A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease

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ABSTRACT

BACKGROUND

Anemia is associated with an increased risk of cardiovascular and renal events among patients with type 2 diabetes and chronic kidney disease. Although darbepoetin alfa can effectively increase hemoglobin levels, its effect on clinical outcomes in these patients has not been adequately tested.

METHODS

In this study involving 4038 patients with diabetes, chronic kidney disease, and anemia, we randomly assigned 2012 patients to darbepoetin alfa to achieve a hemoglobin level of approximately 13 g per deciliter and 2026 patients to placebo, with rescue darbepoetin alfa when the hemoglobin level was less than 9.0 g per deciliter. The primary end points were the composite outcomes of death or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and of death or end-stage renal disease.

RESULTS

Death or a cardiovascular event occurred in 632 patients assigned to darbepoetin alfa and 602 patients assigned to placebo (hazard ratio for darbepoetin alfa vs. placebo, 1.05; 95% confidence interval [CI], 0.94 to 1.17; P=0.41). Death or end-stage renal disease occurred in 652 patients assigned to darbepoetin alfa and 618 patients assigned to placebo (hazard ratio, 1.06; 95% CI, 0.95 to 1.19; P=0.29). Fatal or nonfatal stroke occurred in 101 patients assigned to darbepoetin alfa and 53 patients assigned to placebo (hazard ratio, 1.92; 95% CI, 1.38 to 2.68; P<0.001). Red-cell transfusions were administered to 297 patients assigned to darbepoetin alfa and 496 patients assigned to placebo (P<0.001). There was only a modest improvement in patient-reported fatigue in the darbepoetin alfa group as compared with the placebo group.

CONCLUSIONS

The use of darbepoetin alfa in patients with diabetes, chronic kidney disease, and moderate anemia who were not undergoing dialysis did not reduce the risk of either of the two primary composite outcomes (either death or a cardiovascular event or death or a renal event) and was associated with an increased risk of stroke. For many persons involved in clinical decision making, this risk will outweigh the potential benefits. (ClinicalTrials.gov number, NCT00093015.)

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TYPE 2 DIABETES MELLITUS AND CHRONIC kidney disease frequently coexist, and each disease independently increases the risk of cardiovascular events and end-stage renal disease.[1,2] Intensive treatment of concomitant conventional risk factors such as hypertension and elevated levels of low-density lipoprotein reduces fatal and nonfatal cardiovascular complications and slows the progression of kidney disease.[3-8] Observational studies suggest that anemia can be considered another biomarker of risk, since a lower hemoglobin level is independently associated with a higher rate of cardiovascular and renal events,[9-11] especially among patients with diabetes.[12,13] Whether the use of erythropoiesis-stimulating agents (ESAs) to increase hemoglobin levels lowers this risk is not known.[14]

Early studies involving the use of recombinant human erythropoietin in patients with severe anemia who were undergoing dialysis showed a reduced requirement for blood transfusions and improved quality-of-life assessments, which were considered major advances.[15,16] Extrapolations from these favorable effects to other populations, including patients with anemia and earlier stages of chronic kidney disease, led to the wider use of ESAs. The presumption of the benefits associated with the use of ESAs was so pervasive that major clinical trials considered the use of placebo unnecessary or even unethical.[17-19] In fact, there were no placebo-controlled trials in a recent meta-analysis of the use of ESAs in patients with chronic kidney disease.[20] Although ESAs have been available for more than two decades, the hypothesis that this treatment approach would lower the risks associated with anemia and improve the prognosis has not been examined.[21] We conducted the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) to test the hypothesis that, in patients with type 2 diabetes, chronic kidney disease that does not require dialysis, and concomitant anemia, increasing hemoglobin levels with the use of this agent would lower the rates of death, cardiovascular events, and end-stage renal disease.[22]

METHODS

The TREAT was a randomized, double-blind, placebo-controlled trial conducted at 623 sites in 24 countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The institutional review board or ethics committee at each site approved the protocol, and all patients provided written informed consent. Enrollment occurred from August 25, 2004, through December 4, 2007.

The trial was sponsored by Amgen and designed in collaboration with an academic executive committee. Data collection and management were the responsibility of the sponsor, with oversight by the executive committee. The Statistical Data Analysis Center at the University of Wisconsin prepared the interim unblinded reports for the independent data and safety monitoring committee, which oversaw patient safety and the quality of trial conduct. The independent academic statistical center also performed all analyses for this article and provided the writing group with unrestricted access to the data. The manuscript was prepared by the principal investigator and subsequently revised and edited by all the authors. All the authors decided to submit the article for publication and assume responsibility for the accuracy and completeness of the reported data.

STUDY POPULATION

Patients with type 2 diabetes, chronic kidney disease (an estimated glomerular filtration rate [GFR] of 20 to 60 ml per minute per 1.73 m² of body-surface area, calculated with the use of the four-variable Modification of Diet in Renal Disease formula), anemia (hemoglobin level, ≤11.0 g per deciliter), and a transferrin saturation of 15% or more were eligible for enrollment. Patients with any of the following factors were excluded: uncontrolled hypertension; previous kidney transplantation or scheduled receipt of a kidney transplant from a living related donor; current use of intravenous antibiotics, chemotherapy, or radiation therapy; cancer (except basal-cell or squamous-cell carcinoma of the skin); diagnosed human immunodeficiency virus infection; active bleeding; a hematologic disease; or pregnancy. Patients who had had a cardiovascular event or grand mal seizure, had undergone major surgery, or had received an ESA in the 12 weeks before randomization were also ineligible.

