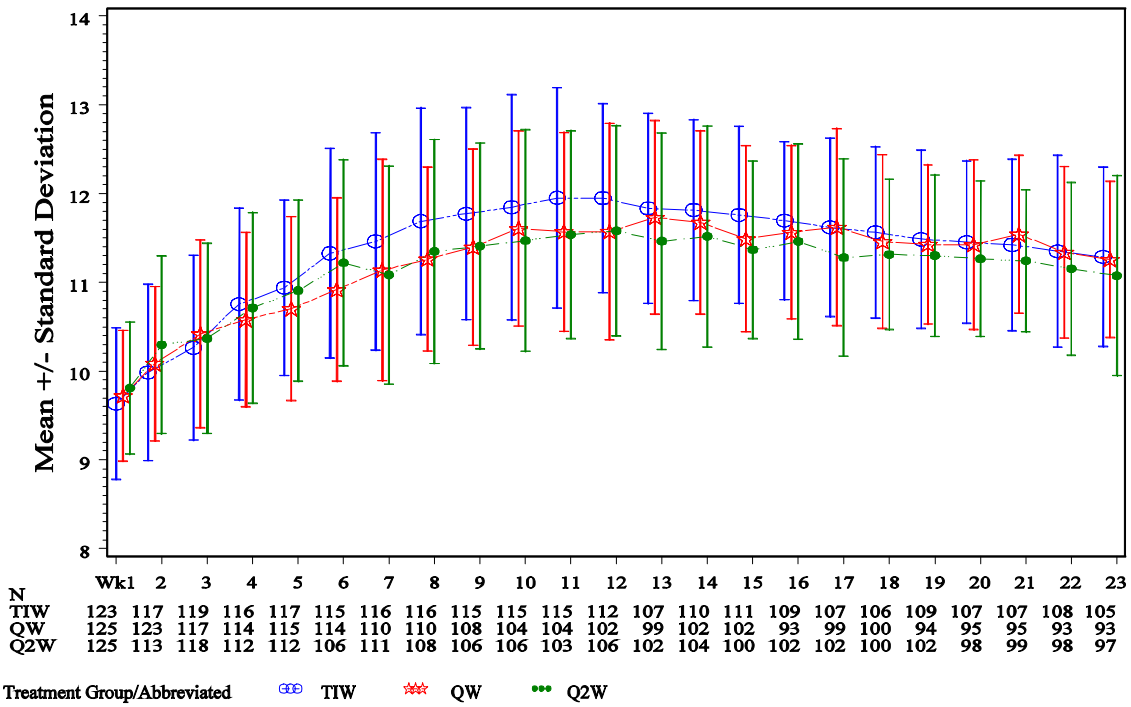
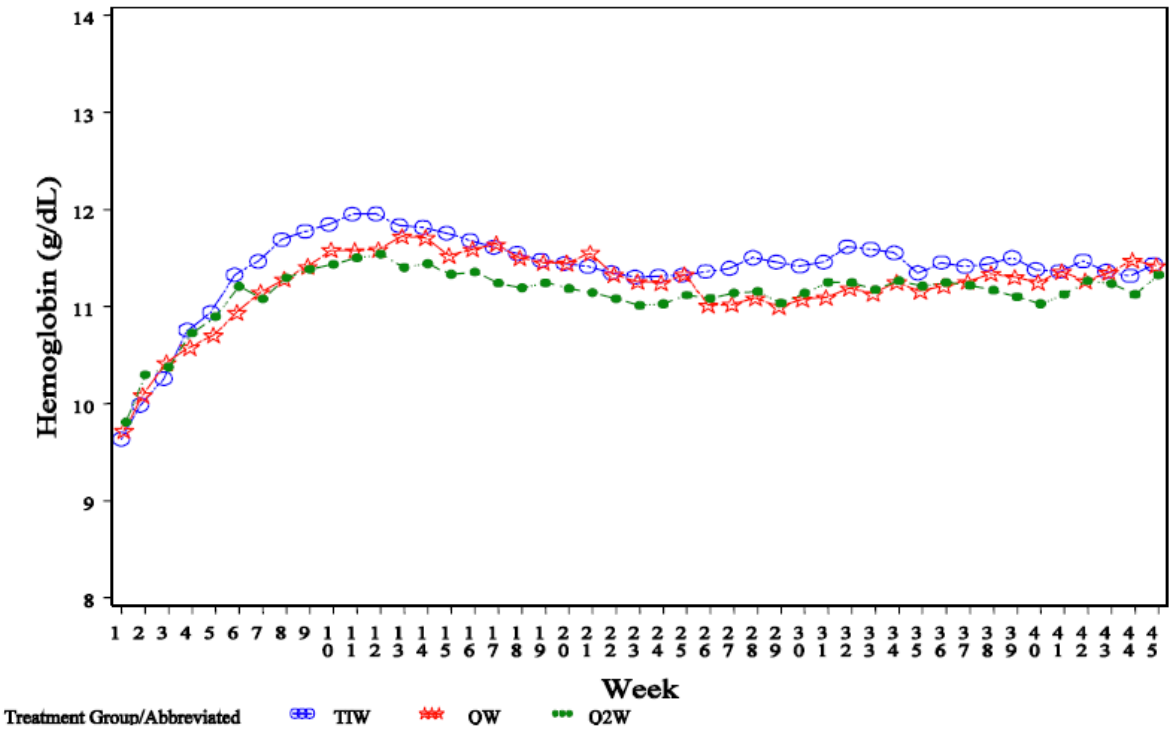


Figure 2 Mean Hemoglobin Concentration over the Entire 44 Weeks - Study AKD-3001



Q2W=every 2 weeks; QW=once weekly; TIW=3 times weekly
Note: Subjects in the 3-times-weekly group were switched to once-weekly dosing after Week 22.
Note: Week 1= Baseline.
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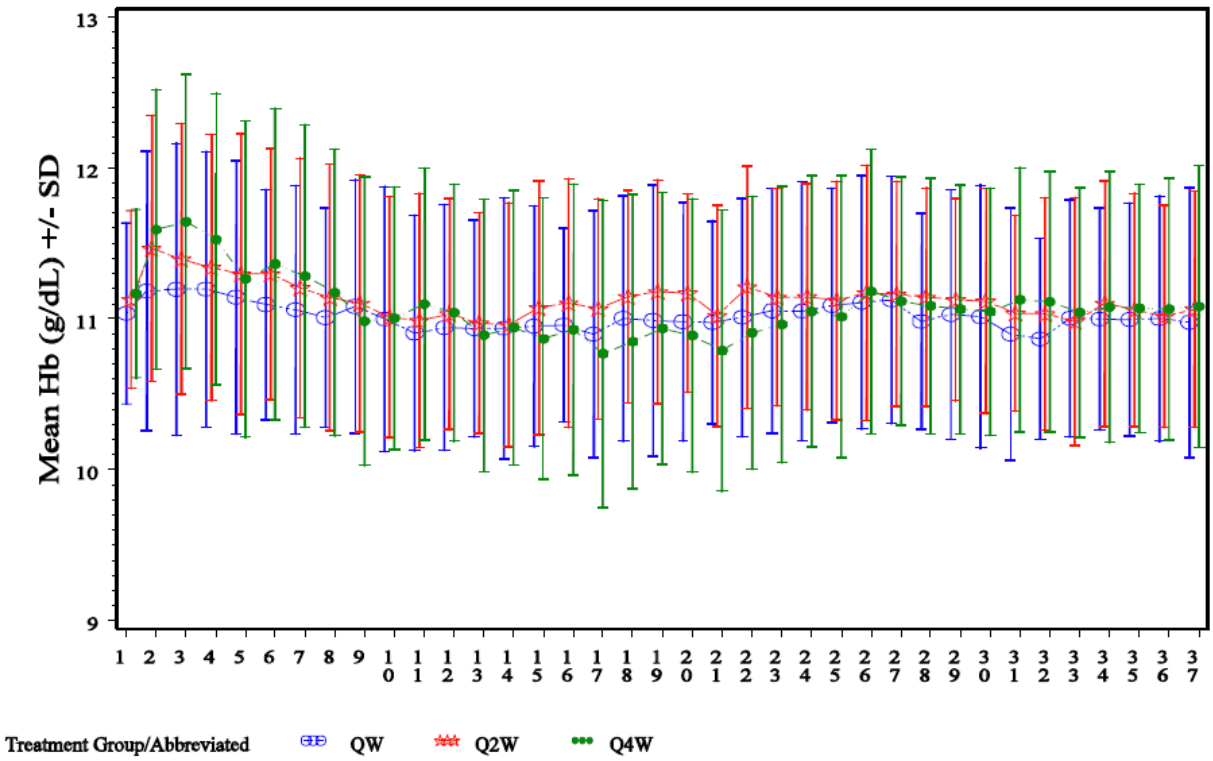
The second company-sponsored study, EPO-AKD-3002, was a randomized, open-label, multicenter, 36-week maintenance treatment study of epoetin alfa, comparing two extended dosing regimens, once every two weeks and once every four weeks, with the once-weekly dosing regimen for maintenance treatment in anemic subjects with CKD.

Eligible subjects (n=430) previously maintained on a stable once weekly (QW) epoetin alfa regimen, were randomized (1:1:2) to epoetin alfa QW s.c, Q2W s.c, or every 4 weeks (Q4W) s.c. The initial dose was calculated based on multiples of the pre-study QW dose at baseline (i.e., 1x, 2x, or 4x), with the initial Q2W dose rounded up to the nearest 10,000 IU and the initial Q4W dose rounded up to the nearest 20,000 IU. Changes to dosing interval were not permitted. The protocol specified maximum doses were 20,000 IU QW, 40,000 IU Q2W, and 80,000 IU Q4W. The mean weekly epoetin alfa dose for each group over the course of the treatment period was

3662 IU for the QW group, 5694 IU for the Q2W group and 6669 IU for the Q4W group. The mean final Hb level achieved for each group is depicted below.

