Empirical Methods to Calculate an Erythropoiesis-Stimulating Agent Dose Conversion Ratio in Nondialyzed Patients with Chronic Kidney Disease

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ABSTRACT

BACKGROUND: Epoetin alfa and darbepoetin alfa are erythropoiesis-stimulating agents (ESAs) indicated for the treatment of anemia in chronic renal failure, including patients on dialysis and patients not on dialysis. Clinical experience demonstrates that the dose conversion ratio (DCR) between epoetin alfa and darbepoetin alfa is nonproportional across the dosing spectrum. However, previous calculations of the dose relationship between epoetin alfa and darbepoetin alfa, described in previous work as the "dose ratio" (DR), (a) used cross-sectional designs (i.e., compared mean doses for patient groups using each ESA) and were therefore vulnerable to confounding or (b) did not adjust for the nonproportional dose relationship. DRs reported in the literature range from 217:1 to 287:1 epoetin alfa (Units [U]):darbepoetin alfa (micrograms [µg]). Payers may need a single DCR that accounts for the nonproportional dose relationship to evaluate the economic implications of converting a nondialyzed patient population with chronic kidney disease (CKD) from epoetin alfa to darbepoetin alfa.

OBJECTIVE: To estimate a single mean maintenance DCR between epoetin alfa and darbepoetin alfa in subjects with CKD not receiving dialysis, using methods that take into account the nonproportional dose relationship between the 2 ESAs.

METHODS: This was a post-hoc analysis of a subset of patients enrolled in an unpublished, open-label, single arm phase 3 clinical trial (ClinTrial. gov identifier NCT00093977) that was completed in 2006. Although the clinical trial enrolled both dialyzed and nondialyzed patients, the present study used a patient subset comprising nondialyzed patients with CKD previously receiving weekly or every-other-week (Q2W) epoetin alfa who were switched to Q2W darbepoetin alfa to maintain hemoglobin (Hb) levels between 11.0 and 13.0 grams per deciliter. A population mean DCR was estimated using 2 methods: (a) a regression-based method in which the log-transformed (natural logarithm) mean weekly darbepoetin alfa dose over the evaluation period of the study (weeks 25 to 33) was regressed on the log-transformed (natural logarithm) weekly epoetin alfa dose over the 2-week screening period; and (b) a mean ratio method in which the DCR was calculated for each individual patient and then averaged for the study population to give a population-level DCR. Sensitivity analyses estimated the DCR in various subgroups.

RESULTS: Of 1,127 patients enrolled in clinical trial NCT00093977, 567 patients on dialysis were excluded. Of the remaining 560 patients, 104 received weekly or Q2W epoetin alfa, were switched to Q2W darbepoetin alfa, received at least 1 non-zero dose of darbepoetin alfa during the evaluation period, and were included in the DCR calculation for the present study. Analysis of the log-log plot for the regression-based method indicated 2 or more possible regression lines with separate slopes. However, based on our a priori analysis plan to estimate a single DCR for the patient sample, the estimated sample mean maintenance DCR in the regression analysis was 330.6 U epoetin alfa to 1 µg darbepoetin alfa. In the mean ratio analysis, the DCR was 375.6 U:1 µg. Sensitivity analyses in which DCRs were calculated for different subgroups with different baseline differences identified a variable DCR range of 302-380 U:1 µg.

CONCLUSIONS: The methodology used in estimating the DCR accounts for the nonproportional dose relationship between epoetin alfa and darbepoetin alfa and may represent an advance over the methods used in previous research. The mean maintenance DCR between the 2 ESAs exceeds a threshold of 300 U:1 µg, which is greater than previously reported DRs. This methodology provides payers the means to compare ESA doses in CKD patients not receiving dialysis.

What is already known about this subject

- Epoetin alfa and darbepoetin alfa are erythropoiesis-stimulating agents (ESAs) indicated for the treatment of anemia in chronic renal failure for patients on dialysis or not on dialysis.
- FDA labels for epoetin alfa and darbepoetin alfa in 2007 included a black box warning of an increased risk for death and serious cardiovascular events when administered to patients with renal failure to a hemoglobin (Hb) target of greater than 12 grams per deciliter (gm per dL), and the black box warning was revised in 2008 to specify individualized dosing to achieve and maintain Hb levels within the range of 10 to 12 gm per dL.
- The dose conversion ratio (DCR) between the 2 ESAs is nonproportional across the dosing spectrum, indicating that no single DCR describes the dose relationship. However, payers may need a single DCR to evaluate the economic implications of converting a patient population from epoetin alfa to darbepoetin alfa.
- Dose ratios previously reported in the literature, expressed as epoetin units (U) to 1 darbepoetin microgram (µg), range from 217:1 to 287:1. These ratios are based primarily on cross-sectional comparisons that are vulnerable to confounding.

What this study adds

- This study examines empirically the DCR that results when a patient population with chronic kidney disease (CKD) not on dialysis converts from epoetin alfa to darbepoetin alfa. Unlike previous cross-sectional comparisons, the present study employed methods in which each patient served as his/her own control.
- In a nondialyzed CKD patient sample that was converted from epoetin alfa to darbepoetin alfa, the estimated sample mean maintenance DCR was 330.6 U epoetin alfa:1 µg darbepoetin alfa using regression analysis of log-transformed doses, and 375.6 U:1 µg when individual patients' DCRs were averaged.
- Sensitivity regression analyses identified a variable DCR range of 302-380 U:1 µg.

Chronic kidney disease (CKD) is a major health issue in the United States. Data from the National Health and Nutrition Examination Survey (NHANES) indicate that 13.1% of noninstitutionalized adults in the United States have kidney disease not requiring dialysis.[1] Anemia is a significant complication in patients with CKD,[2,3] increasing in severity as kidney disease progresses.[4] Anemia in CKD patients contributes to multiple adverse outcomes, including increased morbidity and mortality, increased hospitalization, and decreased health-related quality of life.[5-7] CKD patients with anemia incur higher total health care costs (approximately $78,000 per year in 1999-2001) compared with patients without anemia (approximately $24,000 per year in 1999-2001) and compared with other diseases known to have a high prevalence of associated anemia (such as cancer and congestive heart failure).[8]