STUDY PROCEDURES

During a 2-week screening period, prestudy laboratory assessments were obtained and the eligibility of patients who had provided consent was confirmed. Patients were randomly assigned with the use of a computer-generated, permuted-block

design, in a 1:1 ratio, to receive darbepoetin alfa (Aranesp, Amgen) or placebo. Randomization was stratified according to the study site, the baseline level of proteinuria (with marked proteinuria defined as a ratio of total protein to creatinine [calculated in milligrams per deciliter] of ≥1.0 in a spot urine sample), and an investigator-designated history of cardiovascular disease. Darbepoetin alfa and placebo were supplied in matching prefilled syringes at 12 different strengths. A third party used a point-of-care device to monitor hemoglobin levels and enter the value into an interactive voice-response system that selected the dosage according to a computer algorithm (see the Supplementary Appendix). This algorithm was designed to adjust the dose in order to maintain the hemoglobin level at approximately 13.0 g per deciliter in the patients assigned to darbepoetin alfa.

Patients in the placebo group were assigned to receive darbepoetin alfa as a rescue agent if the hemoglobin level fell below 9.0 g per deciliter, with a return to placebo once the hemoglobin level was 9.0 g per deciliter or higher. The site investigator was to be notified if any patient had a hemoglobin value of 7.0 g per deciliter or less, a value of 16.0 g per deciliter or more, or a decrease of 2.0 g per deciliter or more in a 4-week period.

Measurements of hemoglobin levels and vital signs were performed every 2 weeks during the study-drug–titration period and monthly thereafter. Transferrin saturation and ferritin levels were measured quarterly; other laboratory assessments and spot urine collections were performed at 24-week intervals. Patient-reported outcomes and health resource utilization were assessed at weeks 1, 13, and 25 and every 24 weeks thereafter. At each visit, information was gathered regarding adverse events, hospitalization, transfusions, and the concomitant use of other medications.

EVALUATION OF OUTCOMES

The primary end points were the time to the composite outcome of death from any cause or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and the time to the composite outcome of death or end-stage renal disease (see the Supplementary Appendix). The overall alpha level for the primary end points was split: 0.048 for the cardiovascular composite outcome and 0.002 for the renal composite outcome. All potential end points were adjudicated

by a clinical end-point committee whose members were unaware of the treatment assignments, and the hematocrit and hemoglobin values were redacted from the documents under review. Important secondary end points included time to death, death from cardiovascular causes, and the components of the primary end points, as well as the rate of decline in the estimated GFR and changes in patient-reported outcomes at week 25 measured with the use of the Functional Assessment of Cancer Therapy–Fatigue (FACT-Fatigue) instrument (on which scores range from 0 to 52, with higher scores indicating less fatigue) and the 36-Item Short-Form General Health Survey questionnaire (calculated with norm-based scoring so that 50 is the average score, with higher scores indicating a better quality of life) (added after the second protocol amendment in May 2005).

MONITORING

The independent data and safety monitoring committee reviewed safety reports monthly with formal interim analyses scheduled when approximately 20, 40, 60, and 80% of the total expected cardiovascular composite events had occurred. Initial guidelines for early discontinuation included a symmetric O'Brien–Fleming alpha-spending function. In April 2006, data from a non–placebo-controlled trial of a different ESA in patients with chronic kidney disease showed that treatment aimed at achieving a higher hemoglobin level (13.5 g per deciliter vs. 11.3 g per deciliter) was associated with increased rates of adverse clinical events.[17] This information and more equivocal results from a related, smaller trial[18] were proactively communicated to our patients, investigators, and the data and safety monitoring committee. The committee made no recommendation to alter or terminate the study on the basis of interim data that already reflected more clinical events than the numbers of events in these related trials. The consent form was modified with the addition of the new information regarding potential harm, and all study participants were asked to provide written informed consent again. The executive committee requested that the data and safety monitoring committee adopt a more cautious stopping rule, with the use of a one-sided alpha of 0.05 for harm at each assessment (without adjustment for multiple testing) for either the cardiovascular composite outcome or death. The boundaries for efficacy remained unchanged, and with this new mandatory stop-

ping rule for harm, the committee made no recommendation to terminate the trial before its scheduled conclusion.

STATISTICAL ANALYSIS

The trial was event driven, with a total of 1203 cardiovascular composite events required to provide 80% statistical power to detect a 20% risk reduction for this outcome, with a two-sided type I error of 0.048 (unadjusted for interim analyses). We aimed to enroll approximately 4000 patients; assumptions included an annualized rate of events in the placebo group of 12.5%, a 15% loss to follow-up, and attenuation of the treatment effect due to the anticipated use of ESAs in patients who had progression to end-stage renal disease.

Time-to-event analyses were performed with the use of life-table methods according to the intention-to-treat principle. Kaplan–Meier cumulative incidence curves were compared with the use of a two-sided log-rank test, stratified according to the baseline proteinuria level and the presence or absence of a history of cardiovascular disease. Estimated hazard ratios (for darbepoetin alfa vs. placebo) and 95% confidence intervals were obtained with the use of stratified Cox proportional-hazards models. Patients who discontinued either study drug early, including patients who began treatment with dialysis or underwent transplantation, were followed for study end points.

Categorization of adverse events was based on groupings of preferred terms defined by the standardized queries in the Medical Dictionary for Regulatory Activities.[23] Analyses of patient-reported outcomes were prespecified to impute missing data with the last-observation-carried-forward method and to use t-tests for treatment comparisons, with means and standard deviations. Reported P values are nominal and have not been adjusted for multiple comparisons. Additional statistical methods are described in the Supplementary Appendix.