Figure 3 Plot of Mean Hemoglobin Concentration over Time – Study AKD-3002 (Excluding Data Collected Post dialysis.)



Hb=hemoglobin; Q2W=every 2 weeks; Q4W=every 4 weeks; QW=once weekly; SD=standard deviation
Note: Week 1=Baseline
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The third company-sponsored study, EPO-CKD2001, was a 16-week, phase 2, randomized, open-label, multicenter initiation treatment study in anemic subjects with CKD not on dialysis (estimated GFR, 15-90 mL/min/1.73 m^2) who had not received ESAs within 8 weeks of screening and had an entry Hb concentration of <11.0 g/dL. Subjects were randomized (in a 1:2:2:2 fashion) to receive epoetin alfa at initial doses of 10,000 IU QW s.c., 20,000 IU Q2W s.c., 20,000 IU Q4W s.c., and 40,000 IU Q4W s.c. The maximum permitted doses for each group respectively were 20,000 IU QW, 40,000 IU Q2W, 35,000IU Q2W and 75,000 IU Q4W. The

mean weekly dose for each group over the course of the treatment period was 5943 IU, 7376 IU, 4522 IU, and 8660 IU respectively. The mean baseline to mean final Hb for each group respectively were as follows 10.3 g/dL to 11.5 g/dL (n=36), 10.4 g/dL to 11.3 g/dL (n=66), 10.1 g/dL to 11.2 g/dL (n=62), 10.2 g/dL to 11.4 g/dL (n=65).

The fourth company-sponsored study, EPO-CKD-2002, was a 26 week, phase 2, open label, randomized, multicenter, controlled study of epoetin alfa for the treatment of anemia of CKD in the long-term care setting n subjects with anemia of CKD who were not on dialysis and residing in long-term care facilities.

Eligible subjects were to have a Hb concentration of <11 g/dL at screening and were not permitted to have received an ESA for 8 weeks before randomization. Subjects (n=157) were randomly assigned in a 3:1 ratio to epoetin alfa or standard-of-care (SOC) control group (no ESA).

Subjects assigned to the epoetin alfa group initially received 20,000 IU s.c. Q2W. When a subject's Hb concentration was between 11.0 g/dL and 11.5 g/dL on two consecutive measurements, the dose of epoetin alfa was to be doubled and the dosing interval increased to Q4W. The maximum allowed dose was 30,000 IU Q2W or 60,000 IU Q4W. The mean final weekly dose of epoetin alfa was 6740 IU. The mean baseline to mean final Hb was 10.1 g/dL to 11.0 g/dL for the epoetin alfa treated group (n=114) and 10.2 g/dL to 10.5 g/dL for the control arm (n=39).

In each of these studies, Hb concentrations were well maintained within the target range. The adverse events that occurred in these studies were consistent with the underlying serious co-morbid conditions seen in patients with advanced renal disease. Safety will be discussed in more detail in Section 4.

Transfusion Reduction

In the general population including patients with CKD, allogeneic blood transfusions were associated with various complications such as disease transmission, alloimmunization, immunosuppression, graft-versus-host disease, acute lung injury (4) and iron overload (5). In the CKD population, a number of retrospective studies identified risks related to transfusion support.

In the presence of limited ability to handle increased intravascular volume, transfusion may lead to CHF, particularly in the elderly patients with CKD (4). The repeated administration of red blood cell transfusions over a prolonged period can eventually lead to iron overload (5). Blood transfusions can induce antibodies to human leukocyte antigens that can reduce the success of kidney transplantation or make it more difficult for a successful tissue match, resulting in longer waiting times for a renal transplant. Thus, transfusions generally should be avoided in patients awaiting a renal transplant (6).

The use of ESAs can greatly reduce the need for red blood cell transfusions in patients with anemia of CKD when target Hb concentrations are reached and maintained (7, 8). If Hb concentrations are maintained between 10-12 g/dL, blood transfusions should be necessary only in acute settings, e.g., for patients with acute bleeding (usually GI), acute hemolysis, or severe inflammation or blood loss through surgery, and then only in an emergency or if the patient exhibits rapid deterioration (9-11).

Clinical Trials Supporting the Use of Epoetin Alfa to Successfully Avoid Transfusions in Dialysis Patients

In registration clinical trials for epoetin alfa in hemodialysis patients targeting a hematocrit between 32% and 38% (Hb 10.7 to 12.7 g/dL), chronic transfusion dependence was markedly reduced by ESA therapy (12). In the open-label clinical trial 8601 (N = 426), only 4% of subjects required transfusions after 3 months of treatment with epoetin alfa compared with 54% over the 6 months before treatment was initiated (12). In the placebo-controlled trial 8701 (N = 68), the percentage of subjects requiring transfusions over a 3-month period decreased from 63% to 17% after they were switched from placebo to epoetin alfa. In the same trial, none of the subjects initially randomized to epoetin alfa required transfusions after 3 months of treatment.

In addition, other clinical trials assessed transfusion requirements for dialysis subjects when treated with epoetin alfa to different Hb targets. In the Normal Hematocrit Study, hemodialysis subjects with clinically evident cardiac disease were randomized to treatment with epoetin alfa to a target hematocrit of either 42% ± 3% or 30% ± 3% [Hb 14 ± 1 g/dL or 10 ± 1 g/dL]) (13). Over a median 14-month treatment period, significantly fewer subjects in the higher target group

received transfusions compared with those in the lower target group (21% vs. 31%, $p < 0.001$) (13).

In a sponsored EPREX® registration clinical trial (EP86-004), dialysis subjects were randomized to treatment with placebo or epoetin alfa to a Hb target of either 9.5 to 11.0 g/dL or 11.5 to 13.0 g/dL (14). Based upon the clinical study report, 20 of 40 subjects (50%) in the placebo group received a blood transfusion during the study, while 2 of 78 subjects (3%) in the epoetin alfa groups (1 subject from each target group) required transfusions in this 26-week study (of note, the publication states that 23 placebo-treated subjects received transfusions). There was no significant difference in the change in systolic pressure throughout the study. However, diastolic pressure was significantly increased in patients treated with epoetin alfa compared with placebo ($p < 0.001$). A positive association was observed between both the treatment with epoetin alfa and the incidence of clotting of the vascular access ($p=0.01$) and eye redness ($p=0.04$) (14, 15).

In a company sponsored clinical trial with EPREX® (EPO-INT-68), dialysis subjects were randomized to treatment with epoetin alfa to a Hb target of either 9.5 to 11.5 g/dL or 13.5 to 14.5 g/dL for up to 96 weeks (a 24-week initial phase followed by a 72-week maintenance phase) (16). During the trial, a greater proportion of subjects in the lower Hb target group (19% [58/300]) were transfused compared with the higher Hb target group (9% [27/296]) ($p < 0.001$). The achieved mean Hb concentrations in the lower and higher target Hb groups were 10.8 and 13.1 g/dL, respectively. The most frequently reported adverse events reported during study EPO-INT-68 were hypertension (39%), hypotension (32%), myalgia (28%), headache (25%), and upper respiratory tract infection (24%).

Consistent with these clinical trial results, decreases in transfusion requirements were observed in the dialysis setting following the introduction of epoetin alfa (17), which contributed to increased access to kidney transplants and improved renal transplant survival among kidney transplant patients (18-20).

CKD Patients Not on Dialysis

Registration clinical trials with epoetin alfa have evaluated Hb response in non-dialysis CKD subjects and demonstrated that Hb levels of approximately 10-12 g/dL can be achieved and maintained in these subjects. A survey of anemia management practices in Europe also revealed

that patients treated with an ESA before initiation of dialysis had significantly lower rates of blood transfusion than patients who did not receive an ESA (17% vs. 21%, $p < 0.05$) (21). These data indicate that a reduction in transfusion is also a clinical benefit in non-dialysis CKD patients.

Transfusion data were collected for each study arm in the four most recent company-sponsored studies targeting Hb levels not exceeding 12g/dL (study design described above). Overall, the number of transfused subjects was low and in almost all cases the reason for transfusion was due to an inter-current adverse event such as gastrointestinal bleed or surgery (1-3, 15).

In Study EPO-AKD-3001(2), the proportions of subjects receiving at least one transfusion during treatment were 3%, 7% and 11% respectively in the TIW/QW QW and Q2W groups. The proportions of subjects receiving at least 1 transfusion during treatment in EPO-AKD-3002(3) were 4%, 6%, and 7% in the QW, Q2W, and Q4W groups, respectively (2).

In study EPO-CKD-2001, 5 out of 259 subjects (1.9%) received red blood cell transfusions during the study; 1 subject in the group initiated on epoetin alfa 20,000 IU Q2W and 2 subjects in each of the groups initiated on epoetin alfa 20,000 IU Q4W and 40,000 IU Q4W (1).

There were no transfusions in the SOC group noted in studyEPO-CKD-2002. Four subjects (3.5%) in the EPO group required transfusions. One subject was transfusion-dependent upon study entry. Each of the other 3 subjects had a major medical event that precipitated the need for transfusion, (hip surgery, hemoptysis and gastrointestinal bleed) (15). These numbers are presented in Tables 6-9 in conjunction with safety events of interest.