Darbepoetin alfa and epoetin alfa are erythropoiesis-stimulating agents (ESAs) indicated for the treatment of anemia in patients with chronic renal failure.[9,10] In patients with chronic renal failure, dosage of both products should be targeted to achieve and maintain hemoglobin (Hb) levels in the range of 10 to 12 grams per deciliter (gm per dL),[9,10] and the epoetin alfa product label specifies that nondialyzed patients being considered for therapy should have an Hb level of less than 10 gms per dL.[10]

Darbepoetin alfa has a longer serum half-life and greater biological activity than epoetin alfa and is approved for administration at extended dosing intervals.[11,12] Potential benefits of switching to a less frequent dosing regimen include more convenient dosing schedules for patients and less resource utilization for payers.[13] Clinical trial data from a registrational, multicenter, randomized, double-blind, noninferiority study in hemodialysis patients demonstrated that the dose conversion relationship between epoetin alfa and darbepoetin alfa is nonproportional across the dosing spectrum;[14,15] comparatively lower darbepoetin alfa doses are needed at higher epoetin alfa doses. This nonproportional dose relationship is reflected in the dose conversion table in the U.S. darbepoetin alfa package insert,[9] which is used as a clinical tool for health care providers when initially converting patients with CKD (receiving or not receiving dialysis) from epoetin alfa to darbepoetin alfa.

Although the nonproportional dose relationship indicates that no single dose conversion ratio (DCR) describes the dosing relationship between epoetin alfa and darbepoetin alfa, payers may need a single DCR to evaluate the economic implications of converting a population from epoetin alfa to darbepoetin alfa. Many studies have attempted to calculate a population-level single dose relationship value, described by previous investigators as a "dose ratio" (DR), using real-world observational data.[16-28] However, the majority of this work had significant methodological limitations because the underlying data do not represent the same patients who underwent conversion from one ESA to the other (Table 1).[16-19,21-28] In these studies, researchers used cross-sectional designs to compare the mean epoetin alfa dose in one population with the mean darbepoetin alfa dose in another population—per administration, per week, per hospital stay, or cumulative dose per study period—without controlling for equivalent outcomes (Hb levels) or heterogeneity in patient populations. Another important factor that has not been addressed in reporting the dose relationship in nonconverted[16-19,21-28] and converted[20] (from one ESA to another) CKD patient populations is the nonproportional dose conversion relationship as a function of ESA dose and treatment stage (initiation versus maintenance). Average DRs reported in the literature range from 217:1 to 287:1 epoetin alfa (units [U]): darbepoetin alfa (micrograms [μg]).

The purpose of the present study is to describe a methodology to calculate the DCR to facilitate the assessment of cost comparisons between epoetin alfa and darbepoetin alfa. We calculate a single empirical DCR at the population level using a nondialyzed CKD patient population in which patients were converted from epoetin alfa to darbepoetin alfa while maintaining equivalent Hb level.

■ Methods
Study Inclusion and Exclusion Criteria
This was a post-hoc analysis of data from a subset of subjects from an unpublished 52-week, multicenter, single-arm, open-label study to investigate the safety of darbepoetin alfa for the treatment of anemia in subjects with CKD who were previously maintained on epoetin alfa or darbepoetin alfa (ClinTrial.gov identifier NCT00093977).[29] Subjects included in the present study were aged 18 years or older, were not receiving dialysis, and had estimated glomerular filtration rate (eGFR) from 15 to 60 milliliters per minute per 1.73 square meters of body surface area (mL/min/1.73m²) as determined by the Modification of Diet in Renal Disease 4-variable equation.[30,31] Although clinical trial NCT00093977 enrolled both dialyzed and nondialyzed patients, an a priori decision was made to limit the present study to patients not receiving dialysis because the underlying characteristics of dialyzed and nondialyzed patients may differ. Subjects had Hb levels of 11.0 to 13.0 gm per dL (mean from 2 samples drawn at least 3 days apart during the screening period), had transferrin saturation levels of at least 15.0%, and were clinically stable in the judgment of the investigator. An Hb range of 11.0 to 13.0 gm per dL was clinically acceptable during the time the study was conducted (October 2004 to January 2007) and prior to the current labeled indications that specify an Hb range of 10.0 to 12.0 gm per dL in patients with CKD treated with ESAs.[9,10]

Subjects were excluded from the study if they had uncontrolled hypertension (diastolic blood pressure greater than 110 millimeters of mercury [mm Hg] or systolic blood pressure greater than 180 mm Hg during screening); acute myocardial ischemia, stroke, or major surgery within 3 months prior to screening; or received other investigational products within 30 days before the

TABLE 1 Studies Describing the Dose Relationship Between Epoetin Alfa and Darbepoetin Alfa in Patients with CKD Not Receiving Dialysis[a]

Study First Author and Year	Mean Reported Dose Ratio	Study Design Comparison Method	Limitations
No adjustment for the nonproportional dose relationship between epoetin alfa and darbepoetin alfa; nonconverted, nonmatched patient; no evaluation or control of Hb outcomes			
Mody et al., 2006[23]	219:1	Retrospective chart review. MW epoetin alfa dose to darbepoetin alfa dose over 5-month period. 528 epoetin alfa; 415 darbepoetin alfa	
Vekeman et al., 2008[27]	226:1	Retrospective analysis of hospital electronic records. MC of epoetin alfa to darbepoetin alfa per hospital stay. 65,907 epoetin alfa; 18,879 darbepoetin alfa	• No adjustment for extended duration of action
Barron et al., 2007[16]	232:1	Retrospective claims analysis of managed care organization data. MW epoetin alfa dose to darbepoetin alfa weighted for length of treatment duration. 620 epoetin alfa; 424 darbepoetin alfa	• No control for difference in patient characteristics
Vekeman et al., 2007[28]	242:1	Retrospective analysis of hospital electronic records. MC epoetin alfa dose to darbepoetin alfa per hospital stay. 22,873 epoetin alfa; 2,772 darbepoetin alfa	• No adjustment for extended duration of action • No control for greater disease severity
Smith et al., 2006[26]	257:1	Retrospective analysis of hospital electronic records. Mean daily dose of epoetin alfa dose to darbepoetin alfa weighted for length of hospital stay. 62,674 epoetin alfa; 10,905 darbepoetin alfa	
Lefebvre et al., 2008[22]	270:1	Retrospective claims analysis of managed care organization data. MC epoetin alfa to darbepoetin alfa dose per treatment period. 1,110 epoetin alfa; 723 darbepoetin alfa	• Newly initiated on ESA therapy • No adjustment for extended duration of action
No adjustment for the nonproportional dose relationship between epoetin alfa and darbepoetin alfa; nonconverted, nonmatched patient; evaluation, but no control of Hb outcomes			
Papatheofanis et al., 2006[25]	258:1	Retrospective chart review. MC epoetin alfa to darbepoetin alfa dose over 24-week study duration. 396 epoetin alfa; 393 darbepoetin alfa	• Hb data recorded but not controlled for
Papatheofanis et al., 2007[24]	270:1	Retrospective chart review of large self-insured employer database. MC epoetin alfa to darbepoetin alfa dose over 24-week study duration. 200 epoetin alfa; 200 darbepoetin alfa	• Hb data recorded but not controlled for
No adjustment for the nonproportional dose relationship between epoetin alfa and darbepoetin alfa; nonconverted, nonmatched patient; control for disease severity			
Laliberte et al., 2008[21]	278:1	Retrospective claims analysis of managed care organization data. MC epoetin alfa to darbepoetin alfa dose per treatment period. 1,066 epoetin alfa; 375 darbpoietin alfa	
No adjustment for the nonproportional dose relationship between epoetin alfa and darbepoetin alfa; control for Hb outcomes			
Hymes et al., 2007[20]	287:1	Retrospective chart review, converted from darbepoetin alfa to epoetin alfa, same population pre- to post-switch. MC darbepoetin alfa to epoetin alfa dose over 6-month period pre- and post-switch. 153 patients converted	• Hb data recorded but not maintained for conversion • Single outpatient clinic evaluation only • No washout period considered; carryover effect of darbepoetin alfa not accounted for