RESULTS

PATIENTS

We enrolled a total of 4047 patients, but before unblinding, we excluded all information regarding 9 patients from two sites that did not adhere to Good Clinical Practice guidelines (4 patients who were randomly assigned to darbepoetin alfa and 5 patients who were randomly assigned to placebo). Of the 4038 patients evaluated, 2012 were assigned to receive darbepoetin alfa and 2026 were assigned to receive placebo. The study was event driven and was completed on March 28, 2009, with a median follow-up duration of 29.1 months. At that time, 3523 patients (87.2%) were either still being followed for clinical end points or had died; this group included 1761 patients in the darbepoetin alfa group (87.5%) and 1762 patients in the placebo group (87.0%). The vital status at study termination was unknown for 153 patients in the darbepoetin alfa group (7.6%) and 164 in the placebo group (8.1%) (see the Consolidated Standards for the Reporting of Trials [CONSORT] diagram in the Supplementary Appendix).

The median age was 68 years, and 57.3% of the patients were women; 65.4% of the patients had a history of cardiovascular disease, with similar percentages of patients in each group reporting a history of coronary artery disease, stroke, peripheral arterial disease, and myocardial infarction. There was an imbalance in the proportion of patients with a history of heart failure (31.5% in the darbepoetin alfa group vs. 35.2% in the placebo group, unadjusted P=0.01). There were no clinically meaningful baseline imbalances in vital signs, laboratory data, or the use of medications for cardiovascular disease and diabetes (Table 1).

INTERVENTION AND HEMOGLOBIN VALUES

The overall median hemoglobin level at baseline was 10.4 g per deciliter (interquartile range, 9.8 to 10.9). Between-group differences in hemoglobin values were apparent less than 1 month after randomization, and the differences were significant by 1 month (Fig. 1). From 3 months to the end of treatment, the median achieved hemoglobin level (based on the area under the curve) was 12.5 g per deciliter (interquartile range, 12.0 to 12.8) in the darbepoetin alfa group and 10.6 g per deciliter (interquartile range, 9.9 to 11.3) in the placebo group (P<0.001) (Fig. 1). A total of 84.6% of patients in the darbepoetin alfa group and 86.9% of patients in the placebo group were switched to monthly dosing. Over the course of the study, 46% of the patients assigned to placebo received at least one dose of darbepoetin alfa as rescue therapy. The median monthly dose in patients assigned to placebo was 0 μg (interquartile range, 0 to 5) as compared with 176 μg (interquartile range, 104 to 305) in patients assigned to darbe-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Darbepoetin Alfa (N = 2012)	Placebo (N = 2026)	P Value†
Age (yr)			0.22
Median	68	68	
Interquartile range	60–75	60–75	
Female sex (%)	58.5	56.0	0.10
Race or ethnic group (%)‡			0.84
White	63.1	64.2	
Black	20.6	19.8	
Hispanic	13.6	13.1	
Other	2.7	3.0	
Known duration of diabetes (yr)			0.94
Median	15.3	15.5	
Interquartile range	8.2–21.8	8.4–21.7	
Body-mass index§			0.11
Median	30.5	30.1	
Interquartile range	26.3–35.5	26.2–34.9	
Retinopathy (%)	48.2	45.7	0.12
Laser treatment (%)	29.6	28.6	0.49
Diabetic neuropathy (%)	49.2	46.4	0.07
Amputation	5.7	6.1	0.58
History of cardiovascular disease (%)¶	64.0	66.9	0.05
Coronary artery disease‖	43.2	45.5	0.16
Heart failure	31.5	35.2	0.01
Myocardial infarction	18.4	18.3	0.95
Stroke	11.5	10.7	0.41
Peripheral arterial disease**	21.2	20.8	0.73
Use of pacemaker	4.5	6.1	0.02
Use of automatic implantable cardioverter–defibrillator	1.4	1.4	0.87
Atrial fibrillation (%)	11.0	10.0	0.29
Smoking status (%)			0.88
Current smoker	5.4	4.7	
Former smoker	38.2	39.4	
Blood pressure (mm Hg)			
Systolic			0.25
Median	136	135	
Interquartile range	122–149	123–148	
Diastolic			0.55
Median	71	70	
Interquartile range	64–80	64–80	
Serum creatinine (mg/dl)			0.01
Median	1.8	1.9	
Interquartile range	1.5–2.3	1.5–2.4	
Estimated GFR (ml/min/1.73 m²)			0.03
Median	34	33	
Interquartile range	27–43	26–42	

Table 1. (Continued.)

Characteristic	Darbepoetin Alfa (N = 2012)	Placebo (N = 2026)	P Value†
Ratio of total protein (in mg/dl) to creatinine (in mg/dl) in urine¶			0.73
Median	0.4	0.4	
Interquartile range	0.1–2.0	0.1–1.8	
<1 (%)	65.9	64.9	
≥1 (%)	34.1	35.1	
Potassium (mmol/liter)			0.73
Median	4.7	4.7	
Interquartile range	4.3–5.1	4.3–5.1	
Albumin (g/dl)			0.13
Median	4.0	4.0	
Interquartile range	3.7–4.3	3.7–4.3	
Glycated hemoglobin (%)			0.02
Median	7.0	6.9	
Interquartile range	6.2–8.1	6.2–7.9	
Hemoglobin (g/dl)			0.15
Median	10.5	10.4	
Interquartile range	9.8–11.0	9.8–10.9	
White-cell count (×10^{-9}/liter)			0.32
Median	6.6	6.7	
Interquartile range	5.4–8.1	5.4–8.1	
Platelet count (×10^{-9}/liter)			0.14
Median	241	244	
Interquartile range	195–293	201–295	
Transferrin saturation (%)			0.80
Median	23	23	
Interquartile range	18–29	18–28	
Serum ferritin (μg/liter)			0.17
Median	131	137	
Interquartile range	66–254	68–263	
Cholesterol (mg/dl)			
Total			0.47
Median	169	170	
Interquartile range	142–201	142–203	
LDL			0.41
Median	84	85	
Interquartile range	64–110	63–112	
HDL			0.85
Median	46	46	
Interquartile range	38–56	38–56	
Triglycerides (mg/dl)			0.97
Median	155	154	
Interquartile range	110–230	109–230	

Table 1. (Continued.)