In the recently published Amgen-sponsored TREAT trial, 4038 patients with diabetes and anemia due to CKD were randomly assigned to darbepoetin alfa to achieve a Hb of approximately 13g/dL (n=2012) or to placebo, with rescue darbepoetin alfa when the Hb was less than 9 g/dL (n=2026). Transfusions were required in 24.5% of the placebo group compared with only 14.8% of the ESA treated group ($p < 0.001$) (22).

Improved Patient Reported Outcomes

Dialysis Patients

The "Clinical Experience" section of the current epoetin alfa USPI describes the positive impact of epoetin alfa on the signs and symptoms of anemia in dialysis patients. Physician-assessed and patient reported outcomes statements were approved by the FDA for epoetin alfa in 1994. These claims were originally supported by the results of an open-label, single arm clinical trial, *The Quality Of Life Of Hemodialysis Recipients Treated With Recombinant Human Erythropoietin Trial* (study 8601), which was published in 1990 by Evans et al.,(23), combined with those of a randomized, double-blind trial of exercise capacity, published in 1991 by Lundin et al. (24).

Since the original approval, several other trials have also found positive treatment effects for epoetin alfa using several different patient-reported outcome measures that assessed the signs and symptoms of anemia (12). The remainder of this section summarizes the results from three Amgen sponsored randomized placebo controlled clinical trials Study 8601(12), 8701 (12), and 8904 (12), as well as additional published evidence from clinical trials with ESAs in dialysis subjects where patient-reported outcomes were assessed. Ortho study EP86-004 and Amgen studies 8701 and 8904 are three randomized, double-blind, placebo-controlled trials that assessed patient-reported outcomes in dialysis subjects (Table 1).

Table 1. Designs for Studies EP86-004, 8904, 8701 and 8601.

	EP86-004	8904	8701	8601
Design	Randomized, double-blind	Randomized, double-blind, partial crossover	Randomized, double-blind, partial crossover	Single arm, open label
Sample size (placebo; active)	40; 78	74; 78	32; 36	0; 426
Inclusion criteria				
Dialysis status (eGFR [mL/min/1.73m2])	Hemodialysis	Peritoneal dialysis	Hemodialysis	Hemodialysis
Hemoglobin (g/dL)	< 9	≤ 10 [a]	≤ 10 [a]	≤ 10 [a]
Age (yrs)	18 - 75	≥ 18	≥ 18	≥ 18
Dose administration	3x/wk IV	3x/wk SC	3x/wk IV	3x/wk IV
Hemoglobin target				
Target 1	11.5 -13.0	10.7 - 12.7 [a]	10.7 - 12.7 [a]	10.7 - 12.7 [a]
Target 2	9.5 - 11.0	-	-	-
Placebo	Yes	Yes	Yes	No
Hematopoietic endpoints	Hemoglobin	Hematocrit, blood transfusion		
Patient-reported outcome endpoints	KDQ, SIP, symptoms	Physical function & activity level, anemia symptoms, self-reported health status, sexual activity, sleep, eating behavior, well-being, satisfaction, happiness, work, and productivity		
Exercise endpoints	6-minute walk test, modified Naughton stress test	-	-	-
Patient-reported outcome assessment time points	Correction and maintenance: baseline, 2 mos, 4 mos, 6 mos	Correction: baseline, 12 wks Maintenance: 12 wks	Correction: baseline, 12 wks Maintenance: 12 wks	Correction: baseline, 12 wks Maintenance: 12 wks

[a] Hematocrit converted to hemoglobin concentration. Studies required hematocrit ≤ 30% and targeted hematocrit of 32% to 38%.

eGFR = estimated glomerular filtration rate; IV = intravenous; KDQ = Kidney Disease Questionnaire; SC = subcutaneous; SIP = Sickness Impact Profile

Ortho study EP86-004 (12, 14) was a 3-arm study that compared two target Hb levels with placebo. Patient-reported outcomes were assessed using the Kidney Disease Questionnaire (KDQ) and Sickness Impact Profiles (SIP). The patient reported outcomes measures in this trial were analyzed using repeated-measures analysis of variance comparing the placebo group to the entire group of epoetin alfa-treated subjects (combined data from the two active treatment arms). However, there were limitations to this trial. It was not powered to detect statistical difference in the patient-reported outcome measures and tests for statistical significance were not adjusted for multiple comparisons.

Studies 8701 and 8904 were partial crossover trials in which the control group received placebo for the first 12 weeks, and then were crossed over to epoetin alfa for the subsequent 12 weeks. Patient reported outcomes were assessed in these two trials using the Karnofsky Performance Status instrument administered as a patient-reported outcome, Nottingham Health Profile (NHP), and National Kidney Dialysis and Kidney Transplantation Study (NKDKTS) single item questions. These trials were not powered to detect statistical difference in the PRO measures. Post-hoc statistical testing of differences between placebo and treatment groups at baseline and week 12 was performed for these two trials. A PRO score at week 12 was considered significant when there was a statistically significant difference at follow-up between the epoetin alfa and placebo groups that did not exist at baseline. Tests for statistical significance were not adjusted for multiple comparisons.

Amgen study 8601 (12, 14, 23) (Evans et al, 1990), the original registration trial that was the basis for the inclusion of PRO statements in the epoetin alfa label, is included for comparison.

Energy:

Epoetin alfa therapy improved energy in dialysis subjects, when assessed using multiple validated measures (Table 2) in all 3 randomized, double-blind, placebo-controlled clinical trials). Results are summarized in Appendix Table 1 and Appendix Table 2.

Table 2. Summaries of instruments used to assess PRO in Studies 86-004, 8904 and 8701.

Study	Functional Ability/ Physical Function	Tiredness/ Lack of Energy	Weakness	Shortness of Breath	Exercise Capacity
EP86-004	KDQ Physical[a] SIP	KDQ Fatigue[a]	Patient-generated[a]	Patient-generated[b]	Exercise Stress[a]
	Physical[a]	Patient-generated[a]			6-minute Walk[b]
	Body care movement[a]				
	Home maintenance[a]				
	Ambulation[a]				
8904	Karnofsky (PRO)[b]	NKDKTS item[a] Single item PRO[a] NHP Energy scale[b]	NKDKTS item[a] Single item PRO[a]	NKDKTS item[b]	
8701	Karnofsky (PRO)[c]	NKDKTS item[b] Single item PRO[b] NHP Energy scale[b]	NKDKTS item[b] Single item PRO[b]	NKDKTS item[b]	

[a] Statistically significant improvement in treated arms versus placebo
[b] Numerical improvements in treated arm(s) versus placebo
[c] Not significant and no numerical improvement
KDQ = Kidney Disease Questionnaire; NHP = Nottingham Health Profile; NKDKTS = National Kidney Dialysis and Kidney Transplantation Study; PRO = patient-reported outcome; SIP = Sickness Impact Profile

In Ortho study EP86-004, there was a statistically significant improvement (indicated by higher values) in KDQ Fatigue Scale scores and Fatigue Symptom scores in the combined treatment groups compared to the placebo group ($p < 0.001$). In Amgen Study 8904, there were statistically significant differences between groups for the NKDKTS Energy item ($p = 0.006$) and single item patient-reported outcome ($p < 0.001$). The results were numerically consistent in Amgen Study 8701, but were not statistically significant. Although post-hoc statistical testing could not be performed for the NHP Energy scale, scores on the NHP Energy scale indicated a 50% improvement in epoetin-alfa treated subjects compared to placebo in Amgen study 8904, and a 30% improvement in Amgen Study 8701.

In addition to these three clinical trials, five open-label, single- or double-arm trials in the literature measured energy in dialysis patients (Appendix Table 3). Each of these trials reported statistically significant improvements in energy from baseline to follow-up in subjects treated with epoetin alfa.

Weakness:

Epoetin alfa therapy decreased weakness in dialysis subjects, when assessed using multiple validated measures (Table 2) in all three randomized, double-blind, placebo-controlled clinical trials. Results are summarized in Appendix Table 1 and Appendix Table 2. In Ortho Study EP86-004, there was a statistically significant improvement in the Decreased Strength symptom scores in the treatment groups compared to the placebo group ($p < 0.001$). In Amgen Study 8904, there were statistically significant differences between groups for the NKDKTS Weakness/Lack of strength item ($p = 0.01$) and single item Muscle Weakness patient-reported outcome ($p = 0.001$). The results were numerically consistent in Amgen Study 8701, but were not statistically significant. In addition to these three clinical trials, one open-label, single-arm trial [25] reported a statistically significant improvement ($p < 0.01$) in weakness from baseline to follow-up in subjects treated with epoetin alfa.

Shortness of Breath:

Epoetin alfa therapy improved shortness of breath in dialysis subjects, when assessed using multiple validated measures (Table 2) in all three randomized, double-blind, placebo-controlled clinical trials. Results are summarized in Appendix Table 1 and Appendix Table 2. In Ortho Study EP86-004, there was a numerical improvement in shortness of breath in all groups relative to baseline, although the effect did not achieve statistical significance. It should be noted that the effect size for shortness of breath was equivalent to or larger than the effect observed for weakness and energy in this trial; however, the sample size was smaller for evaluating shortness of breath than for those two endpoints.

In Amgen studies 8904 and 8701, shortness of breath was measured using the NKDKTS Symptom Checklist and the results were directionally consistent with the improvements shown in Ortho Study EP86-004. In addition to these three clinical trials, one open-label, single-arm trial [25] reported a statistically significant improvement in dyspnea from baseline to follow-up in subjects treated with epoetin alfa ($p < 0.01$).