[a]*List is limited to studies that assessed DCRs in the CKD nondialysis populations. This list is not exhaustive.*
CKD = chronic kidney disease; DCR = dose conversion ratio; ESA = erythropoiesis-stimulating agents; Hb = hemoglobin; MC = mean cumulative; MW = mean weekly.

start of the study. Additional exclusion criteria included having received a blood transfusion within 8 weeks prior to screening; having active bleeding; having clinical evidence of systemic infection, inflammatory or hematologic disease, or cancer (except superficial skin cancer); or testing positive for human immunodeficiency virus (HIV) antibody or hepatitis B surface antigen.

Population and Dosing Paradigm

Subjects included in the present study were receiving maintenance epoetin alfa administered either weekly (QW) or every other week (Q2W) at study entry. Subjects were converted to Q2W darbepoetin alfa and received at least 1 dose of darbepoetin alfa. For subjects previously receiving QW epoetin alfa, the QW

FIGURE 1   Darbepoetin Alfa Dosing Decision Chart for the Unpublished Clinical Trial (NCT00093977)[a]
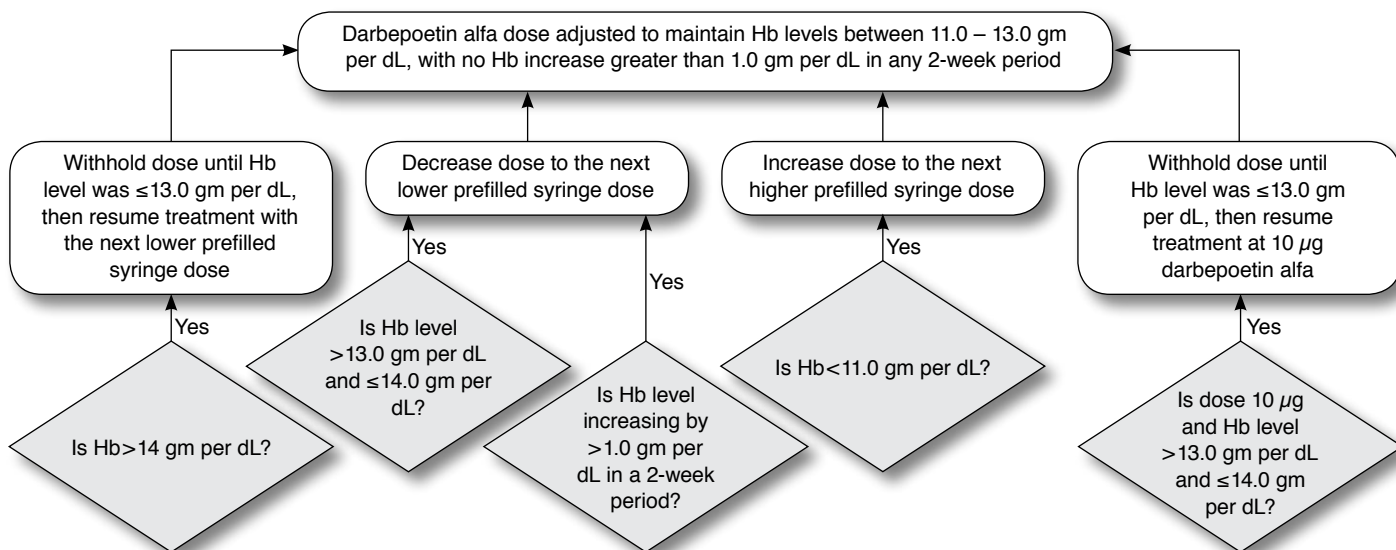
[a]ClinTrial.gov identifier NCT00093977.[29]

gm per dL = grams per deciliter; Hb = hemoglobin; μg = microgram.

dose was doubled to calculate the Q2W darbepoetin alfa conversion dose. For subjects receiving Q2W epoetin alfa at screening, the Q2W epoetin alfa dose was used to estimate the darbepoetin alfa dose. Dose conversions for the study differed in 2 ways from those recommended in the U.S. darbepoetin alfa package insert.[9] First, dose conversions in the trial were done using Q2W doses compared with QW doses as described in the package insert. Second, subjects who were receiving weekly epoetin alfa doses of less than 2,500, 2,500 to 4,999, and 5,000 to 10,999 U were converted to 10, 15, and 30 μg weekly darbepoetin alfa doses, respectively, to accommodate the dose provided in darbepoetin alfa pre-filled syringes at the time the study was conducted (syringes available were 10, 15, 20, 30, 40, 50, 60, 80, 100, 150, 200, and 300 μg). All other epoetin alfa dose ranges were converted to darbepoetin alfa doses as indicated in the package insert. As per the study protocol, darbepoetin alfa doses were adjusted to maintain Hb levels between 11.0 and 13.0 gm per dL, with no Hb increase greater than 1.0 gm per dL in any 2-week period. Dose adjustments were not to be made more frequently than once every 4 weeks except to hold the doses for Hb values exceeding 14 gm per dL. (Note: protocol specified dose withholds were counted as zero doses.) When necessary, changes in dose were made as shown in Figure 1.

