PROCRIT® (epoetin alfa)
Once Every Two Weeks Dosing of PROCRIT in Chronic Kidney Disease

SUMMARY

- **Singh et al (2006)**[1] conducted a study in predialysis chronic kidney disease (CKD) patients with anemia (N=1432), treating with epoetin alfa (EPO) (initially administered once weekly [QW] and maintenance every 2 weeks [Q2W]). Attaining a hemoglobin (Hb) target of 13.5 g/dL. was associated with an increased risk of mortality and cardiovascular (CV) morbidity compared with a Hb target of 11.3 g/dL.
    - This study was considered investigational as target Hb levels of 13.5 g/dL exceeded the recommended upper limit of Hb as described within the Food and Drug Administration (FDA)-approved PROCRIT Prescribing Information.[2]
- **Spinowitz et al (2008)**[3] assessed Hb response in nondialysis CKD patients with anemia, treated with 1 of 4 initiation regimens of EPO (10,000 international units [IU] QW; 20,000 IU Q2W; 20,000 IU every 4 weeks [Q4W]; and 40,000 IU Q4W; N=262). The mean Hb change from baseline was not inferior for the Q4W EPO group vs the Q2W group and adverse events (AEs) were similar between groups.
- **Pergola et al (2009)**[4] conducted a study in patients with anemia due to CKD not on dialysis (N=375), mean change in Hb from baseline through week 22 with EPO 10,000 IU QW or 20,000 IU Q2W was not inferior to that reported with EPO 50 IU/kg 3 times a week (TIW). Serious adverse events (SAEs) included cardiac failure, chronic renal failure, hypoglycemia, and myocardial infarction (MI).
- **Provenzano et al (2005)**[5] conducted the PROMPT study (N=519), Hb levels ≥11.0 g/dL were maintained in ~90% of patients who received either EPO 10,000 IU QW or 20,000 IU Q2W, and >75% of patients administered either EPO 30,000 IU once every 3 weeks (Q3W) or 40,000 IU Q4W. The most frequent AEs were hypertension (HTN), peripheral edema, urinary tract infection, and headache.
- **Pergola et al (2010)**[6] conducted a study in anemic CKD patients not on dialysis (N=430). Both Q2W and Q4W dosing with EPO demonstrated noninferiority to QW dosing with respect to the change in Hb concentration from baseline to the average of the last 12 weeks of treatment. The most common SAEs were congestive heart failure (CHF), acute renal failure, chest pain, and anemia.
- **Patel et al (2012)**[7] conducted a study of EPO administered at extended-dosing intervals in anemia CKD patients not on dialysis (N=157) compared with standard of care (SOC). The mean change in Hb level from baseline to endpoint was 0.9 g/dL in the EPO group and 0.3 g/dL in the SOC group (*P*=0.006). Rates of AEs and SAEs were similar in both groups. Rates of thromboembolic events were 5.9% in the EPO group and 2.5% in the SOC group.
- **McGowan et al (2008)**[8] conducted a pharmacokinetic (PK) study in anemic CKD patients not on dialysis (N=39) and reported that each of the 4 different dosing regimens of EPO (TIW, QW, Q2W, and Q4W) administered subcutaneously (SC) resulted in a similar pharmacodynamic (PD) response, despite modest differences in PK response.

PRODUCT LABELING

Please refer to the BOXED WARNINGS and the WARNINGS AND PRECAUTIONS section 5.1 of the PROCRIT Prescribing Information that discusses the findings from the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study.[2]

CLINICAL DATA

Singh et al (2006)[1] investigated whether targeting anemia correction with EPO in CKD patients not receiving dialysis to high Hb level of 13.5 g/dL would decrease mortality and CV morbidity compared with treating to a lower Hb level of 11.3 g/dL (N=1432).

Study Design/Methods

- This was an open-label, randomized, multicenter study that enrolled 1432 patients from 130 United States sites.
- Patients were initially assigned to a high-Hb group (13-13.5 g/dL, n=715) or a low-Hb group (10.5-11.0 g/dL, n=717).
- Hb targets were later redefined as 13.5 g/dL and 11.3 g/dL, for high- and low-Hb groups, respectively. At the time of the amendment, 347 of the 1432 patients (24.2%) were enrolled.
- EPO was initially administered at 10,000 IU SC QW for 3 weeks. The maximum total dose of EPO for each group was 20,000 IU per week. Subsequent doses were administered weekly based on a prespecified dosing algorithm to achieve the Hb target. Patients with stable Hb for 1 month received twice the previous dose administered Q2W.