Functional Ability and Activity Level; Physical Function:

Epoetin alfa therapy improved physical function and functional ability in dialysis subjects, when assessed using multiple validated measures (Table 2) in all three randomized, double-blind, placebo-controlled clinical trials. Results are summarized in Appendix Table 1 and Appendix Table 2.

- In Ortho study EP86-004, there were statistically significant improvements in the KDQ Physical Symptoms scores and the SIP Physical Function scale ($p < 0.001$; $p = 0.005$) in the combined treatment groups compared to the placebo group. There were also statistically significant improvements in all of the remaining SIP scales (Body Care Movement; Home Maintenance; and Ambulation).
- In Amgen studies 8904 and 8701, Functional Ability was measured using the patient-reported Karnofsky Performance Scale. In Study 8904, numerical improvement in the Karnofsky patient-reported outcome favored the treatment group compared to placebo for the Karnofsky patient-reported outcome. No difference was observed between groups in Study 8701.
- In addition to these three clinical trials, 15 open label, single- or double-arm trials in the literature measured Functional Ability or Physical Function in CKD patients (Appendix Table 4). Statistically significant improvements in Functional Ability or Physical Function from baseline to follow-up in subjects treated with Epoetin alfa were observed in 13 of 17 analyses from these trials[12].

Exercise Capacity:

In addition to functional ability, exercise capacity was assessed through standardized measures. The most commonly used exercise capacity measures are VO2 max, exercise stress test (maximal exercise test), and the 6-minute walk test. VO2 max measures the maximum amount of oxygen in milliliters that can be consumed in one minute per kilogram of body weight. The exercise stress test measures the maximum number of minutes exercised on a treadmill or stationary bicycle under changing conditions that include speed and incline. The 6-minute walk test evaluates the distance (in meters) covered in 6 minutes.

In EP84-004, exercise capacity was assessed using an exercise stress test and a 6-minute walk test (Table 2). As shown in Appendix Table 1, a statistically significant improvement in minutes

walked was observed in the treatment groups compared to the placebo group ($p < 0.05$). Although there was a numerical improvement in distance walked in the 6-minute walk test, the effect was not statistically significant. In addition to this randomized, double-blind, placebo-controlled trial, nine open-label, single-arm clinical trials in the literature measured exercise capacity using VO2 max (seven trials); exercise time (five trials) and/or 6-minute walk distance (one trial).

In the 13 analyses from these trials, statistically significant improvements in exercise capacity were observed from baseline to follow-up in subjects treated with epoetin alfa (Appendix Table 5). Minimally important or greater improvements in exercise capacity were observed in 11 of 13 analyses in which minimally important differences could be assessed (12).

Summary of Improved Patient Reported Outcomes in Dialysis Patients

The results from three randomized, double-blind, placebo-controlled clinical trials and published literature support the numerical or statistically significant improvements in physician-assessed and PRO and exercise capacity in dialysis subjects treated with epoetin alfa relative to those administered placebo.

Statistically significant differences or numerical improvements in physician-assessed and PRO were observed in three randomized, double-blind, placebo-controlled trials with epoetin alfa (Ortho Study EP86-004 and Amgen Studies 8904 and 8701). These results were attained using several different PRO measures that appear to be adequately validated in this population. The results were of sufficient magnitude to be clinically meaningful by standard criteria.

In Ortho Study EP86-004, all measures for energy, weakness, physical function, and exercise stress show statistically significant improvements in treated subjects compared with placebo. Numerical improvements in shortness of breath and 6-minute walk favored treatment over placebo. In Amgen Studies 8701 and 8904, all scores for energy, weakness, and shortness of breath favored treatment with epoetin alfa. In Amgen Study 8904, measures of energy and weakness were statistically significant. A numerical improvement in the Karnofsky Performance Status Instrument, administered as a patient-reported outcome, was observed among treated subjects in Study 8904, with no differences in Study 8701.

In addition, published clinical trials measuring physical function, exercise capacity, energy or weakness have shown improvements associated with epoetin alfa treatment. In 31 of 37 analyses, the results were statistically significant.

Non-Dialysis CKD Patients

Ten clinical trials in anemic, non-dialysis CKD subjects treated with epoetin alfa were identified in which physician-assessed and PRO were evaluated.

Results of these clinical trials are summarized in Appendix Table 6. Two of the trials (26, 27) used a double-blind, randomized, placebo-control design and were included in the original registration application. One study conducted in collaboration with the US Recombinant Human Erythropoietin Group, randomized 117 subjects to one of three epoetin alfa groups or placebo (26). Study duration was 8 weeks. A questionnaire was used to collect measurements of patient-reported energy and work capacity. This questionnaire was not a validated tool.

- More subjects in the epoetin alfa treated groups reported increased energy or work capacity compared with those in the placebo group.
- In addition, overall quality of life as measured by visual analogue scale was statistically significantly improved with epoetin alfa treatment compared with placebo in a small (N = 14), 12-week study (27). The remaining eight trials used open-label designs. Three of the trials (28-30) evaluated the relationship between hematocrit and PRO; correlations ranged from r = 0.15 to 0.45, reflecting small to moderate associations between increased hematocrit and improvements in PRO.

Three of the trials (29, 31, 32) were company sponsored studies that evaluated quality of life using Linear Analogue Self Assessment, KDQ, and SF-36. The analyses of the latter three trials used an accepted definition for a clinically meaningful difference in patient-reported outcome in chronic disease of approximately 50% of the standard deviation of scores at baseline (33). Clinically relevant differences in the context of anemia correction with epoetin alfa were identified for energy, activity, physical symptoms, fatigue, depression, relationship, and vitality (Appendix Table 6). This literature review for health-related quality of life in nondialysis CKD patients provides further evidence of the beneficial impact of ESA therapy on physician-assessed and PRO in patients with CKD.

Correction of Anemia and Outcomes in Renal Insufficiency, (CHOIR) was a large, open label, multicenter, investigational study to explore the risks and benefits of the correction of anemia in patients with CKD [32]. Patients with CKD and anemia (Hb < 11.0 g/dL) were treated with epoetin alfa to achieve and maintain a Hb level of 11.3 g/dL or a Hb level of 13.5 g/dL. This study is discussed in more detail in the Safety Section of this document. Several PRO instruments were used to assess whether treatment to a higher Hb level resulted in differences in health-related quality of life. The results are summarized in Table 3. While there were no differences in health-related quality of life between the group treated to the higher verses the lower Hb level, health-related quality of life was significantly improved in the low Hb target arm as well as the high Hb target arm over the course of the study compared with baseline assessments.

Another recent publication examined the relationship between Kidney Disease Quality of Life (KDQoL) questionnaire domains and Hb levels in 1200 patients with CKD not on dialysis followed in 7 CKD centers. Quality of life (QofL) measures were compared in stepwise fashion for a range of Hb levels, from <11 to >13 g/dL. Analysis of variance (ANOVA) was used to examine the relationship between QoL scores and Hb level, age, CKD stage, and serum albumin level. The results demonstrated that with increasing Hb levels there was a significant increase in the physical domains, energy/vitality domain and the physical composite score of the SF-36, and the general health score on the kidney disease component of the questionnaire. The greatest improvements in the various domains were seen between the <11 and the 11-12 g/dL group. The authors concluded that higher Hb levels were associated with improved patient reported outcomes relating to physical activity and general well being (34).

Table 3. Secondary Endpoints [32] in the CHOIR trial [reproduced with permission from NEJM]

EndPoint	High-Hemoglobin Group (N=715)	Low-Hemoglobin Group (N=717)	Hazard Ratio (95% CI)	P Value†
	no. of patients (%)			
Clinical results				
Components of the primary end point‡				
Death	52 (7.3)	36 (5.0)	1.48 (0.97-2.27)	0.07
Hospitalization for congestive heart failure (without renal replacement therapy)	64 (9.0)	47 (6.6)	1.41 (0.97-2.05)	0.07
Myocardial infarction	18 (2.5)	20 (2.8)	0.91 (0.48-1.73)	0.78
Stroke	12 (1.7)	12 (1.7)	1.01 (0.45-2.25)	0.98
Renal replacement therapy				
Any renal replacement therapy§	155 (21.7)	134 (18.7)	1.19 (0.94-1.49)	0.15
Hospitalization for renal replacement therapy	99 (13.8)	81 (11.3)	1.25 (0.93-1.68)	0.13
Hospitalization				
Cardiovascular causes	233 (32.6)	197 (27.5)	1.23 (1.01-1.48)	0.03
Any cause	369 (51.6)	334 (46.6)	1.18 (1.02-1.37)	0.03
	High-Hemoglobin Group		Low-Hemoglobin Group	P Value¶
	Baseline	Change from Baseline‖	Baseline	Change from Baseline**	
Quality of life††					
LASA score					
Energy	38.1±23.7	16.6±28.6	38.2±23.1	15.5±28.6	0.67
Activity	40.8±25.9	15.0±39.9	42.5±25.8	13.3±29.8	0.98
Overall quality of life	46.3±26.2	11.2±29.7	46.1±25.4	11.9±28.1	0.46
KDQ total score	20.3±5.80	1.6±5.6	20.6±6.00	1.1±5.6	0.26
SF-36 score					
Physical function	41.9±28.2	3.2±24.0	42.4±27.3	2.1±23.3	0.49
Physical role	31.9±38.9	6.4±40.7	32.5±39.2	7.5±43.2	0.32
Pain	57.8±28.5	0.4±28.1	58.0±27.1	2.4±26.7	0.15
General health	41.3±20.1	3.0±19.2	42.6±20.1	1.8±17.8	0.87
Vitality	35.2±22.6	10.0±23.8	36.6±22.4	8.2±20.6	0.58
Social function	63.7±29.5	1.3±33.1	63.7±29.0	3.5±28.7	0.16
Emotional role	57.2±43.6	0.8±48.3	57.4±43.3	5.9±48.1	0.01
Mental health	69.6±19.5	1.7±18.5	70.2±20.1	2.4±18.2	0.31