Primary and Sensitivity Analyses Endpoints
The a priori primary analysis endpoint for the present study was the estimation of a maintenance DCR at the population level for subjects who received at least 1 nonzero dose of dar-

bepoetin alfa during the evaluation period (weeks 25 to 33). A period of 25 weeks after initiating darbepoetin alfa treatment allows total washout of red blood cells produced by epoetin alfa and ensures that patients were at their respective maintenance darbepoetin alfa doses.[32] An evaluation period of 8 weeks was chosen to accommodate the inter-individual variability in Hb levels. Sensitivity analyses were conducted in pre-specified (a priori) population subgroups. These included (a) subjects aged 65 years or older; (b) subjects who maintained Hb within 11.0 to 13.0 gm per dL at all measurement points; (c) subjects receiving QW epoetin alfa at screening; (d) subjects receiving Q2W epoetin alfa at screening; (e) subjects with an eGFR of 30 to 60 mL/min/1.73m²; (f) subjects with an eGFR of < 30 mL/min/1.73m²; (g) a modified sample that included subjects who did not receive a dose of darbepoetin alfa during the evaluation period for whom missing doses were imputed using last observation carried forward (LOCF); (h) subjects who did not receive red blood cell transfusion within 90 days prior to the evaluation period; and (i) subjects who received at least 1 nonzero dose during the end of the study period (weeks 45 to 53 of the evaluation period).

Statistical Analyses
Descriptive statistics were calculated for all continuous variables and included the number of nonmissing values, mean, median, standard deviation (SD), and the interquartile range. The number and percentage of subjects in each category for categorical

variables were also calculated. The weekly epoetin alfa dose at screening was determined by either the most recent QW dose for those receiving QW epoetin alfa or the Q2W dose divided by 2 for those receiving Q2W epoetin alfa. The weekly darbepoetin alfa dose during the evaluation period was calculated by dividing the Q2W dose by 2 for the week it was administered and assigning the same half dose the following week. The average of all weekly darbepoetin alfa doses was determined by taking the sum of all nonmissing weekly darbepoetin alfa doses and dividing by the number of weeks of nonmissed dosing during the evaluation period.

The population mean maintenance DCR was assessed using 2 methods. First, the log-transformed (natural logarithm) darbepoetin alfa dose in the evaluation period was regressed on the log-transformed (natural logarithm) epoetin alfa dose at screening using ordinary least squares regression analysis. Log transformation accounted for nonproportionality. The regression line can be represented by the equation $D_i = a + \beta (E_i)$, where D_i is each patient's log-transformed mean weekly darbepoetin alfa dose (µg per week) during the evaluation period; E_i is the patient's log transformed epoetin alfa weekly dose (U, measured at screening); α is the y-intercept parameter; and β is the slope parameter. To estimate E and D for the sample, the arithmetic mean of E_i was calculated, then log-transformed, then inserted into the regression equation to produce a mean predicted log-transformed value of D_i. The mean predicted log-transformed darbepoetin alfa dose was retransformed (exponentiated), and the DCR was then estimated by taking the ratio of the arithmetic mean epoetin alfa dose (before log transformation) to the exponentiated predicted mean darbepoetin alfa dose.

Our a priori analysis plan was to derive a single regression line from the scatter plot to estimate a single DCR for the patient population used in this analysis. The method described here is consistent with that submitted to the Centers for Medicare & Medicaid Services (CMS) and previously used by the CMS during 2003 and 2004 in the deliberations of their DCR reimbursement policy for darbepoetin alfa.[33] We did not adjust for covariates in the regression analysis because patients served as their own controls and because the sensitivity analyses described above assessed a variety of factors that could influence DCR estimates.

The second method of estimating DCR was based on the arithmetic means of the DCRs for each individual patient (mean ratio method). The mean ratio was calculated as follows:

DCR for each patient =

$$\frac{\textit{Patient's weekly epoetin alfa dose at screening}}{\textit{Patient's mean weekly darbepoetin alfa dose administered over the evaluation period}}$$

Mean population level DCR = $\dfrac{\Sigma\ \textit{(DCR per patient)}}{n}$

where n = number of patients.

| **TABLE 2** Patient Demographics, Baseline Characteristics, and Outcomes	
	Total (N = 104)
Sex, n (%)	
Female	45 (43.3)
Male	59 (56.7)
Race, n (%)	
White or Caucasian	76 (73.1)
Black or African American	24 (23.1)
Hispanic or Latino	3 (2.9)
Asian	1 (1.0)
Mean [SD] age, years	70.8 [12.0]
Mean [SD] weight, kg	87.2 [20.5]
Frequency of epoetin alfa at screening, n (%)	
QW	36 (34.6)
Q2W	68 (65.4)
Mean TSAT, % [SD]	28.1 [9.8]
eGFR	
Mean, mL/min/1.73 m^2 [SD]	28.1 [9.2]
0 to < 15 mL/min/1.73 m^2, n (%)	1 (1.0)
15 to < 30 mL/min/1.73 m^2, n (%)	61 (58.7)
30 to < 60 mL/min/1.73 m^2, n (%)	42 (40.4)
With diabetes, n (%)	66 (63.5)
Baseline Hb level	
Mean [SD], gm per dL	11.7 [0.6]
Median (IQR), gm per dL	11.7 (11.2-12.2)
Evaluation period Hb level (weeks 25 to 33)	
Mean [SD], gm per dL	11.8 [0.8]
Median (IQR), gm per dL	11.8 (11.2-12.4)
Hb change from baseline to evaluation period	
Mean [SD], gm per dL	0.03 [1.0]
Median (IQR), gm per dL	0.02 (-0.57-0.54)
Epoetin alfa at screening	
Mean [SD], U per week	8,858.2 [6,815.7]
Median (IQR), U per week	9,500.0 (5,000.0-10,000.0)
Darbepoetin alfa during evaluation period	
Mean [SD], µg per week	31.4 [28.5]
Median (IQR), µg per week	22.5 (15.0-36.3)

dL = deciliter; eGFR = estimated glomerular filtration rate; gm = gram; Hb = hemoglobin; IQR = interquartile range; kg = kilogram; mL/min/1.73 m^2 = milliliters per minute per 1.73 square meters of body surface area; QW = weekly; Q2W = every other week; SD = standard deviation; TSAT = transferrin saturation; U = units; µg = microgram.