Results

Patient Characteristics

- Patient estimated glomerular filtration rate (eGFR) was ≥15 mL/min/1.73 m^2 and ≤50 mL/min/1.73 m^2.
- A total of 17.4% of patients in the high-Hb group and 13.5% of patients in the low-Hb group had a self-reported history of coronary bypass graft (*P*=0.05). A total of 95.8% of patients in the high-Hb group and 93.2% of patients in the low-Hb group had a history of HTN (*P*=0.03).

Study Outcomes

- Data and Safety Monitoring Board recommended study termination in May 2005 primarily because the conditional power for demonstrating benefit for the high-Hb group by the end of study was <5% for all plausible values of the true effect for the remaining data.
- Mean and median follow-ups were 16 months with 661 patients (46.2%) completing 36 months of the study or withdrawing at the point of the study termination without experiencing an AE.
- A total of 549 patients (38.3%) withdrew prior to study termination without experiencing a composite event.
- The mean change in the Hb from baseline was 2.5 g/dL in high-Hb group and 1.2 g/dL in low-Hb group (*P*<0.001).
- Mean EPO doses administered to maintain Hb were 11,215 IU/week vs 6276 IU/week in high-Hb vs low-Hb groups, respectively.
- A total of 222 primary composite events (death, MI, CHF hospitalization without renal replacement therapy (RRT), or stroke) occurred, of which 125 (17.5%) were reported in patients in high-Hb group and 97 events (13.5%) among patients in low-Hb group (*P*=0.03; HR [hazard ratio]=1.34 [95% confidence interval (CI): 1.03-1.74]).
- Of the 222 composite events, there were 65 deaths (29.3%), 101 CHF hospitalizations without RRT (45.5%), 25 MI (11.3%), and 23 strokes (10.4%). Death and CHF hospitalization accounted for 74.8% of the composite events. Seven patients (3.2%) were hospitalized for CHF and had MI on the same day. One patient (0.5%) died after having a stroke on the same day.
- A per protocol analysis (n=1395; 37 patients were excluded who did not meet criteria required by the protocol and were incorrectly randomized) showed HR of 1.34 (95% CI: 1.03-1.75) (*P*=0.03). HR was similar when considering intent-to-treat (ITT) population and including all events from randomization to study termination or 30-days poststudy medication or from randomization to 90-days poststudy medication (1.30, *P*=0.04 [95% CI: 1.01-1.68] and 1.30, *P*=0.04, [95% CI: 1.01-1.66], respectively).
- In the high-Hb group with 715 patients, death was reported in 52 patients (7.3%) vs 36 patients (5%) in the low-Hb group with 717 patients (*P*=0.07), respectively. CHF

hospitalization without RRT was reported in 64 patients (9%) vs 47 patients (6.6%) in the high-Hb group vs low-Hb group (*P*=0.07), respectively.

Safety

- Mean systolic blood pressure decreased from baseline in the high-Hb group (-2.3±22.8 mm Hg) and the low-Hb group (-2.6±21.9 mm Hg) (*P*=0.27). Mean diastolic blood pressure increased by 0.2±12.9 mm Hg in the high-Hb group and decreased by -0.7±12.4 mm Hg in the low-Hb group (*P*=0.02).
- A total of 376 (54.8%) patients in the high-Hb group and 334 (48.5%) patients in the low-Hb group experienced at least 1 SAE (*P*=0.02).
- SAEs were similar between the high-Hb and low-Hb groups with the exception of CHF (11.2% vs 7.4%, respectively, *P*=0.02). SAEs experienced by 2% or more of patients in either treatment group included: CHF, MI, gastrointestinal hemorrhage, chest pain, cellulitis, pneumonia, and renal failure.
- A total of 98 patients died from the study initiation and through the 90-day study follow-up period: 52 patients in the 13.5 g/dL arm and 36 patients in the 11.3 g/dL arm.[9]
- The most frequent (>5%) causes of deaths were cardiac arrest, acute MI, sepsis or infection, stroke, renal disease, and other non-CV causes.[9]

Q2W or Q4W Initiation EPO

Spinowitz et al (2008)[3] evaluated the feasibility of initiating therapy with EPO using dosing intervals of up to Q4W in anemic CKD patients not receiving dialysis (N=262).