Characteristic	Darbepoetin Alfa (N=2012)	Placebo (N=2026)	P Value†
Medications (%)			
Insulin	48.7	49.8	0.49
Oral hypoglycemic agent	57.5	56.1	0.36
Thiazolidinedione	25.2	23.5	0.22
Sulfonamide	36.3	34.5	0.24
Biguanide	17.1	17.2	0.91
Angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker	79.7	80.0	0.82
Angiotensin-converting–enzyme inhibitor and angiotensin-receptor blocker	10.3	9.8	0.55
Beta-blocker	49.9	48.7	0.43
Aldosterone-receptor blocker	5.4	4.9	0.49
Statin	59.6	57.5	0.16
Statin or other lipid-lowering agent	64.6	64.0	0.72
Aspirin	42.0	42.8	0.63
Aspirin or other antiplatelet agent	48.0	48.6	0.68
Vitamin K antagonist	7.2	6.6	0.46
Iron			
Oral	41.8	42.7	0.57
Intravenous	1.4	1.6	0.63
Previous use of erythropoietic agent	8.8	10.2	0.14

* All tests for baseline laboratory values were performed by a central laboratory except hemoglobin levels, which were measured at the site with the use of a hemoglobin point-of-care device. GFR denotes glomerular filtration rate, HDL high-density lipoprotein, and LDL low-density lipoprotein. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.
† P values have not been adjusted for multiple comparisons.
‡ Race or ethnic group was self-reported.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ These data were derived from the clinical database.
‖ This category includes coronary artery disease with or without myocardial infarction, coronary-artery bypass grafting, and percutaneous coronary intervention.
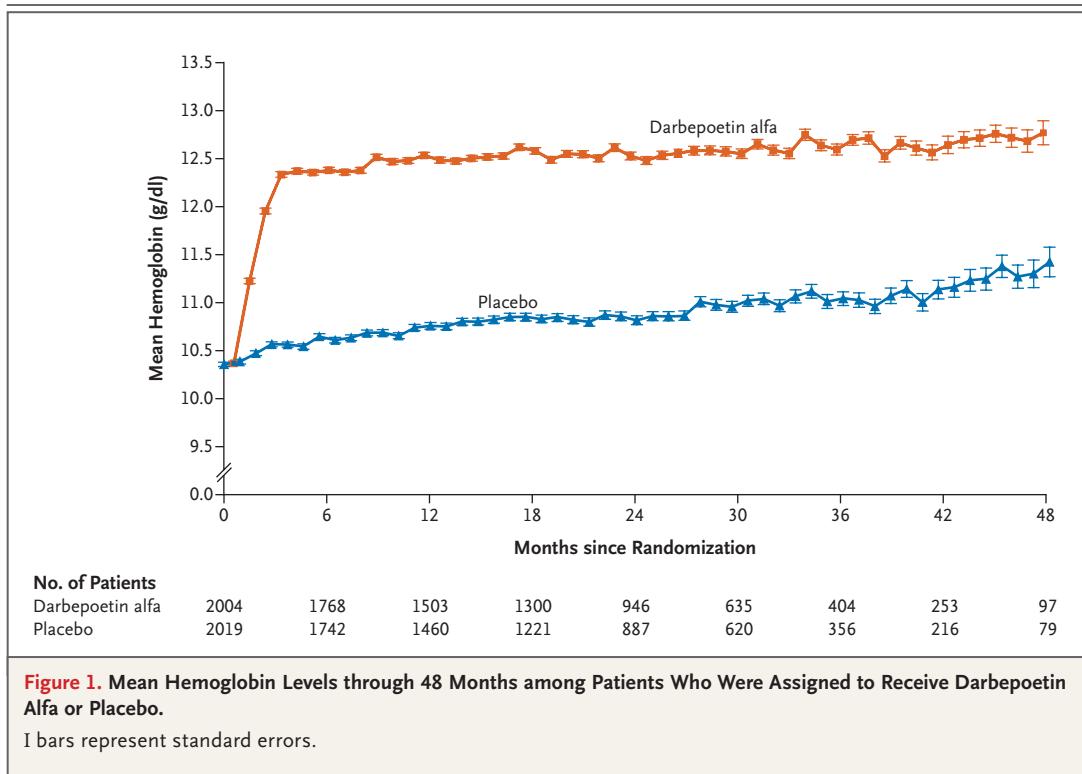** This category includes peripheral arterial disease with or without peripheral arterial revascularization.

poetin alfa. Among the patients who had not died or progressed to end-stage renal disease, 93.9% of the patients in the darbepoetin alfa group and 90.4% of those in the placebo group were receiving the assigned treatment at 6 months; 87.4% and 83.7%, respectively, at 1 year; and 74.3% and 69.3%, respectively, at 2 years. There was no significant difference in the proportions of patients receiving oral iron during the study (66.8% of those in the darbepoetin alfa group and 68.6% of those in the placebo group, P=0.25); however, more patients in the placebo group received intravenous iron (20.4%, vs. 14.8% of patients assigned to darbepoetin alfa; P<0.001). Red-cell transfusions were administered in 297 patients in the darbepoetin alfa group (14.8%) and in 496 patients in the placebo group (24.5%) (hazard ratio for darbepoetin alfa vs. placebo, 0.56; 95% confidence interval [CI], 0.49 to 0.65; P<0.001).