Sensitivity analyses using both the regression-based and mean ratio methods were performed for the subgroups described above. Finally, we estimated a DR, similar to that reported in a previous publication in which the DR was calculated as the ratio of the average weekly epoetin alfa and darbepoetin alfa doses.[20]

Mean population level DR =

$$\frac{\textit{Sample mean epoetin alfa dose at screening}}{\textit{Sample mean darbepoetin alfa dose administered over the evaluation period}}$$
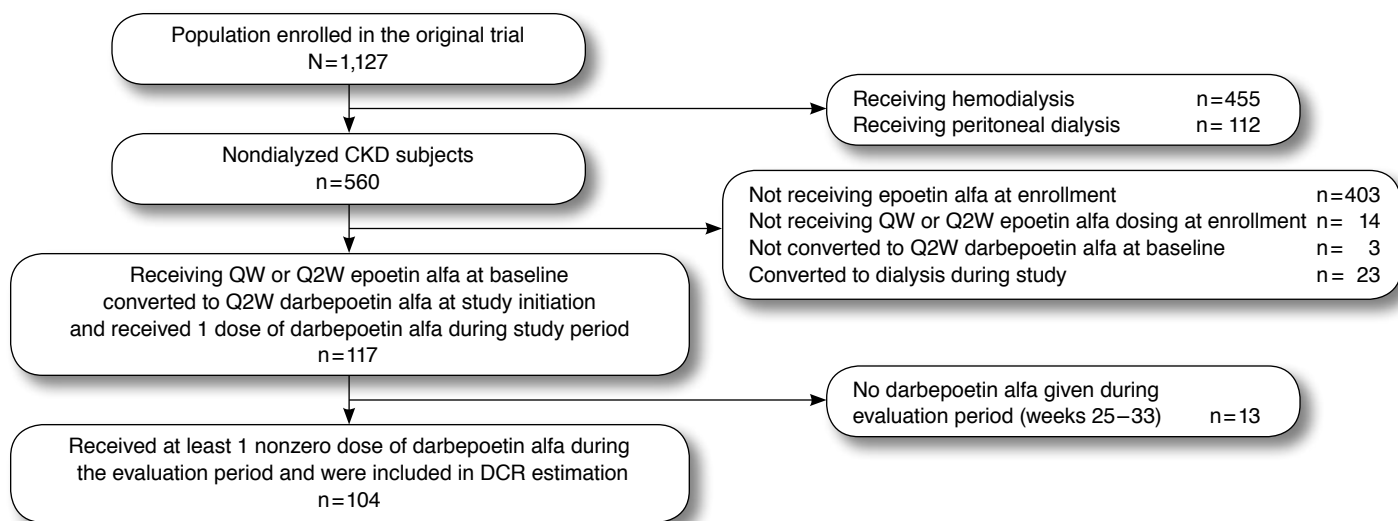
CKD = chronic kidney disease; DCR = dose conversion ratio; QW = weekly; Q2W = every other week.

Results

A total of 1,127 subjects with CKD (receiving and not receiving dialysis) were enrolled in the study; 560 of these were CKD subjects not receiving dialysis. Of these, 117 received QW or Q2W epoetin alfa and at least 1 dose of Q2W darbepoetin alfa over the course of the study; 13 of the 117 did not receive darbepoetin alfa during the evaluation period, leaving 104 for analysis (Figure 2). Subjects were predominantly white (73.1%) and male (56.7%; Table 2). The mean (SD) age at screening was 70.8 (12.0) years. Mean (SD) baseline eGFR was 28.1 (9.2) mL/min/1.73m². The majority of subjects (58.7%) had stage 4 CKD (eGFR of 15 to <30 mL/min/1.73m²), 40.4% had stage 3 CKD (eGFR 30 to <60 mL/min/1.73m²), and 1 subject (1.0%) had stage 5 CKD (eGFR 0 to <15 mL/min/1.73m²) but was not receiving dialysis. Of the total, 63.5% had diabetes at study entry. Mean (SD) baseline and evaluation period (weeks 25 to 33) Hb levels were 11.7 (0.6) gm per dL and 11.8 (0.8) gm per dL, respectively.

For subjects included in the primary analysis, the mean (SD) weekly maintenance epoetin alfa dose at screening was 8858.2 (6815.7) U per week, and the mean (SD) of the mean weekly darbepoetin alfa dose during the evaluation period was 31.4 (28.5) µg per week.

Dose Relationship in the Primary and Sensitivity Analyses

Primary Analyses. The scatter plot of the untransformed dose values for the patient population is shown in Figure 3a. A plot of the log-log transformed data gives a more informative picture of the relationship between epoetin alfa and darbepoetin alfa dose values (Figure 3b). Analysis of the log-log plot for the regression-

based method indicates that there may be 2 or more possible regression lines with separate slopes. However, based on our a priori analysis plan to estimate a single DCR to represent the entire CKD population, we derived the following dose relationship between epoetin alfa and darbepoetin alfa for this patient population:

Ln(mean predicted weekly maintenance darbepoetin alfa dose)
$$= -1.84340 + 0.56458 \times Ln(\text{sample arithmetic}$$
$$\text{mean epoetin alfa dose at screening})$$
$$= -1.84340 + 0.56458 \times Ln(8858.2)$$

Using this formula, the predicted log-transformed mean weekly darboepoetin alfa dose is 3.288123, or 26.79 µg per week after exponentiation. Taking the ratio of doses (8858.2 U epoetin alfa ÷ 26.79 µg darbepoetin alfa) yields a DCR of 330.6 (95% confidence interval [CI] = 291.1–375.5) U epoetin alfa to 1 µg darbepoetin alfa. Using the mean ratio method of DCR estimation, the mean DCR for the population was 375.6 (95% CI = 323.5–427.6).

Sensitivity Analyses. DCRs were calculated for each subgroup in the sensitivity analysis after generating a log-log regression line (as described above) for each group. Figure 4 shows the mean maintenance DCRs and 95% CIs for the sensitivity analyses subgroups using the regression model. DCR estimates ranged from 302.4:1 (95% CI = 256.0–357.2) for subjects with an eGFR of <30 mL/min/1.73m² to 379.5:1 (95% CI = 313.6–459.1) for those subjects with an eGFR 30 to 60 mL/min/1.73m² U epoetin alfa to 1 µg darbepoetin alfa.