Study Design/Methods

- This was a prospective, open-label, randomized, multicenter, 16-week study.
- The study enrolled adult patients with Hb <11 g/dL.
- CKD was defined as GFR 15-90 mL/min/1.73 m^2.
- Target Hb was 11-12 g/dL.
- Patients were randomized in a 1:2:2:2 ratio to receive the following extended EPO regimens SC for 16 weeks: 10,000 IU QW; 20,000 IU Q2W; 20,000 IU Q4W; or 40,000 IU Q4W.
- Dose titrations were allowed starting at week 5.
- The maximum doses allowed were: 20,000 IU for QW regimen; 40,000 IU for Q2W regimen; 35,000 IU for 20,000 IU Q4W regimen; and 70,000 IU for 40,000 IU Q4W regimen.

Results

Patient Characteristics

- The mean Hb level was 10.2 g/dL and the mean GFR was 30.2 mL/min/1.73 m^2.

Efficacy

- A total of 230 (87.8%) patients completed the study and 32 (12.2%) withdrew.
- Modified intent-to-treat (mITT) or safety population (randomized patients who received ≥1 dose of EPO) consisted of 259 patients.
- The mean change in Hb for Q4W dosing regimens was not inferior to that of the Q2W dosing regimen. The difference in mean Hb change for 40,000 IU Q4W group vs 20,000 IU Q2W group was 0.12 (95.2% CI: -0.21 to 0.44). The difference in mean Hb change for 20,000 IU Q4W group vs 20,000 IU Q2W group was -0.05 (95.2% CI: -0.38 to 0.28).
- During the study, the following proportion of patients in each group achieved Hb >11 g/dL and an increase ≥1 g/dL:
    - 10,000 IU QW (85%)

- 20,000 IU Q2W (81%)
- 20,000 IU Q4W (65%)
- 40,000 IU Q4W (77%)

- The mean weekly dose was 5943 IU for the EPO 10,000 IU QW group; 7376 IU for the EPO 20,000 IU Q2W group; 4522 IU for the EPO 20,000 IU Q4W group; and 8660 IU for the EPO 40,000 IU Q4W group.
- Most of the dose adjustments were dose reductions which were most frequent in the 10,000 IU QW group and least frequent in the 20,000 IU Q4W group.

Safety

- The overall incidence of AEs was similar amongst all groups.
- The most common AEs (≥10%) were diarrhea, constipation, and headache; these events were considered possibly, probably, or very likely related to study drug in only 1 patient for each event.
- The following thrombo-vascular events (TVE) were noted: 10,000 IU QW: n=1 (chest pain); 20,000 IU Q2W: n=0; 20,000 IU Q4W: n=1 (MI); and 40,000 IU Q4W: n=3 (MI, chest discomfort, and peripheral vascular disorder). MI and peripheral vascular disorder were considered clinically relevant. Of the 5 patients who experienced a TVE, none had a Hb >12 g/dL or a Hb rise in excess of 1.0 g/dL over the previous 2-week period at the time that the event occurred.
- Two deaths were reported in the 20,000 IU Q2W group and 1 in the 20,000 IU Q4W group during the study.

Q2W Initiation/Maintenance EPO

Noninferiority Study: TIW vs QW or Q2W

Pergola et al (2009)[4] evaluated the efficacy and safety of EPO administered SC QW and Q2W to show that these extended dosing regimens are not inferior to that observed with TIW EPO regimen in patients with anemia due to CKD not on dialysis (N=375).