PRIMARY COMPOSITE OUTCOMES AND COMPONENTS
Death, Myocardial Infarction, Unstable Angina, Heart Failure, and Stroke
The primary cardiovascular composite outcome — death or a nonfatal cardiovascular event — occurred in 632 patients in the darbepoetin alfa group (31.4%) and in 602 patients in the placebo group (29.7%) (hazard ratio for darbepoetin alfa vs. placebo, 1.05; 95% CI, 0.94 to 1.17; P=0.41) (Table 2 and Fig. 2A). There were no significant

2025

No. of Patients

Darbepoetin alfa	2004	1768	1503	1300	946	635	404	253	97
Placebo	2019	1742	1460	1221	887	620	356	216	79

Figure 1. Mean Hemoglobin Levels through 48 Months among Patients Who Were Assigned to Receive Darbepoetin Alfa or Placebo.

I bars represent standard errors.

between-group differences in the time to the first occurrence of the following components, when considered individually: death from any cause, fatal or nonfatal congestive heart failure, fatal or nonfatal myocardial infarction, or hospitalization for myocardial ischemia (Table 2 and Fig. 2B, 2C, and 2D). However, fatal or nonfatal stroke was more likely to occur in the patients assigned to darbepoetin alfa (101 patients [5.0%] vs. 53 patients [2.6%]; hazard ratio, 1.92; 95% CI, 1.38 to 2.68; P<0.001) (Table 2 and Fig. 2E).

The prespecified stratification characteristics of a history of cardiovascular disease and marked proteinuria (urinary protein-to-creatinine ratio, ≥1) both identified higher-risk groups regardless of the assigned treatment for the cardiovascular composite outcome. The overall null effect of darbepoetin alfa was observed in each subgroup, with no significant interaction. Similarly, there were no significant interactions for any of the other five prespecified subgroups based on age, sex, race or ethnic group, region, or baseline estimated GFR (see the Supplementary Appendix).

Cardiac revascularization procedures were performed less frequently in the patients assigned to darbepoetin alfa than in those assigned to placebo (84 patients [4.2%] vs. 117 patients [5.8%]; hazard ratio, 0.71; 95% CI, 0.54 to 0.94; P=0.02).

Renal Outcomes

Death or end-stage renal disease occurred in 652 patients in the darbepoetin alfa group (32.4%) and in 618 patients in the placebo group (30.5%) (hazard ratio for darbepoetin alfa vs. placebo, 1.06; 95% CI, 0.95 to 1.19; P=0.29) (Fig. 3A). End-stage renal disease occurred in 338 patients in the darbepoetin alfa group (16.8%) and in 330 patients assigned to placebo (16.3%) (hazard ratio, 1.02; 95% CI, 0.87 to 1.18; P=0.83) (Fig. 3B).

The stratification characteristics of a history of cardiovascular disease and marked proteinuria also identified groups at higher risk for the composite outcome of death or end-stage renal disease, with no significant interaction in either subgroup. No significant interactions were observed in the other five prespecified subgroups, with the exception of a nominally significant interaction for race or ethnic group. The 653 patients described as nonwhite and nonblack in the darbepoetin alfa group had the greatest excess risk (hazard ratio, 1.46; 95% CI, 1.10 to

Table 2. Composite and Component End Points.*

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.

1.95); among the 2570 white patients, the hazard ratio was 1.05 (95% CI, 0.92 to 1.21), and among the 815 black patients, the hazard ratio was 0.87 (95% CI, 0.68 to 1.10; P=0.03 for the interaction, uncorrected for multiple comparisons).

PATIENT-REPORTED OUTCOMES

The primary prespecified 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 greater 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). Other prespecified quality-of-life assessments, in the domains of energy and physical functioning as measured with the 36-Item Short-Form General Health Survey, did not differ significantly between 1138 patients assigned to darbepoetin alfa and 1157 patients assigned to placebo (mean change in the score for energy, 2.6±9.9 points vs. 2.1±9.7 points; P=0.20; mean change in the score for physical functioning, 1.3±9.2 vs. 1.1±8.8; P=0.51).

BLOOD PRESSURE

There was no significant difference in systolic blood pressure between the two groups; the median systolic blood pressure over time was 134 mm Hg (interquartile range, 126 to 143) in both groups. Diastolic blood pressure was higher in the patients assigned to darbepoetin alfa than in those assigned to placebo (median over time, 73 mm Hg [interquartile range, 67 to 78] vs. 71 mm Hg [interquartile range, 65 to 77]; P<0.001).