DCR estimates using the mean ratio method (data not shown in figure) were calculated separately for subgroups of subjects
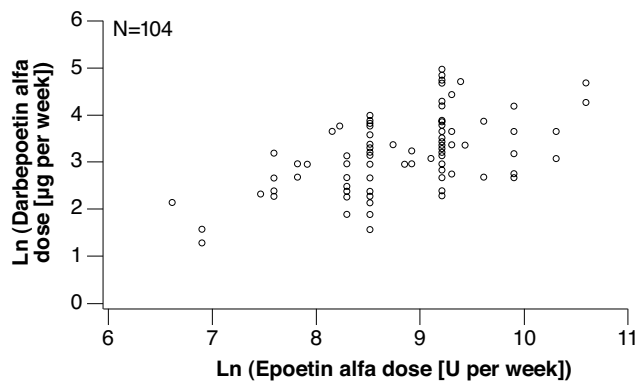
FIGURE 3a Scatterplot of Doses of Epoetin Alfa at Screening and Darbepoetin Alfa During the Evaluation Period
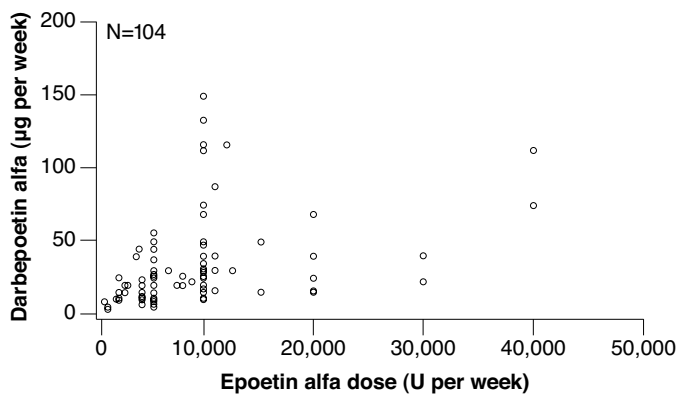
U = units; μg = micrograms.

FIGURE 3b Log-Log Scatterplot of Doses of Epoetin Alfa at Screening and Darbepoetin Alfa During the Evaluation Period

Ln = natural logarithm; U = units; μg = micrograms.

who received QW (n = 36) or Q2W (n = 68) epoetin alfa at screening and for subjects stratified by eGFR. The mean (95% CI) DCRs for subjects who received QW and Q2W epoetin alfa at screening (U epoetin alfa to 1 μg darbepoetin alfa) were 426.9 (330.5–523.3) and 348.4 (286.3–410.4), respectively. The mean (95% CI) DCR for subjects who had an eGFR of 30 to 60 mL/min/1.73m^2 (n = 42) was 412.7 (323.9–501.5), and for subjects who had an eGFR of <30 mL/min/1.73m^2 (n = 62) it was 350.4 (285.7–415.1).

DR Estimation Using Previously Published Methodology. As described above, the mean (SD) weekly maintenance epoetin alfa dose at screening was 8858.2 (6815.7) U and the mean (SD) of the mean weekly darbepoetin alfa dose at the evaluation was 31.4 (28.5) μg/week. Taking the ratio of the mean epoetin alfa dose for the sample at screening and the mean of the mean weekly darbepoetin alfa dose for the sample during the evaluation period to calculate the DR for this patient population, the DR was 282.1 (8858.2 U epoetin alfa ÷ 31.4 μg darbepoetin alfa), which is far less than the 330.6:1 or 375.6:1 ratios obtained using the regression-based and mean ratio methods, respectively.

■ Discussion

The present study improves the understanding of the complex relationship between epoetin alfa and darbepoetin alfa doses that maintain Hb levels when patients are converted from one product to another and provides a more accurate method to calculate a population-level DCR estimate that is relevant to payers. The methodology described accounts for the nonproportional dosing relationship between epoetin alfa and darbepoetin alfa and may represent an advance over the methods used in previous research. Both mathematical approaches described in this study are feasible for payers with access to ESA dosing data, although

the mean ratio method is simpler. The estimated population mean maintenance DCRs between epoetin alfa and darbepoetin alfa were 330.6:1 (U epoetin alfa to 1 μg darbepoetin alfa), using the regression-based method, and 375.6:1, using the mean ratio method. Sensitivity analyses from both the regression and mean ratio methods indicated that the DCR, as expected, varied depending on subject baseline characteristics. In this case, DCRs ranged from 302 to 380 U epoetin alfa to 1 μg darbepoetin alfa, using the regression-based method, and from 348 to 427 U epoetin alfa to 1 μg darbepoetin alfa, using the mean ratio method.

Previous studies of the dose relationship between epoetin alfa and darbepoetin alfa had significant limitations. Most of these studies, as noted, compared 2 nonmatched cohorts, with each cohort receiving only 1 of the products, instead of directly studying the effect of converting from one product to the other.[16-19,21-28] A few studies adjusted DRs to address confounding factors, including disease severity[21] and Hb levels,[20,24,25] but none used appropriate techniques such as propensity score matching, marginal structural modeling, or instrumental variable analyses to address the issues of confounding by indication. Additionally, important but unaddressed factors include dosing frequency, the stage of treatment (i.e., whether at initiation or during maintenance), and patient age. Hb outcomes, that is, the Hb level to which patients were treated, were also not reported in most of these studies. Finally, none of these studies considered the nonproportional relationship between epoetin alfa and darbepoetin alfa.