Study Design/Methods

- This was a prospective, open-label, randomized, multicenter study that included anemic adult patients (age ≥18 years) with GFR ≥15 and <60 mL/min/1.73 m^2 (CKD Stage 3-4).
- Patients were randomized 1:1:1 to receive 1 of 3 EPO dosing regimens SC to increase and maintain Hb level within the range of 11.0-11.9 g/dL: EPO TIW for 22 weeks (initial dose 50 IU/kg), followed by QW for an additional 22 weeks (initial dose 10,000 IU regardless of prior weekly dose) or EPO QW for 44 weeks (initial dose 10,000 IU) or EPO Q2W for 44 weeks (initial dose 20,000 IU).
- Dose maximum was 150 IU/kg TIW, 20,000 IU QW, or 40,000 IU Q2W.

Results

Patient Characteristics

- The mean baseline eGFR was approximately 30 mL/min/1.73 m^2 in each group.

Efficacy

- Of the 375 randomized patients, 369 comprised the mITT population.
- Median weekly EPO doses were 4382, 4364, and 6091 IU for the TIW, QW, and Q2W groups, respectively.
- The QW and Q2W EPO dosing regimens were found to be noninferior to the TIW regimen based on mean change of Hb during the study.

- The mean change in Hb from baseline (standard deviation [SD]) was 1.81 (0.9) g/dL for the 121 patients in the TIW/QW treatment group, 1.59 (1.0) g/dL for the 124 patients in the QW treatment group, and 1.27 (0.9) for the 123 patients in the Q2W treatment group.
- Mean final Hb levels were within the target range of 11.0-11.9 g/dL across dosing groups.
- The number of patients requiring transfusion over the 44-week treatment period was higher in the extended dosing groups compared with the TIW dosing arm (2.5% [n=3] in the TIW/QW arm, 6.5% [n=8] in the QW arm, and 10.5% [n=13] in the Q2W arm).

Safety

- The following statements refer to safety data that was collected over the entire treatment period (44 weeks). The overall incidence of AEs was comparable among the 3 dosing regimens (TIW/QW: 80% [n=98], QW: 78% [n=98], Q2W: 86% [n=107]). The TIW dosing regimen was associated with more Hb excursions over the target (Hb >11.9 g/dL) than QW or Q2W regimens.
- Treatment-emergent SAEs occurring in at least 2% but ≤5% of patients in any treatment group included: cardiac failure, chronic renal failure, hypoglycemia, MI, acute renal failure, pneumonia, gastrointestinal hemorrhage, hip fracture, dehydration, syncope, urinary tract infection, anemia, chest pain, deep vein thrombosis, dyspnea, fall, diarrhea, osteoarthritis, and upper gastrointestinal hemorrhage.
- The incidence of SAEs, HTN, AEs leading to study discontinuation, and death was similar in the TIW/QW, QW, and Q2W treatment groups.

Q2W Maintenance EPO

Provenzano et al (2005)[5] evaluated if extended EPO dosing schedules of up to Q4W were as effective as QW dosing in maintaining Hb levels ≥11 g/dL in CKD patients not on dialysis (N=519).

Study Design/Methods

- This was a prospective, randomized, open-label, multicenter, 16-week study.
- The Clinical Evaluation of PROCRIT for Maintenance Phase Treatment of Patients with Anemia due to Chronic Kidney Disease (PROMPT) study included CKD patients (serum creatinine: 1.5-6.0 mg/dL for females, 2.0-6.0 mg/dL for males) receiving maintenance EPO for treatment of anemia for ≥2 months.
- Patients were randomized to receive 1 of 4 dosing regimens SC for up to 16 weeks: 10,000 IU SC QW, 20,000 IU SC Q2W, 30,000 IU SC Q3W, or 40,000 IU SC Q4W.
- Dose reductions were allowed during the study, but dose escalations were not.

Results

Patient Characteristics

- Mean baseline Hb and GFR for all patients were 11.9±0.8 g/dL and 21.1±8.0 mL/min/1.73m^2, respectively.

Efficacy

- Of the 519 patients enrolled, 413 (79.6%) completed the 16-week study.