PRESPECIFIED CATEGORIES OF ADVERSE EVENTS

Hypertension occurred in 491 patients in the darbepoetin alfa group and in 446 patients in the placebo group (P=0.07) (see the Supplementary Appendix). Convulsions were reported in nine patients in the darbepoetin alfa group and in four patients in the placebo group. No cases of antibody-mediated pure red-cell aplasia were reported in either group.
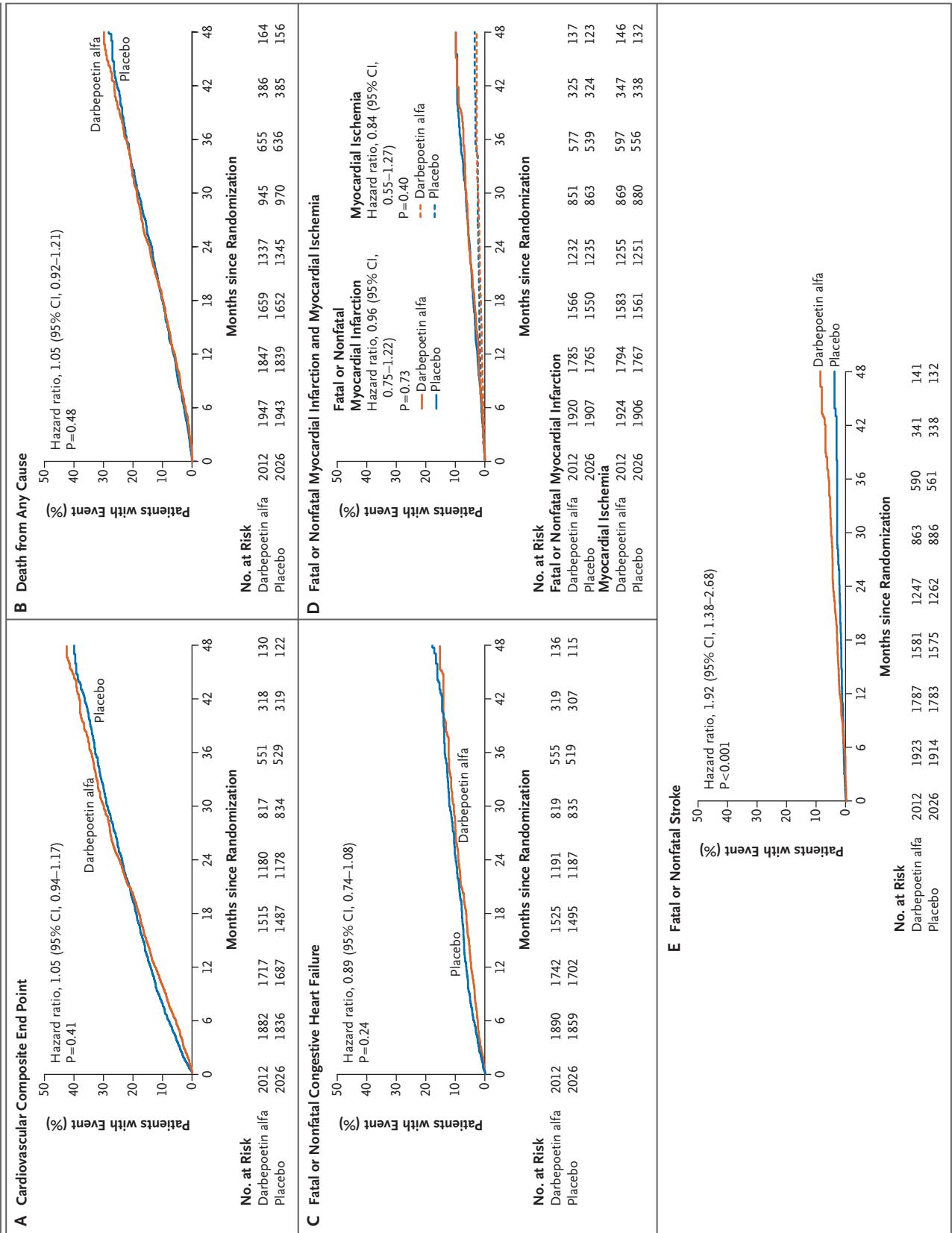
A Cardiovascular Composite End Point

Hazard ratio, 1.05 (95% CI, 0.94–1.17)
P=0.41

Patients with Event (%) — Months since Randomization

Darbepoetin alfa
Placebo

No. at Risk

	0	6	12	18	24	30	36	42	48
Darbepoetin alfa	2012	1882	1717	1515	1180	817	551	318	130
Placebo	2026	1836	1687	1487	1178	834	529	319	122

B Death from Any Cause

Hazard ratio, 1.05 (95% CI, 0.92–1.21)
P=0.48

Patients with Event (%) — Months since Randomization

Darbepoetin alfa
Placebo

No. at Risk

	0	6	12	18	24	30	36	42	48
Darbepoetin alfa	2012	1947	1847	1659	1337	945	655	386	164
Placebo	2026	1943	1839	1652	1345	970	636	385	156

C Fatal or Nonfatal Congestive Heart Failure

Hazard ratio, 0.89 (95% CI, 0.74–1.08)
P=0.24

Patients with Event (%) — Months since Randomization

Placebo
Darbepoetin alfa

No. at Risk

	0	6	12	18	24	30	36	42	48
Darbepoetin alfa	2012	1890	1742	1525	1191	819	555	319	136
Placebo	2026	1859	1702	1495	1187	835	519	307	115

D Fatal or Nonfatal Myocardial Infarction and Myocardial Ischemia

Fatal or Nonfatal Myocardial Infarction
Hazard ratio, 0.96 (95% CI, 0.75–1.22)
P=0.73

Myocardial Ischemia
Hazard ratio, 0.84 (95% CI, 0.55–1.27)
P=0.40

Darbepoetin alfa
Placebo
--- Darbepoetin alfa
--- Placebo

Patients with Event (%) — Months since Randomization

No. at Risk
Fatal or Nonfatal Myocardial Infarction

	0	6	12	18	24	30	36	42	48
Darbepoetin alfa	2012	1920	1785	1566	1232	851	577	325	137
Placebo	2026	1907	1765	1550	1235	863	539	324	123

Myocardial Ischemia

	0	6	12	18	24	30	36	42	48
Darbepoetin alfa	2012	1924	1794	1583	1255	869	597	347	146
Placebo	2026	1906	1767	1561	1251	880	556	338	132

E Fatal or Nonfatal Stroke

Hazard ratio, 1.92 (95% CI, 1.38–2.68)
P<0.001

Patients with Event (%) — Months since Randomization

Darbepoetin alfa
Placebo

No. at Risk

	0	6	12	18	24	30	36	42	48
Darbepoetin alfa	2012	1923	1787	1581	1247	863	590	341	141
Placebo	2026	1914	1783	1575	1262	886	561	338	132

Venous thromboembolic events were reported in 41 patients in the darbepoetin alfa group (2.0%), as compared with 23 patients in the placebo group (1.1%) (P=0.02). Arterial thrombo-embolic events (some of which were adjudicated as cardiovascular events) were also reported more frequently in the darbepoetin alfa group (in 178 patients [8.9%] vs. 144 patients [7.1%], P=0.04).