In the 1 study where patients were converted from epoetin alfa to darbepoetin alfa, cumulative dose, or total dose during treatment, for patients at the population level was used to calculate the DR.[20] As shown, a similar analysis applied to our data results

FIGURE 4   *Sensitivity Analyses of Dose Relationships in Patient Subgroups Using the Regression-Based Method*
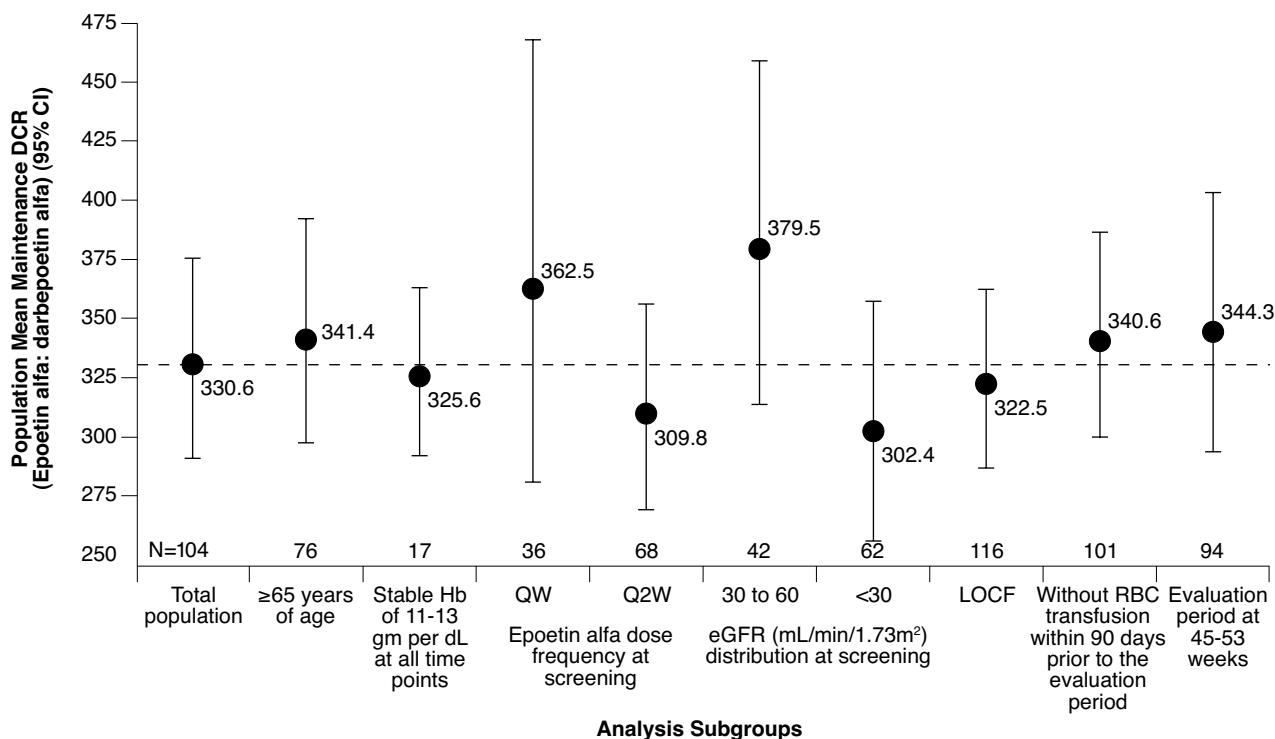
Horizontal line indicates a DCR of 330.6, which is the estimated population mean maintenance DCR.
CI = confidence interval; DCR = dose conversion ratio; eGFR = estimated glomerular filtration rate; gm per dL = grams per deciliter; Hb = hemoglobin; LOCF = last observation carried forward; mL/min/1.73m² = milliliters per minute per 1.73 square meters of body surface area; QW = weekly; Q2W = every other week; RBC = red blood cell.

in a lower DR for the study sample used in this analysis, even though our study included patients converted from epoetin alfa to darbepoetin alfa.

It is important to note that the DCR methodology presented here has relevance for a managed care audience despite changes in Hb targets established by regulatory agencies.[9,10] The fundamental element of using this method is not the Hb target itself, but that the target Hb pre- and post-conversion from one ESA to another is maintained at the same level in the patient population.

Limitations

First, the DCRs shown in this analysis are applicable only to the present study sample and cannot be used at the individual level to convert patients from one treatment to another or extrapolated to other patient populations. For any other patient group, one would derive a log-log scatter plot analysis of the doses specific to that group, as we did for the subgroups analyzed in the present study. The scatter plot obtained in this analysis revealed 2 or more slopes rather than a single linear slope. Although assessing

those slopes might have provided additional information, these slopes were not further examined because of the a priori analysis plan to determine a single DCR.

Second, exponentiation of the predicted log-transformed mean darbopoetin dose derived from the regression analysis yields a predicted geometric mean. Calculating the ratio of a geometric mean to an arithmetic mean (the mean epoetin alfa dose at screening) may have produced a systematic bias in the regression-based estimates. However, the DCR result of the mean ratio analysis, which yields an arithmetic mean and would include the effects of outliers, indicated that the regression-based method errs on the side of a conservative DCR estimate.

Third, as per the clinical trial protocol, only a single epoetin alfa dose for each patient was used before conversion, limiting our ability to account for epoetin alfa dose adjustments that occur over time. The DCR assumption is based on just a single dose of epoetin alfa. Fourth, because some of the subgroup sizes in our sensitivity analyses were small, estimates for these subgroups may not be as informative as those for the sample as a whole.

■ Conclusions

The DCR calculation methodology presented here provides an empirical way of evaluating the dose relationship between epoetin alfa and darbepoetin alfa, while addressing the nonproportional dosing relationship and other potential confounding factors. In the present study sample, the mean maintenance DCR between epoetin alfa and darbepoetin alfa exceeds a threshold of 300 U epoetin alfa to 1 µg darbepoetin alfa, which is greater than previously reported ratios. Investigators in future studies should consider using these methods to evaluate the population-level mean maintenance DCR in a real-world setting in which patients have been converted from epoetin alfa to darbepoetin alfa.

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REFERENCES

1. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA.* 2007;298(17):2038-47.

2. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). *Arch Intern Med.* 2002;162(12):1401-08.

3. McClellan W, Aronoff SL, Bolton WK, et al. The prevalence of anemia in patients with chronic kidney disease. *Curr Med Res Opin.* 2004;20(9):1501-10.

4. Kazmi WH, Kausz AT, Khan S, et al. Anemia: an early complication of chronic renal insufficiency. *Am J Kidney Dis.* 2001;38(4):803-12.

5. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol.* 2001;38(4):955-62.

6. Holland DC, Lam M. Predictors of hospitalization and death among pre-dialysis patients: a retrospective cohort study. *Nephrol Dial Transplant.* 2000;15(5):650-58.

7. Perlman RL, Finkelstein FO, Liu L, et al. Quality of life in chronic kidney disease (CKD): a cross-sectional analysis in the Renal Research Institute-CKD study. *Am J Kidney Dis.* 2005;45(4):658-66.

8. Ershler WB, Chen K, Reyes EB, Dubois R. Economic burden of patients with anemia in selected diseases. *Value Health.* 2005;8(6):629-38.