* Plus-minus values are means ±SD. Hazard ratios are for the comparison of the high-hemoglobin group with the low-hemoglobin group.
† P values were calculated by the log-rank test.
‡ Components of the primary end point were analyzed separately. For example, if a patient had more than one type of event, each event was counted the first time it occurred. Therefore, a patient could be included in more than one category of events. In the primary analysis of the composite events, a patient was counted only once (e.g., if a myocardial infarction occurred before a stroke, then only the time from randomization to the myocardial infarction was included in the composite event for the patient).
§ A total of 47 patients (24 in the high-hemoglobin group and 23 in the low-hemoglobin group) had a composite event.
¶ P values were calculated by analysis of covariance with the baseline score as a covariate.
‖ P values for comparisons of the change from baseline were between <0.001 and 0.02 for all scales except for three subscales on the SF-36: pain (P=0.63), social function (P=0.23), and emotional role (P=0.81).
** P values for comparisons of change from baseline were between <0.001 and 0.01.
†† Quality of life was measured with the LASA (scores range from 0 to 100, with higher scores indicating better function), the KDQ (total scores range from 4 to 35, with higher scores indicating better health), and the SF-36 (for each subscale, scores range from 0 to 100, with higher scores indicating better health).

Finally, in the recently published TREAT trial [22] the primary pre-specified analysis for the patient reported outcomes was the change from baseline to 25 weeks in the FACT-Fatigue score. Among patients with both baseline and week-25 scores, from a baseline score of 30.2 in the group of 1762 patients assigned to darbepoetin alfa and a baseline score of 30.4 in the 1769 patients assigned to placebo, there was a modest, yet statistically significant, degree of improvement in the mean (±SD) score in the darbepoetin alfa group than in the placebo group (an increase of 4.2±10.5 points vs. 2.8±10.3 points, P<0.001 for between-group changes). An increase of three or more points (considered to be a clinically meaningful improvement) occurred in 963 of 1762 patients assigned to darbepoetin alfa (54.7%) and 875 of 1769 patients assigned to placebo (49.5%) (P = 0.002).

Conclusion: Clinical Benefits of ESAs in the Treatment of Anemia in Patients with CKD

Anemia in CKD patients is an important clinical condition. ESAs have established benefits in increasing and maintaining Hb levels, reducing the need for transfusions as well as improved quality of life. Studies over two decades have shown that ESA use significantly increases and maintains Hb levels, reduces the risk of transfusion and has a positive effect in favor of an improved PRO for patients on epoetin alfa. Clinical guidelines continue to recommend ESAs for symptomatic patients with anemia from CKD [35].

3. Safety of Erythropoietic stimulating agents in the Treatment of Anemia in Patients with Chronic Kidney Disease

Two large trials in non-dialysis patients have tested the hypothesis that normalization of Hb levels (≥13 g/dL) with an ESA would result in greater improvement in cardiovascular, renal and mortality outcomes when compared with either partial correction of Hb levels with epoetin alfa (Hb of 11.3 g/dL in CHOIR or rescue therapy with darbepoetin alfa for Hb < 9 g/dL in TREAT) [22, 32]. The results of these trials failed to demonstrate the ability of targeting Hb to levels greater than 12.0 g/dL to improve cardiovascular outcomes. These trials did reveal an increased risk of adverse events when the Hb was targeted to levels of 13 g/dL or greater. As a result ESA labels were amended to carry warnings advising clinicians not to target Hb levels > 12 g/dL.

A trial in maintenance hemodialysis patients, the Normal Hematocrit Trial [13], was also designed to evaluate whether treatment to a hematocrit of 42% (Hb of 14.0 g/dL) compared with those treated to a hematocrit of 30% (Hb of 10.0 g/dL) were associated with improvements in myocardial infarction and mortality. This trial also showed an increased in risk for the patients treated to the higher Hb level. While the event rates were not statistically significantly different between the two treatment groups, there were numerically more myocardial infarctions (Table 4) and deaths in the group treated to the higher Hb level and the study was stopped early.

Table 4. Incidence of Seven Secondary Endpoints in the Normal Hematocrit Trial [13] [reproduced with permission from NEJM]

End Point	Normal-Hematocrit Group (N=618)	Low-Hematocrit Group (N=615)	P Value*
	no. (%)		
Red-cell transfusion	129 (21)	192 (31)	<0.001
Hospitalization for all causes	445 (72)	425 (69)	0.29
Congestive heart failure requiring hospitalization	80 (13)	90 (15)	0.41
Angina pectoris requiring hospitalization	78 (13)	76 (12)	0.93
Coronary-artery bypass grafting	20 (3)	21 (3)	0.88
Nonfatal myocardial infarction	19 (3)	14 (2)	0.48
Percutaneous transluminal coronary angioplasty	17 (3)	15 (2)	0.86

*The P values were calculated with Fisher's exact test.

The CHOIR trial (32) hypothesis was that treatment with epoetin alfa targeting a Hb of 13.5 g/dL would result in improved cardiovascular outcomes of stroke, congestive heart failure hospitalization, myocardial infarction, and all cause mortality compared with treatment with epoetin alfa to a Hb of 11.3 g/dL. The primary endpoint was a composite of these events.

Subjects with the anemia of CKD and Hb<11.0g/dL were treated with epoetin alfa to achieve and maintain a Hb of 11.3 g/dL (low target arm) or a Hb of 13.5 g/dL (high target arm). A total of

1432 subjects, 717 in the low target arm and 715 subjects assigned to the high target arm were randomized. The planned study duration was expected to be three years to demonstrate a 25% reduction in the composite event rate for the high target arm. However, the study was halted early at the recommendation of the Data Safety Monitoring Board.

The results of this trial demonstrated an increased risk for this composite endpoint (stroke, myocardial infarction, congestive heart failure hospitalization, and all cause mortality) in the higher Hb treatment arm. Median study duration was 16 months. The number of patients who experienced a composite event was 125 (17%) in the higher Hb target arm and was 97 (13.5%) in the lower Hb target arm. The event rates over time for the two treatment groups were significantly different (p=0.03, log rank test). The hazard ratio for experiencing a composite event between randomization and termination for the high Hb group vs. the low Hb group was 1.33 (95% CI 1.025, 1.743) indicating that a patient in the higher target arm (13.5 g/dL) was 1.33 times as likely to experience a composite event as a patient in the group treated to the lower Hb target (11.3 g/dL).

In the TREAT trial (22), a study of 4,038 subjects with type 2 diabetes and anemia and CKD, 2012 subjects were randomly assigned to achieve a Hb level of approximately 13.0 g/dL and 2026 subjects to placebo, with darbepoetin alfa rescue when the Hb was <9.0 g/dL. The primary endpoints were the composite outcomes of death or a cardiovascular event (non-fatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and of death or end-stage renal disease (Table 5). Median follow up duration was 29 months.

Death or a cardiovascular event occurred in 632 subjects in the treatment arm and 602 in the placebo arm (HR 1.05; 95% CI, 0.94 to 1.17; P=0.41). Death or end-stage renal disease occurred in 652 subjects in the treatment and 618 in the placebo arm (HR 1.06; 95% CI, 0.95 to 1.19; P=0.29). An evaluation of the individual components of the primary endpoint revealed that fatal or non-fatal stroke occurred in 101 subjects in the treatment arm and 53 subjects in the placebo arm, resulting in a two-fold increase in the risk of stroke in the treatment arm (HR 1.92; 95% CI, 1.38 to 3.68; P<0.001). These results differ from CHOIR, in which the overall primary composite event rate was higher in the group treated to the higher Hb target, while the incidence of stroke was the same in the two treatment groups (fatal or non-fatal stroke, 12 subjects in the higher Hb target arm, and 12 subjects in the lower Hb target arm).

Table 5. Composite and Component Endpoints of the TREAT Trial [22] [reproduced with permission from NEJM]

End Point	Darbepoetin Alfa (N = 2012)	Placebo (N = 2026)	Hazard Ratio (95% CI)	P Value†
	number (percent)			
Primary end points				
Cardiovascular composite end point‡	632 (31.4)	602 (29.7)	1.05 (0.94–1.17)	0.41
Death from any cause	412 (20.5)	395 (19.5)	1.05 (0.92–1.21)	0.48
Myocardial infarction§	124 (6.2)	129 (6.4)	0.96 (0.75–1.22)	0.73
Stroke§	101 (5.0)	53 (2.6)	1.92 (1.38–2.68)	<0.001
Heart failure§	205 (10.2)	229 (11.3)	0.89 (0.74–1.08)	0.24
Myocardial ischemia	41 (2.0)	49 (2.4)	0.84 (0.55–1.27)	0.40
Renal composite end point (ESRD or death)	652 (32.4)	618 (30.5)	1.06 (0.95–1.19)	0.29
ESRD	338 (16.8)	330 (16.3)	1.02 (0.87–1.18)	0.83
Additional adjudicated end points				
Death from cardiovascular causes	259 (12.9)	250 (12.3)	1.05 (0.88–1.25)	0.61
Cardiac revascularization	84 (4.2)	117 (5.8)	0.71 (0.54–0.94)	0.02

* ESRD denotes end-stage renal disease.
† P values have not been adjusted for multiple comparisons.
‡ A patient may have had multiple cardiovascular events of different types. The cardiovascular composite end point reflects only the first occurrence of any of the components.
§ This category includes both fatal and nonfatal events.