CANCER

There was no significant between-group difference in the number of patients reporting a cancer-related adverse event: 139 in the darbepoetin alfa group (6.9%) and 130 in the placebo group (6.4%) (P=0.53). Overall, 39 deaths were attributed to cancer in the 2012 patients in the darbepoetin alfa group and 25 deaths were attributed to cancer in the 2026 patients in the placebo group (P=0.08 by the log-rank test). Among patients with a history of a malignant condition at baseline, there were 60 deaths from any cause in the 188 patients assigned to darbepoetin alfa and 37 deaths in the 160 patients assigned to placebo (P=0.13 by the log-rank test). In this subgroup, 14 of the 188 patients assigned to darbepoetin alfa died from cancer, as compared with 1 of the 160 patients assigned to placebo (P=0.002 by the log-rank test).

DISCUSSION

The main purpose of the TREAT was to determine whether treatment of a low hemoglobin level with darbepoetin alfa would reduce the risk of death and major cardiovascular and renal events among patients with type 2 diabetes mellitus, chronic kidney disease, and anemia. There was no significant difference in the overall rates of either the primary cardiovascular composite end point or the primary renal composite end point with the use of the therapeutic strategy of increasing the hemoglobin level with darbepoetin alfa (to attempt to reach a target hemoglobin level of 13.0 g

per deciliter) versus placebo (with darbepoetin alfa as rescue therapy if hemoglobin values decreased below 9.0 g per deciliter). In this study involving 4038 patients randomly assigned to a study group, with 9941 patient-years of follow-up and with 1234 patients who had a composite outcome of a cardiovascular event and 1270 patients who had a composite outcome of a renal event, we found no overall significant differences in the hazard rates for these clinically important outcomes or in the rates of death, heart failure, myocardial infarction, admission for myocardial ischemia, or end-stage renal disease.

Although there was no significant increase in the overall cardiovascular composite outcome in the group assigned to darbepoetin alfa, there was an increased incidence of stroke (annualized event rate, 2.1%, vs. 1.1% in the placebo group). Data from a study of patients undergoing dialysis suggested this risk of stroke[19]; however, this risk was not identified in either the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study (ClinicalTrials.gov number, NCT00211120)[17] or a meta-analysis.[24] This previously undocumented and clinically important finding of a heightened risk of stroke is not explained by an increase in systolic blood pressure. In a recent report of a randomized, placebo-controlled trial of intravenous erythropoietin in the early phase of an acute ischemic stroke,[25] there were more deaths in the group assigned to the ESA (42 of 256 patients [16.4%]) as compared with the group assigned to placebo (24 of 266 patients [9.0%]). This study also provides support for an adverse relationship between ESAs and stroke. We also confirmed previous findings of increased rates of venous thromboembolic events among patients treated with ESAs.

Our findings appear to differ from those of the CHOIR trial, the next largest trial involving patients with chronic kidney disease who were not undergoing dialysis, which used epoetin alfa and was discontinued prematurely after a median follow-up of 16 months and after 222 patients had a primary event.[17] Both groups in the CHOIR trial were randomly assigned to receive epoetin alfa, and in that study, there was a higher risk of cardiovascular events in the group assigned to a target hemoglobin level of 13.5 g per deciliter than in the group assigned to a target level of 11.3 g per deciliter (hazard ratio, 1.34; 95% CI, 1.03 to 1.74; P=0.03). This excess of cardiovas-

Figure 3. Kaplan–Meier Estimates of the Probability of Renal Outcomes.