Study Results[5]

Epoetin Alfa	QW 10,000 IU	Q2W 20,000 IU	Q3W 30,000 IU	Q4W 40,000 IU
n=445[a]	108	114	114	104
Mean baseline Hb, g/dL (95% CI)	11.9 (11.7-12.0)	11.9 (11.8-12.0)	11.9 (11.8-12.1)	11.9 (11.8-12.0)
Mean final Hb, g/dL (95% CI)	12.2 (12.0-12.4)	11.9[b] (11.7-12.2)	11.2 (11.0-11.4)	11.4[b] (11.1-11.7)
% of patients maintaining Hb ≥11 g/dL	93.5	89.5	77.2	76.0

Abbreviations: CI, confidence interval; Hb, hemoglobin; IU, international units; QW, once weekly; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks.
[a]Five patients did not have a final Hb measurement and are not included in the above analysis.
[b]Significant 1-sided P-value testing noninferiority from QW (defined as greater than -10% of the final mean Hb measurement of the QW group).

- Approximately 90% of patients administered EPO Q2W and >75% of patients administered EPO Q3W or Q4W maintained Hb levels ≥11 g/dL.
- Difference in mean final Hb between QW and both Q2W and Q4W met the criteria for noninferiority ($P<0.001$ and $P=0.024$, respectively) but did not meet criteria for noninferiority between Q3W and QW (-1.0 g/dL) ($P=0.084$, 1-sided). The ITT analysis showed that all 3 groups were noninferior to the QW group.
- GFR remained stable during the 16-week maintenance phase in all dosing groups and 14 patients progressed to dialysis.

Safety

- The incidence of AEs was low and comparable across the study groups.
- The most frequent AEs reported by at least 5% of patients in any group included HTN (6.8%), peripheral edema (5.7%), urinary tract infection (4.3%), and headache (3.3%).
- Clinically significant AEs possibly related to vascular thrombosis were reported in 13 (2.5%) of patients.
- Sixteen (3.1%) of patients withdrew from the study due to AEs.

As a follow on to **Pergola et al (2009)**[4] study, a companion study by **Pergola et al (2010)**[6] evaluated whether EPO treatment Q2W or Q4W was inferior to QW EPO in patients with anemia and CKD (N=430).

Study Design/Methods

- This was a randomized, open-label, multicenter, parallel-group study that included anemic patients with CKD (GFR ≥15 and <60 mL/min/1.73 m^2) not on dialysis.
- Patients maintained on a stable QW dose were randomized in a 1:1:2 ratio to receive 1 of 3 EPO dosing regimens SC: EPO QW for 36 weeks (initial dose: the same as the last prerandomization dose of EPO treatment), EPO Q2W for 36 weeks (initial dose: twice the QW prerandomization dose of EPO rounded to nearest 10,000 IU), or EPO Q4W for 36 weeks (initial dose: 4 times the QW prerandomization dose of EPO rounded to nearest 20,000 IU).
- The safety population was defined as receiving at least 1 dose of study drug (N=430).
- The mITT population was defined as receiving ≥1 dose of study drug and having ≥1 postrandomization Hb measurement (N=428).
- The maximum dose was 20,000 IU QW, 40,000 IU Q2W, or 80,000 IU Q4W.

Results

Patient Characteristics

- The median baseline GFR was 26 mL/min/1.73 m^2.
- At baseline, the mean Hb concentrations were 11.0, 11.1, and 11.2 g/dL for the QW, Q2W, and Q4W groups, respectively.

Efficacy

- Median weekly doses over the course of the study were 2967 IU for the QW group, 4529 IU for the Q2W group, and 5423 IU for the Q4W group.
- Hb maintenance was noninferior in both the Q2W and Q4W dosing groups compared with the QW dosing arm. For the Q2W and QW groups, the estimated mean difference was -0.03 g/dL (95% CI: -0.21 to 0.15); for the Q4W and QW groups, the estimated mean difference was -0.09 g/dL (95% CI: -0.25 to 0.06).
- In all 3 treatment groups, the mean final Hb levels were 11.0 g/dL (average Hb over last 12-week period).
- The mean proportion of weeks per patient in which the Hb concentration was 10.0-11.9 g/dL, inclusive, during weeks 13-37 was 81% of the 107 patients in the QW treatment arm, 81% of the 106 patients in the Q2W treatment arm, and 75% of the 215 patients in the Q4W treatment arm.
- A total of 24 patients (5.6%) received transfusions: 3.7% in the QW treatment arm, 5.7% in the Q2W treatment arm, and 6.5% in the Q4W treatment arm.
- The majority of patients receiving a transfusion (n=20) received transfusions for an acute decrease in Hb associated with hospitalization for an intercurrent medical illness or surgical procedure.