In the TREAT trial, there was no significant difference between the two groups with respect to the number of subjects reporting a cancer-related adverse event. Overall, 39 deaths were attributed to cancer in the 2012 subjects in the darbepoetin alfa group and 25 deaths were attributed to cancer in the placebo group (P=0.08 by the log rank test). Among subjects with a history of malignancy at baseline, there were 60 deaths from any cause in the 188 subjects assigned to darbepoetin alfa and 37 deaths in the 160 subjects assigned to placebo (P=0.13 by the log rank test). However, in this subgroup, 14 of the 188 darbepoetin treated subjects died from cancer, as compared with 1 of the 160 subjects assigned to placebo (P=0.002 by the log rank test).

Four recent, prospective, company sponsored trials, (EPO-AKD-3001, EPO-AKD-3002, EPO-CKD-2001 and EPO-CKD-2002) used dosing algorithms designed to maintain target Hb levels not to exceed 12g/dL (study design is described in section 3). All of these trials evaluated the

safety and efficacy of the use of epoetin alfa in extended dosing intervals. In three of these trials [1-3], all of the subjects received active treatment however subjects were randomized to different dosing intervals. One trial, conducted in the long term care setting [15], had a control arm in which subjects received standard of care, which included any treatment for anemia except an ESA . All of these trials had a very low incidence of adverse events including low incidences of death, thromboembolic events (TVEs) and hypertension. Adverse events of interest, death, which include stroke, SAEs, progression to dialysis, transfusion requirements, cardiac events and hypertension are summarized in Tables 6-9. We are focusing on these events as there is a high burden of cardiovascular disease in this patient population. Hypertension and TVEs are adverse events that are noted in the epoetin alfa label and are events for which clinicians caring for this patient population should be aware. The safety data from these four studies demonstrate that transfusion requirements were modest and limited to transfusion support for acute inter-current illness and the adverse events of interest appear to be similar to the overall adverse event profile of the elderly anemic patient with CKD, independent of ESA treatment.

Table 6 summarizes adverse events of interest in the initiation and maintenance trial EPO-AKD-3001. Events are reported separately for the first 22 weeks of the study (the point at which subjects being dosed TIW were switched to QW) as well as for the entire 44 weeks. Deaths were greatest in the QW group at both time points. TVEs were greater in the Q2W group but only after 44 weeks. SAEs were reported in more subjects in the extended dosing arms. More subjects were transfused in the Q4W group at both time points. Cardiac events were more numerous in the more extended dosing arms. However, hypertension was greatest in the TIW group over the first 22 weeks and least in the Q2W arm over the full 44 weeks.

Table 6 EPO-AKD-3001– Events of Interest

Event	**TIW/QW N=123**	**QW N=125**	**Q2W N=125**
Death – 1st 22 weeks (%)	0	5	2
44 weeks (%)	3	5	3
TVE – 1st 22 weeks (%)	2	2	2
44 weeks (%)	2	4	6
SAE - 1st 22 weeks (%)	15	22	22
44 weeks (%)	29	33	34
Dialysis - 1st 22 weeks (%)	2	2	2
44 weeks (%)	7	5	9
Transfusion - 1st 22 weeks (%)	1	4	7
44 weeks (%)	3	7	11
Cardiac events - 1st 22 weeks (%)	2	7	4
44 weeks (%)	5	14	9
Hypertension - 1st 22 weeks (%)	11	9	5
44 weeks (%)	13	14	10

Table 7 summarizes adverse events of interest in the maintenance trial EPO-AKD-3002. Deaths, TVEs, progression to dialysis and hypertension were numerically similar. There were more SAEs and transfusions in the Q2W and Q4W groups. Cardiac events were greatest in the QW group.

Table 7. EPO-AKD-3002– Events of Interest

Event	**QW N=108**	**Q2W N=107**	**Q4W N=215**
Death (%)	4	3	4
TVE (%)	3	5	3
SAE (%)	22	26	26
Dialysis (%)	2	2	2
Transfusion (%)	4	6	7
Cardiac events (%)	14	11	10
Hypertension (%)	12	13	12

Table 8 summarizes adverse events of interest in trial EPO-CKD-2001 over the 16-week treatment duration of the study. Numbers of deaths and TVEs were low with no apparent trend. SAEs and transfusions show an increasing trend as dosing intervals are lengthened. Cardiac events and hypertension show an increasing trend with more frequent dosing

Table 8. EPO-CKD-2001– Events of Interest

Event	**10, 000 IU QW N=39**	**20,000 IU Q2W N=76**	**20,000 IU Q4W N=72**	**40,000 IU Q4W N=72**
Death (%)	0	2.6	1.4	1.4
TVE (%)	2.6	0	1.4	2.8
SAE (%)	10.3	15.8	16.7	16.7
Transfusion (%)	0	1.3	2.8	2.8
Cardiac events (%)	12.8	10.5	5.6	4.2
Hypertension (%)	5.1	2.6	2.8	2.8

Table 9 summarizes adverse events of interest in trial EPO-CKD-2002 over the 26-week treatment duration of the study. Deaths, TVEs, progression to dialysis and cardiac events were numerically similar between groups. There were twice as many TVEs in the treated group. SAEs were reported more frequently in the Standard of Care group; however, no patients in the standard of care group required a transfusion or reported an adverse event of hypertension.

Table 9. EPO-CKD-2002– Events of Interest

Event	**Epoetin alfa N=118**	**Standard of Care N=39**
Death (%)	16.1	15.4
TVE (%)	5.9	2.5
SAE (%)	33.0	35.8
Dialysis (%)	0	0
Transfusion (%)	3.5	0
Cardiac events (%)	10.1	10.2
Hypertension (%)	5.9	0

In summary, while safety data from clinical trials targeting Hb concentrations ≥13.0 g/dL demonstrate a higher risk of death, cardiovascular events and stroke (which is addressed in the current epoetin alfa label); the safety data from these trials demonstrate that for subjects treated to Hb levels <12.0 g/dL, the safety profile is consistent with events expected in this patient population.

The clinical study data described here represent over 20 years of research in the treatment of the anemia of CKD. Like all studies, these studies have limitations. They are strictly controlled by protocol so they do not completely replicate the real world use of the drug. Some of these studies did not have a placebo treatment arm comparator, so efficacy and safety in the face of no treatment is difficult to ascertain. However, most of these studies had control arms that compared no treatment to treatment or treatment with different dosing regimens that could be compared. In the TREAT trial, the largest placebo controlled trial ever carried out in CKD patients, there were

only modest benefits in transfusion reduction and patient reported outcomes and an observed higher risk of stroke in darbepoetin alfa-treated subjects treated to a Hb target of 13 g/dL. Despite the limitations of these studies, careful consideration of their results demonstrates that epoetin alfa or darbepoetin is an important therapeutic advance in the treatment of the inexorable anemia due to CKD.

Management of the Patient with reduced Hb response to ESA treatment (Hyporesponsiveness)

At the CMS MedCAC meeting held March 24, 2010, there was discussion related to patients who fail to reach target Hb while being treated with ESA therapy. These patients are referred to as hyporesponsive. Hyporesponsiveness is of concern as it has been identified as a risk factor for increased cardiovascular events in patients with CKD. In both the Normal Hematocrit Study (patients treated with maintenance hemodialysis), and the CHOIR trial, (patients with CKD, not on dialysis), post-hoc exploratory analyses indicated that study subjects who did not achieve target Hb levels were more likely to have an adverse event of interest compared with subjects who did reach target Hb levels. This was true for both the high and the low Hb target arms in each trial (12). As a result of these analyses, the PROCRIT package insert was revised to include directions to health care providers regarding management of patients who's Hb cannot be maintained within the range of 10-12 g/dL despite appropriate dose titrations over a 12 week period.

Retrospective Observational Studies of Real World Anemia Management

The following section summarizes data from retrospective observational studies to provide insight into real world anemia management patterns in CKD patients not on dialysis. Temporal trends in epoetin alfa use and Hb values both at baseline and during epoetin alfa treatment were analyzed. These analyses provide insight into the potential impact of the changes in the ESA full prescribing information and the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Recommendations for anemia treatment in CKD[†] [36]

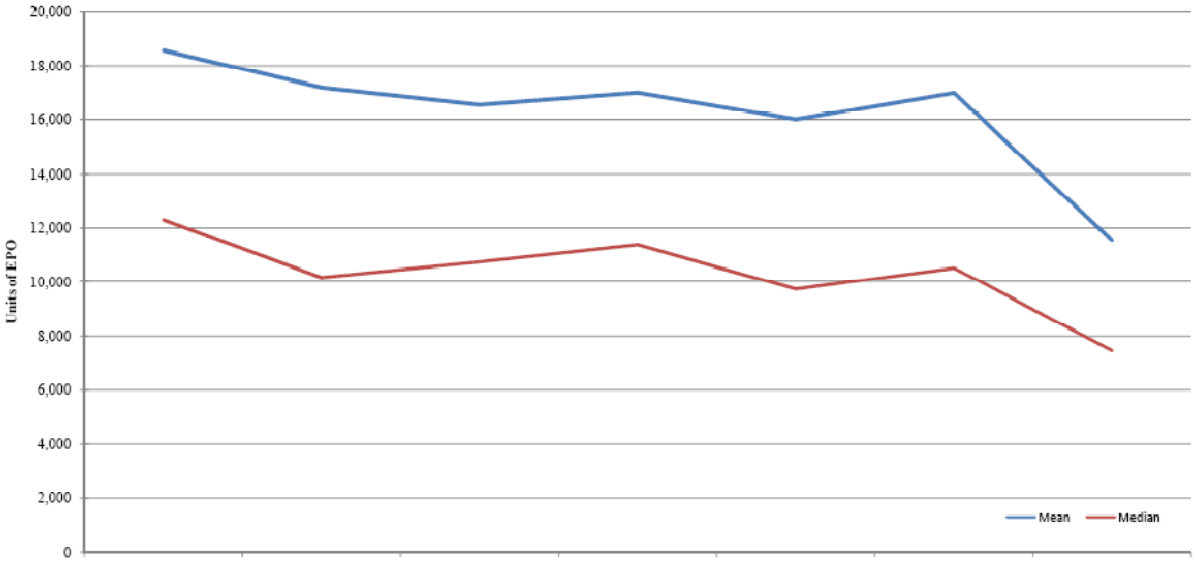
[†] The National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Recommendations for Anemia Treatment in CKD were changed in April 2007. The upper limit of the Hb target range was changed reflect the increased risk for targeting Hb values > 12 g/dL with ESA treatment.