Panel A shows the primary renal composite end point (end-stage renal disease [ESRD] or death), and Panel B shows the end-point component of ESRD. P values have not been adjusted for multiple comparisons.
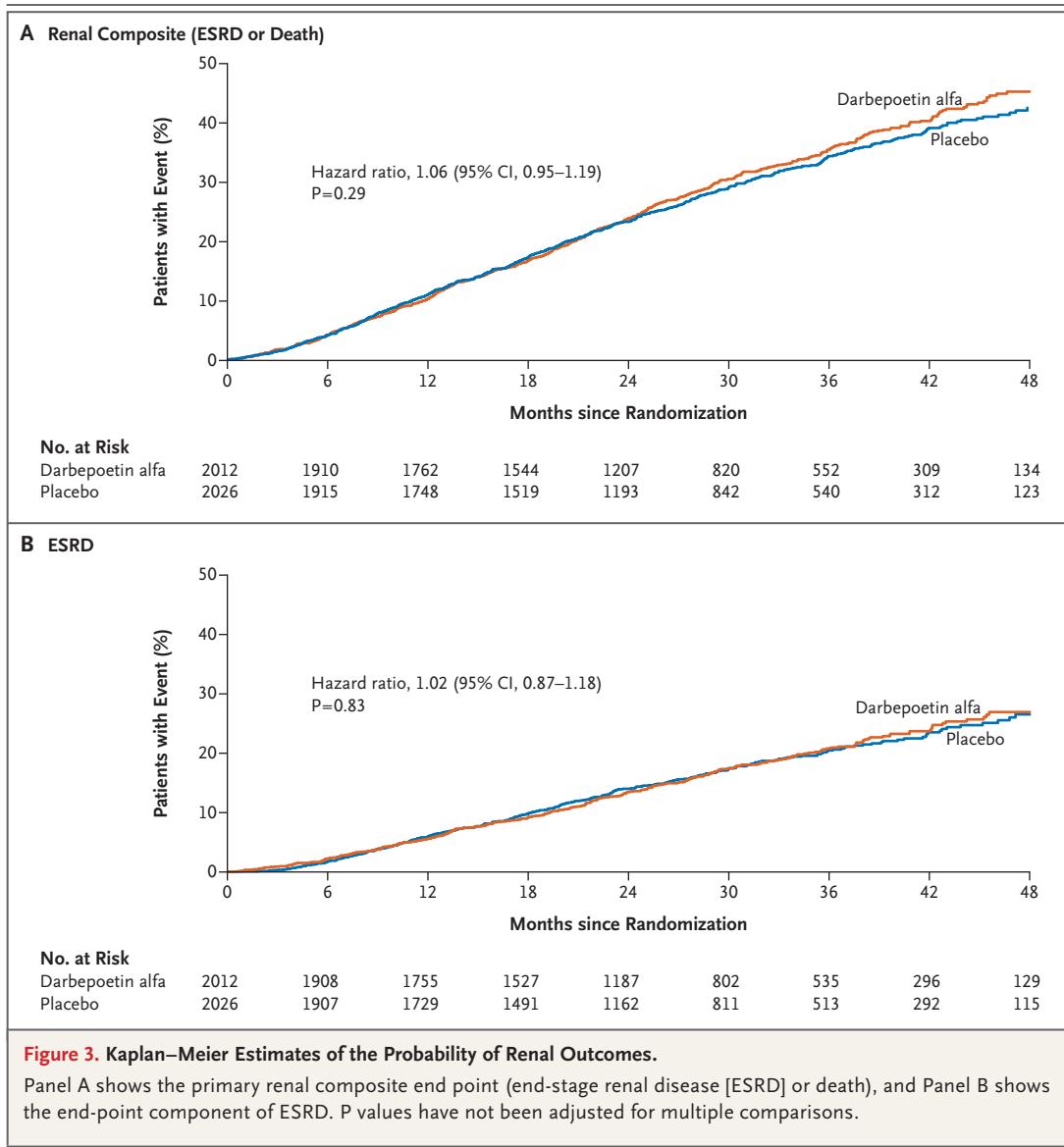
cular events was largely accounted for by more deaths and heart-failure events; only 12 patients in each group had a stroke. These findings led to the suggestion that our trial should be discontinued.[26] However, by that time, there were more accumulated cardiovascular composite events in our trial than in the CHOIR trial, and the independent data and safety monitoring committee recommended continuation.[27] The TREAT executive committee updated the consent form to reflect the results from the CHOIR trial, and our patients again were asked to provide written informed consent. The final results of our study demonstrate the importance of completing the

planned follow-up of trials and the potential to draw misleading conclusions when premature discontinuation results in an insufficient number of events to allow for a reliable estimation of the effect of treatment.[28,29]

Before we conducted our study, there was a suggestion that ESAs might increase mortality among patients with cancer, so patients with an active malignant condition were excluded from our trial.[30] During the trial, mounting concern led to new regulatory warnings about the use of ESAs in patients with "anemia of cancer,"[31] prompting a protocol amendment to discontinue the study drug in patients in whom cancer developed. Al-

though the number of these patients did not differ significantly between the study groups, among the 348 patients with a history of cancer at baseline, mortality was higher among those assigned to darbepoetin alfa than among those assigned to placebo; these findings are consistent with those in a recent meta-analysis.[32]

Our trial provides long-term, placebo-controlled data on the use of ESAs in patients with diabetes, chronic kidney disease, and moderate anemia who are not undergoing dialysis. No single trial can address the multitude of pertinent issues without limitations, and our data may not be fully applicable to other patient populations. It is possible that other dosing strategies could be developed to mitigate the risk of stroke while conserving the modest benefits of treatment. In light of the baseline imbalances between the study groups, additional sensitivity analyses were conducted, and they did not alter our results. More extensive analyses of the patient-reported outcome measures are needed to assess the durability of the rather modest improvement we observed only in the FACT-Fatigue score.

The long-standing presumption of a benefit of ESAs in this patient population led to non–placebo-controlled trials, which, by design, cannot provide a reliable assessment of risk and benefit.[21] The present trial supplies these missing data, which may assist physicians and patients in making more informed decisions about individual care. It is our view that, in many patients with diabetes, chronic kidney disease, and moderate anemia who are not undergoing dialysis, the increased risk of stroke and possibly death among patients with a history of a malignant condition will outweigh any potential benefit of an ESA.

Cravario, R. Damato, K. Dellacroce, K. DiRocco, D. Donovan, B. Doria, M. Dougherty, J. Droge, A. Grewal, L. Guimaraes, P. Haynes, J. Hevy, T. Jambusaria, N. James, A. Kacprzak, M. Kasenda, S.R.K. Reddy, R. Kewalramani, H. Kirby, C. Klacker, T. Kocsis, A. Kondo, M. Lauw, M. Liebelt, P. McElligott, B. Mesquita, C. Mix, A. Mueller, S. O'Callaghan, H. Ocampo, K. Olson, S. Perez, J. Pillai, A. Pollock, F. Poloni, K. Polu, R. Poston, G. Ramirez, A. Rasmussen, L. Reeves, M. Rocha, A.P. Ross, J. Rossert, B. Sahl, T. See, S. Shahinfar, K. Shart, C. Stehman-Breen, A. Teh, L. Tierra, M. Vaghela, C. White. Enrollment by country was as follows (numbers of patients are in parentheses): Argentina (84), Australia (58), Austria (3), Brazil (190), Bulgaria (28), Canada (176), Chile (14), Czech Republic (96), Denmark (10), Estonia (16), France (11), Germany (135), Hungary (70), Italy (87), Latvia (51), Mexico (150), Poland (213), Portugal (17), Romania (47), Russia (117), Slovakia (65), Slovenia (12), United Kingdom (49), United States (2339).

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