Safety

- Among the 3 treatment groups, the incidence of AEs was comparable.
- The most commonly reported AEs across treatment arms: HTN (11%), urinary tract infection (8%), edema (8%), and hyperkalemia (2%).
- Death occurred in 4%, 3%, and 4%; TVEs occurred in 3%, 5%, and 3%; and SAEs occurred in 22%, 26%, and 26% of patients in the QW, Q2W, and Q4W treatment groups, respectively.
- The most commonly reported SAEs across treatment arms were CHF (4%), acute renal failure (3%), chest pain (2%), and anemia (2%).

Patel et al (2012)[7] evaluated the use of extended-dosing frequencies for EPO over a 27-week period for patients who resided in long-term care facilities (N=157).

Study Design/Methods

- This was a prospective, open-label, multicenter, controlled study and patients were randomized in a ratio of 3:1 to receive EPO (n=118) or SOC (n=39).
- Patients were initiated on EPO 20,000 IU SC Q2W. Doses were titrated to maximum doses of 60,000 IU.

Results

Patient Characteristics

- The mean baseline Hb level was 10.1±0.8 g/dL and the mean eGFR was 45.7±17.1 mL/min/1.73 m^2 in the EPO group; corresponding values in the SOC group were 10.2±0.9 g/dL and 43.4±15.1 mL/min/1.73 m^2, respectively.

Efficacy

- The mean change in Hb level from baseline to endpoint was 0.9 g/dL in the EPO group and 0.3 g/dL in the SOC group (*P*=0.006).
- Hb responses (2 consecutive Hb levels ≥11.0 g/dL or increases ≥1.0 g/dL) were achieved in 85.1% of patients in the EPO group and in 53.8% of patients in the SOC group (*P*<0.001).
- Thirty-three patients (28.9%) converted from the Q2W to Q4W dosing regimen.
- No patient who converted to the Q4W dosing regimen had to be returned to the Q2W dosing regimen.
- Median time to Hb response was 41 days in the EPO group and 114 days in the SOC group (*P*<0.0001).
- Four patients in the EPO group required transfusions. None of the patients in the SOC group required a transfusion.

Safety

- The percentages of patients who had treatment-emergent AEs, SAEs, or who died during or within 30 days of the end of the study were similar between the EPO group and the SOC group.
- The most frequent AEs reported by ≥10% of patients in the EPO group included pain in extremity (10.1%), peripheral edema (11.0%), and upper respiratory tract infection (16.9%).
- Thromboembolic vascular AEs occurred in 5.9% of patients in the EPO group and in 2.5% of patients in the SOC group.

Pharmacokinetic Study

PK and PD profiles of 4 different dosing regimens of EPO administered SC in anemic CKD patients were evaluated during a prospective, open-label, randomized, multicenter study (N=39).[8] The following dosing regimens were studied: 50 IU/kg TIW X 12 doses; 10,000 IU QW X 4 doses; 20,000 IU Q2W X 2 doses; and 40,000 IU Q4W X 2 doses. Median time to achieve maximum endogenous erythropoietin concentration ranged from 12 to 24 hours postdose across all treatment groups. Maximum observed serum concentration and area under the curve increased proportionally with increasing doses of EPO. Except for the TIW group, mean half-life ($t_{1/2}$) values were similar across all treatment groups. Terminal $t_{1/2}$ was difficult to determine in the TIW group due to more frequent dosing in this group.

LITERATURE SEARCH

A literature search of Ovid MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File databases (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 13 July 2023. To streamline this document and provide the most relevant information, literature from noncomparative studies has been excluded. A prospective, noncomparative study investigating Q2W EPO dosing has been published.[10] Post hoc analyses of the PROMPT study[5] are also available.[11-13] In addition, Q2W EPO dosing has been evaluated in other retrospective studies and meta-analyses.[14-19]

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