Multiple observational studies reported EPO dosing consistent with prescribing information and decreasing EPO utilization trends over time.

Analyses from multiple datasets were conducted to understand epoetin alfa use in the treatment of anemia in CKD patients not on dialysis given that some have speculated concerns regarding epoetin alfa doses of greater than 20,000 U/week. The described studies evaluated temporal epoetin alfa dosing trends to assess the potential impact of the changes in the epoetin alfa prescribing information and in the KDOQI anemia treatment recommendations.[37]

A retrospective observational analysis of a managed care medical claims database was conducted to assess epoetin alfa use in 1645 CKD patients initiated on epoetin alfa treatment between 1/1/2002 and 6/30/2008. Analyzed by year of treatment initiation, the mean (SD) weekly epoetin alfa dose declined from 18,483 (47,411) units for patients initiating treatment in 2002 to 12,338 (11,596) units for patients initiating treatment in the first half of 2008, representing a 33% decline in the mean weekly dose. Similar trends were observed in the median (interquartile range) doses 9,381 (5,424-16,830) units for patients initiated in 2002 and 8,333 (5,282-15,000) units for patients initiated in the first half of 2008, representing an 11% decline in the median weekly epoetin alfa dose [15]. The observations were similar in a subset analysis of the 853 patients aged > 65 years old. The mean (SD) weekly epoetin alfa dose declined from 18,566 (18,214) units initiated on epoetin alfa in 2002 to 11,531 (11,973) units in patients initiating treatment in the first half of 2008, representing a 38% decline in the mean weekly epoetin alfa dose. The median (interquartile range) epoetin alfa doses declined from 12,297 (7,368-24,138) units in 2002 to 7,463 (5,085-13,188) units in 2008, representing a 39% decline in the median weekly dose (see figure below). The 75th percentile of weekly epoetin alfa dose decreased from 24,138 to 13,188 units per week [15].

Mean and Median Weekly Dose by Year
Predialysis CKD population - Age ≥65 years



	2002	2003	2004	2005	2006	2007	2008
N Episodes	57	77	108	128	244	163	76
Mean	18,566	17,184	16,552	16,992	16,005	16,985	11,531
SD	18,214	18,911	17,048	16,234	23,869	24,161	11,973
Median	12,297	10,158	10,734	11,364	9,718	10,500	7,463
(P25 - P75)	(7,368 - 24,138)	(5,986 - 21,000)	(6,276 - 17,649)	(6,920 - 20,000)	(5,250 - 17,455)	(5,211 - 20,000)	(5,085 - 13,188)

The Medicare 5% Sample was analyzed between 2006 and 2007 to evaluate temporal trends in cumulative epoetin alfa dosing. Analysis was performed to compare epoetin alfa dosing in CKD patients initiating treatment prior to 3/31/2007 (Pre-KDOQI change) to those initiating treatment after 3/31/2007 (Post KDOQI change). In the 1,850 epoetin alfa treated CRF patients not on dialysis, a 14% decrease in the mean cumulative epoetin alfa dose was observed after the KDOQI Anemia Treatment recommendations were changed [38].

These retrospective, observational analyses reported epoetin alfa use in the real world setting is consistent with the current epoetin alfa prescribing information recommendations of 10,500-21,000 Units/week [29]. Additionally, the temporal epoetin alfa dosing trends suggest that the mean weekly epoetin alfa dose trended downward after the changes in the prescribing information and the KDOQI anemia treatment recommendations.

Hb Outcomes:

To provide insight into real world Hb outcomes in ESA-treated CKD patients not on dialysis, retrospective observational analyses were conducted. An evaluation of hemoglobin (Hb) values in epoetin alfa treated CKD patients not on dialysis was conducted using a retrospective chart audit between 7/1/2001 and 6/30/2009. Baseline Hb values prior to epoetin alfa treatment initiation and during epoetin alfa treatment were analyzed before and after 3/31/2007 to evaluate the potential impact of changes in the KDOQI anemia treatment recommended Hb target ranges.

In the 1,109 patients with baseline Hb values, the mean baseline (SD) Hb declined from 10.5 (1.3) g/dL before 3/31/2007 to 10.2 (1.2) g/dL after that date. In the 8,944 patients with Hb values available during epoetin alfa treatment, the mean (SD) Hb declined from 11.4 (1.4) g/dL to 11.0 (1.3) g/dL. The percent of patients with Hb levels > 12 g/dL during epoetin alfa treatment also decreased from 28.5% before 3/31/2007 to 15.1% after that date [15]. Similar trends were observed in an analysis of a random sample of 10,232 ESA-treated CKD patients treated in the nephrology clinic setting from 2005 through 2007. A decline in the mean (SD) achieved Hb values from 11.3 (1.3) g/dL in 2005 to 11.1 (1.2) g/dL in 2007 in CKD patients treated with an ESA [39].

These retrospective, observational analyses suggest that Hb values at baseline and during ESA treatment have declined after the recent changes in the ESA full prescribing information and the KDOQI anemia treatment recommendations.

Conclusions

The data presented here reflect more than 20 years of clinical experience with epoetin alfa and demonstrate that with use of ESAs in the anemic CKD patient, Hb values are well maintained and blood transfusions, with their associated risks, are reduced. When patients with anemia of CKD are treated to Hb levels greater than 12 g/dL, there appears to be a greater risk for adverse outcomes compared to patients treated to Hb targets less than 12 g/dL. The current labels for ESAs marketed in the United States provide guidance on the appropriate Hb range for patients with chronic renal failure and dosage and administration guidance to initiate and maintain the Hb within the range of 10-12 g/dL for all these patients.

4. References

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Appendix Tables

Appendix Table 1. Analysis of Baseline and Month 6 Scores Comparing Combined Epoetin alfa Groups to Placebo, Study EP86-004 (Dialysis Subjects)

	EP86-004			
Mean (SD)	Placebo	Low Erythropoietin Group	High Erythropoietin Group	p-value
Energy				
KDQ Fatigue Scale				
Baseline	4.5 (1.1)	4.0 (1.3)	4.3 (1.4)	
Month 6	4.5 (1.2)	5.0 (1.1)	5.3 (1.1)	< 0.001[a]
Patient-generated Fatigue				
Baseline	4.1	3.1	3.7	
Month 6	4.1	5.4	5.0	< 0.001[b]
Weakness				
Patient-generated Weakness/Decreased Strength				
Baseline	4.1	2.8	4.0	
Month 6	4.2	5.3	5.3	< 0.001[b]
Shortness of Breath				
Patient-generated Shortness of Breath				
Baseline	3.6	4.3	4.2	
Month 6	4.4	5.9	5.8	NS
Functional Ability/Physical Function				
KDQ Physical				
Baseline	4.2 (1.0)	3.7 (1.1)	3.9 (1.0)	
Month 6	4.6 (1.0)	5.2 (1.1)	5.3 (1.0)	< 0.001[a]
SIP Physical				
Baseline	4.3 (4.8)	6.6 (7.3)	6.1 (6.4)	
Month 6	4.2 (5.7)	2.6 (3.4)	2.4 (3.9)	0.005[a]
Exercise Capacity				
Exercise Stress Test (min)				
Baseline	11.9 (5.3)	11.9 (5.0)	14.9 (5.6)	
Month 6	13.2 (5.7)	15.0 (5.2)	19.7 (6.4)	0.025[a]
6-minute Walk Test (m)				
Baseline	446 (115)	426 (102)	469 (110)	
Month 6	440 (120)	451 (109)	524 (174)	NS

[a] p-values are based on the change from baseline using analysis of variance comparing placebo versus the combined erythropoietin group at each time point

[b] p-values are based on the response profile comparing placebo versus the combined erythropoietin group

NS = Not significant

Appendix Table 2. Post-hoc Analysis of Baseline and First Follow-up Scores Comparing Epoetin alfa and Placebo Groups for Anemia Symptoms in Amgen Studies 8904 and 8701 (Dialysis Subjects)