9. Aranesp U.S. package insert. Available at: http://www.aranesp.com/pdf/aranesp_pi.pdf. Accessed November 9, 2009.

10. Epogen U.S. package insert. Available at: http://www.epogen.com/pdf/epogen_pi.pdf. Accessed November 9, 2009.

11. Egrie JC, Dwyer E, Browne JK, Hitz A, Lykos MA. Darbepoetin alfa has a longer circulating half-life and greater in vivo potency than recombinant human erythropoietin. *Exp Hematol.* 2003;31(4):290-99.

12. Padhi D, Ni L, Cooke B, Marino R, Jang G. An extended terminal half-life for darbepoetin alfa: results from a single-dose pharmacokinetic study in patients with chronic kidney disease not receiving dialysis. *Clin Pharmacokinet.* 2006;45(5):503-10.

13. Richter A, Anton SE, Koch P, Dennett SL. The impact of reducing dose frequency on health outcomes. *Clin Ther.* 2003;25(8):2307-35.

14. Nissenson AR. Dosing darbepoetin alfa. *Am J Kidney Dis.* 2002;40(4):872.

15. Nissenson AR, Swan SK, Lindberg JS, et al. Randomized, controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. *Am J Kidney Dis.* 2002;40(1):110-18.

16. Barron JJ, Grochulski WD, Mody SH, Bookhart B, McKenzie RS. Erythropoietic therapy: dosing patterns and calculated cost assessment for pre-dialysis chronic kidney disease patients in managed care setting. *Pharm Ther.* 2007;32(12):661-70.

17. Cremieux PY, Van Audenrode M, Lefebvre P. The relative dosing of epoetin alfa and darbepoetin alfa in chronic kidney disease. *Curr Med Res Opin.* 2006;22(12):2329-36.

18. Duh MS, Mody SH, McKenzie RS, et al. Dosing patterns and treatment costs of erythropoietic agents in elderly patients with pre-dialysis chronic kidney disease in managed care organisations. *Drugs Aging.* 2006;23(12):969-76.

19. Duh MS, Mody SH, Scott McKenzie R, et al. Dosing patterns and costs of erythropoietic agents in patients with chronic kidney disease not on dialysis in managed care organizations. *Clin Ther.* 2006;28(9):1443-50.

20. Hymes J, Bickimer T, Jackson JH, et al. Dosing patterns, drug costs, and hematologic outcome in anemic patients with chronic kidney disease switching from darbepoetin alfa to epoetin alfa. *Curr Med Res Opin.* 2007;23(8):1931-37.

21. Laliberte F, Lefebvre P, Vekeman F, et al. Drug utilization and cost considerations of predialysis chronic kidney disease patients receiving erythropoiesis-stimulating agents through pharmacy benefits [abstract]. *Am J Kidney Dis.* 2008;51:a25, no 130. Poster presented at: National Kidney Foundation (NKF) Spring Clinical Meetings; April 2-6, 2008; Dallas, TX.

22. Lefebvre P, Laliberte F, Lafeuille MH, et al. Assessment of drug utilization patterns and costs for erythropoietic stimulating agents for patients with chronic kidney disease [abstract]. *Am J Kidney Dis.* 2008;51:a25, no 140. Poster presented at: National Kidney Foundation (NKF) Spring Clinical Meetings; April 2-6, 2008; Dallas, TX.

23. Mody SH, Padmanabhan V, McKenzie RS, Bookart BK. Epoetin alfa and darbepoetin alfa dosing patterns in pre-dialysis chronic kidney disease patients. [poster PUK5]. Poster presented at: International Society for Pharmacoeconomics and Outcomes Research (ISPOR) meeting; May 20-24, 2006; Philadelphia, PA.

24. Papatheofanis F, Smith C, Mody S, et al. Dosing patterns, hematologic outcomes, and costs of erythropoietic agents in anemic predialysis chronic kidney disease patients from an observational study. *Am J Ther.* 2007;14(4):322-27.

25. Papatheofanis FJ, McKenzie RS, Mody SH, Suruki RY, Piech CT. Dosing patterns, hematologic outcomes, and costs of erythropoietic agents in pre-dialysis chronic kidney disease patients with anemia. *Curr Med Res Opin.* 2006;22(5):837-42.

26. Smith J, He J, Mahoney A, et al. Hospital inpatient utilization of eopetin alfa (EPO) and darbepoetin alfa (Darb) in patients with cancer and pre-dialysis chronic kidney disease (pCKD) [poster PCN6]. Poster presented at: International Society for Pharmacoeconomics and Outcomes Research (ISPOR) meeting; May 20-24, 2006; Philadelphia, PA.

27. Vekeman F, Bailey RA, McKenzie RS, Herrera A, Lefebvre P. Comparison of Epoetin alfa (EPO) and darbepoetin alfa (DARB) dosing patterns and costs in a pre-dialysis chronic kidney disease (CKD) inpatient population [abstract]. *J Am Soc Nephrol.* 2008;18:323A, TH-PO942. Poster presented at: American Society of Nephrology (ASN) Annual Meeting; November 4-9, 2008; Philadelphia, PA.

28. Vekeman F, McKenzie RS, Lefebvre P, et al. Dose and cost comparison of erythropoietic agents in the inpatient hospital setting. *Am J Health Syst Pharm.* 2007;64(18):1943-49.

29. ClinicalTrials.gov. Phase III clinical trial NCT00093977. Study to assess darbepoetin alfa in subjects with chronic kidney disease. Available at: http://clinicaltrials.gov/ct2/show/NCT00093977?term=NCT00093977&rank=1. Accessed November 9, 2009.

30. Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine [abstract]. *J Am Soc Nephrol.* 2000;11:A0828.

31. Manjunath G, Sarnak MJ, Levey AS. Prediction equations to estimate glomerular filtration rate: an update. *Curr Opin Nephrol Hypertens.* 2001;10(6):785-92.

32. Uehlinger DE, Gotch FA, Sheiner LB. A pharmacodynamic model of erythropoietin therapy for uremic anemia. *Clin Pharmacol Ther.* 1992;51(1):76-89.

33. CMS. Rules and Regulations. *Federal Register.* 2004;69(219):65796-97. Available at: http://www.cms.hhs.gov/quarterlyproviderupdates/downloads/CMS1427FC_3.PDF. Accessed November 13, 2009.