		8904			8701		
		Placebo	EPO	p-value	Placebo	EPO	p-value
Energy	NKDKTS Energy item (% reporting Tires easily/ No energy)						
	Baseline	97.4%	89.2%	0.146	87.5%	76.7%	0.289
	12 Weeks	97.5%	76.5%	0.006	77.3%	60.0%	0.159
	Single item PRO (% reporting Very full of energy/Fairly energetic)						
	Baseline	10.0%	16.2%	0.419	26.9%	39.4%	0.314
	12 Weeks	4.9%	52.8%	<0.001	40.7%	53.3%	0.336
	Nottingham Health Profile Energy Scale						
	Baseline (mean)	64.8	48.5	n/a [a]	47.2	31.5	n/a [a]
	12 Weeks (mean)	63.1	33.4	n/a [a]	34.3	24.2	n/a [a]
Muscle weakness	NKDKTS Energy item (% reporting Weakness/Lack of strength)						
	Baseline	94.9%	77.8%	0.027	84.0%	67.7%	0.152
	12 Weeks	87.2%	61.8%	0.010	76.0%	51.6%	0.055
	Single item PRO (% reporting Muscle weakness)						
	Baseline	76.9%	63.9%	0.211	60.0%	60.0%	1.000
	12 Weeks	82.5%	47.1%	0.001	56.0%	34.4%	0.097
Shortness of breath	NKDKTS Shortness of Breath Symptom Score (% Reporting Shortness of Breath/Difficulty Breathing)						
	Baseline	60.0%	54.1%	0.601	46.2%	51.6%	0.680
	12 Weeks	43.9%	35.3%	0.441	46.2%	33.3%	0.313
Physical function	Karnofsky PRO (% ≥ 90/normal)						
	Baseline	12.5%	25.0%	0.158	25.0%	23.0%	0.858
	12 Weeks	27.5%	44.5%	0.120	45.2%	44.4%	0.951

[a] n/a = not available: standard deviations were not reported and post-hoc statistical testing could not be performed; PRO = patient-reported outcome

Appendix Table 3. Summary of Literature on Epoetin alfa Trials Measuring Energy (Dialysis Subjects)

Measure	Study	Design	Improvement	MID
NHP Energy Scale	Auer et al, 1990	Single-arm	stat sig	62%[a*]
	Auer et al, 1992	Single-arm	stat sig	66%[b*]
KDQ Fatigue	Muirhead et al, 1992a	RCT	stat sig	0.5 point[c*]
	Foley et al, 2000	RCT	stat sig	0.01 point[c†]
Other: Fatigue Symptoms	Harris et al, 1991	Single-arm	stat sig	N/E

KDQ = Kidney Disease Questionnaire; N/E = not evaluable; NHP = Nottingham Health Profile; RCT = randomized clinical trial; stat sig = statistically significant; MID = minimally important difference

* Change meets criteria for clinically meaningful or minimally important difference

† Change does not meet criteria for clinically meaningful or minimally important difference

[a] approximate 50% reduction of % patients with 'low energy' is clinically meaningful

[b] Standard response mean (SRM) ≥0.5 is clinically meaningful and SRM > 0.8 is large change

[c] 0.5 mean change in score represents minimally important difference; 1.0 mean change represents large change

Appendix Table 4. Summary of Literature on Epoetin alfa Trials Measuring Functional Ability/Physical Functioning (Dialysis Subjects)

Measure	Study	Design	Improvement	MID
Physician-assessed Karnofsky	Evans et al, 1990	single-arm	stat sig	a*
	Delano, 1989	single-arm	NS	11 points[b*]
	Harris et al, 1991	single-arm	stat sig	12 points[b*]
	Lee et al, 2004	Open-label, High vs low Hematocrit groups	NS	N/E
Patient-reported Karnofsky	Moreno et al, 1996	controlled	stat sig	12.6 points[b*]
	Moreno et al, 2000	single-arm	stat sig	2.8 points[b†]
SIP Physical Function	McMahon and Dawborn, 1992	crossover	stat sig	4.4 SD[c*]
	Moreno et al, 1996	controlled	stat sig	0.43 SD[c†]
	McMahon et al, 2000	DB, crossover	Numerical	1.7 SD[c*]
KDQ Physical Symptoms	Muirhead et al, 1992a	RCT	stat sig	0.9 point[d*]
	Foley et al, 2000	RCT	Numerical	1.17 points[d*]
	Furuland et al, 2003	RCT	stat sig	0.66 point[d*]
SF-36 Physical Functioning	Beusterien et al, 1996	controlled	stat sig	3.7 point[e†]
	Besarab et al, 1998	RCT	stat sig	N/E
Other				
Percent 'Very Active'	Eschbach et al, 1989	single-arm	stat sig	a*
Physical Activity	Bárány et al, 1990	single-arm	stat sig	0.5 SD[c*]
Physical Activity	Bárány et al, 1993	controlled	stat sig	N/E

DB = double-blind; KDQ = Kidney Disease Questionnaire; N/E = not evaluable; RCT = randomized clinical trial; SD = standard deviation; SIP = Sickness Impact Profile; stat sig = statistically significant; MID = minimally important difference; NS = not significant

* Change meets criteria for clinically meaningful or minimally important difference

† Change does not meet criteria for clinically meaningful or minimally important difference

[a] approximate doubling of % of patients with 'normal' function is clinically meaningful

[b] > 10.0 mean change from baseline is clinically meaningful

[c] effect size ≥ 0.5 SD is clinically meaningful

[d] 0.5 mean change in score represents minimally important difference; 1.0 mean change represents large change

[e] 8.0 mean change is clinically meaningful

Appendix Table 5. Summary of Literature on Epoetin alfa Trials Measuring Exercise Capacity (Dialysis Subjects)

Measure	Study	Design	Improvement	MID
VO_2 max	Lundin et al, 1991	single-arm	stat sig	1.54 SD [a]
	Robertson et al, 1990	single-arm	stat sig	0.48 SD [b]
	Mayer et al, 1998	single-arm	stat sig	1.23 SD [a]
	Grunze et al, 1990	single-arm	stat sig	0.7 SD [a]
	Lewis et al, 1993	single-arm	stat sig	1.21 SD [a]
	Metra et al, 1991	single-arm	stat sig	1.24 SD [a]
	Marrades et al, 1996	single-arm, health control	stat sig	1.77 SD [a]
Exercise stress test (min)	Lundin et al, 1991	single-arm	stat sig	1.17 SD [a]
	Robertson et al, 1990	single-arm	stat sig	0.47 SD [b]
	Lewis et al, 1993	single-arm	stat sig	1.15 SD [a]
	Hase et al, 1993	single-arm	stat sig	1.42 SD [a]
	Metra et al, 1991	single-arm	stat sig	0.89 SD [a]
6-minute Walk Test (m)	Harris et al, 1991	single-arm	stat sig	0.58 SD [a]

MID = minimally important difference, defined as effect size ≥ 0.5 standard deviation (SD); SD = standard deviation; Stat sig = statistically significant

[a] Clinically meaningful or minimally important difference

[b] Change does not meet criteria for clinically meaningful or minimally important difference

Appendix Table 6. Summary of Physician-assessed and PRO from 10 Clinical Trials with Epoetin alfa in Nondialysis CKD Subjects

Study	Physician Assess/ PRO Measure (Hematologic Measure)	Study Design	Hematologic Improvement	Physician Assess/PRO Improvement	CMD[a]
Singh et al (2006)[b]	LASA, KDQ, SF-36 (Hb)	Open-label, randomized High vs low Hb target	Stat sig	Stat sig	LASA: Energy: 68.38%, Activity: 55.04%
Benz et al (2007)[c]	LASA, SF-36 (Hb, Hct)	Open-label, single arm	Stat sig	Stat sig	LASA: Energy: 100.49%, Activity: 74.24% Overall: 66.67% SF-36: Vitality: 59.75%
Provenzano et al (2004)[d]	KDQ, LASA (Hb, Hct)	Open-label, single arm	Stat sig	Stat sig	LASA: Energy: 138.12%, Activity: 106.52% Overall: 98.69% KDQ: Physical Symptoms 136.36% Fatigue 93.33% Depression 50.00% Relationship 57.14% Total: 87.10%
The US Recombinant Human EPO Group (1991)	Energy Level and Work Capacity (Hct)	Placebo-controlled	Stat sig	Stat sig	Not reported

Appendix Table 6. (Cont) Summary of Physician-assessed and PRO from 10 Clinical Trials with Epoetin alfa in Nondialysis CKD Subjects

Study	Physician Assess./ PRO Measure (Hematologic Measure)	Study Design	Hematologic Improvement	Physician Assess/PRO Improvement	CMD[a]
Kleinman et al (1989)	LASA (Hct)	Placebo-controlled	Stat sig	Stat sig	Not reported
Revicki et al (1995)	SIP, SF-36 (Hct)	Open-label, parallel group Treated vs untreated	Stat sig	Stat sig	Not reported
Roger et al (2004)	SF-36, RQLP (Hb)	Open-label, randomized High vs low Hb target	Stat sig	Numerical (RQLP)	Not reported
Rossert et al (2006)	SF-36 (Hb, Hct)	Open-label, randomized Early-complete vs delayed-partial anemia correction	Not available	Stat sig	Not reported
Drüeke et al (2006)	SF-36	Open-label, parallel group	Not applicable	Stat sig	Not reported
Ritz et al (2007)	SF36 (Hb)	Open-label, parallel group High vs low Hb target	Stat sig	Stat sig	Not reported

Assess = assessment; CMD = clinically meaningful difference; Hb = hemoglobin; Hct = hematocrit; KDQ = Kidney Disease Questionnaire; LASA = Linear Analogue Self Assessment; RQLP = Renal Quality of Life Profile; SF-36 = Medical Outcomes Study 36-Item Health Survey; PRO = patient-reported outcome; SIP = Sickness Impact Profile; Stat sig = statistically significant change from baseline

[a] Mean change from baseline as a fraction of the baseline standard deviation was ≥ 50%.

[b] PR00-06-014 (CHOIR)

[c] PR03-06-001

[d] PR00-06-009 (POWER)