1. TITLE PAGE

Study Title:	Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT)
Investigational Product:	Darbepoetin alfa
Indication:	Treatment of anemia in subjects with chronic kidney disease (CKD)
Brief Description:	An international, multicenter, randomized, double-blind, placebo-controlled study designed to assess the effect of the treatment of anemia with darbepoetin alfa on all-cause mortality and nonfatal cardiovascular events, and the effect of darbepoetin alfa treatment in reducing the risk of progression to end-stage renal disease in subjects with CKD and type 2 diabetes mellitus.
Study Sponsor:	Amgen Inc., Thousand Oaks, CA USA
Study No.:	20010184
IND No.:	11621
Study Phase:	3
Study Initiation Date:	25 August 2004 (first subject enrolled)
Study Completion Date:	28 March 2009 (final endpoint date defined by Amgen in anticipation of 1203 subjects experiencing a primary cardiovascular endpoint event) 23 July 2009 (last subject last assessment)
Principal Investigators:	This was a multicenter study conducted at 623 study centers in the United States, Australia, Canada, Latin America, and Europe. Study centers and principal investigators are listed in Appendix 4.
Clinical Study Manager:	[redacted], PharmD One Amgen Center Drive Thousand Oaks, CA 91320-1799 USA [redacted]
Good Clinical Practice:	This study was conducted in accordance with applicable country regulations and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH GCP.
Report Date:	18 February 2010

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2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Aranesp®

Name of Active Ingredient: Darbepoetin alfa

Title of Study: Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT)

Investigator(s) and Study Center(s): This study was conducted at 623 study centers in the United States, Australia, Canada, Latin America, and Europe (Appendix 4).

Publication(s)

Pfeffer MA, Burdmann EA, Chen C-Y, et al. A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease. *N Engl J Med*. 2009;361:2019-32.

Pfeffer MA, Burdmann EA, Chen C-Y, et al. Baseline Characteristics in the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT). *Am J Kidney Dis*. 2009;54:59-69.

Mix TC, Brenner RM, Cooper ME, et al. Rationale--Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT): evolving the management of cardiovascular risk in patients with chronic kidney disease. *Am Heart J.* 2005;149:408-413.
Correction. *Am Heart J*. 2005;150:53.

Rao M, Pereira B. Prospective trials on anemia of chronic disease: The Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT). *Kidney Int*. 2003;64:s12-s19.

Study Period: 25 August 2004 (first subject enrolled) to 23 July 2009 (last subject last assessment). The final endpoint date, 28 March 2009, was identified by Amgen in anticipation of 1203 subjects experiencing a primary cardiovascular composite endpoint event.

Development Phase: 3

Objectives

Primary: To assess the effect of anemia therapy with darbepoetin alfa on the composite event comprising all-cause mortality and cardiovascular (CV) events (including myocardial ischemia, congestive heart failure [CHF], myocardial infarction [MI], and cerebrovascular accident [CVA]) and on the composite event comprising all-cause mortality and end-stage renal disease (ESRD) in subjects with both chronic kidney disease (CKD) and type 2 diabetes mellitus (DM).

Secondary

To assess the effect of anemia therapy with darbepoetin alfa on CV mortality and the individual components of the composite event: all-cause mortality and CV events.

To assess the effect of darbepoetin alfa on the time to ESRD, the change in the rate of decline in estimated glomerular filtration rate (eGFR), and patient-reported fatigue.

Within the overall study, a functional capacity substudy was conducted in a subset of subjects to assess the distance walked in 6 minutes.

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Methodology: In this multicenter (United States, Australia, Canada, Latin America, and Europe), randomized, double-blind, placebo-controlled study, approximately 4000 subjects with hemoglobin levels ≤ 11.0 g/dL, CKD, eGFR ≥ 20 mL/min/1.73 m^2 and ≤ 60 mL/min/1.73 m^2, and type 2 DM were to be enrolled. Eligible subjects were randomized in a 1:1 ratio (stratified by study center, level of baseline proteinuria [spot urine protein/urine creatinine ratio ≥ 1 or < 1 g/g], and history of CV disease) to receive either subcutaneous (SC) darbepoetin alfa to achieve and maintain a hemoglobin of 13.0 g/dL or SC placebo. For subjects in the placebo group whose hemoglobin concentration fell to < 9.0 g/dL, rescue with darbepoetin alfa was administered until the hemoglobin concentration increased to ≥ 9.0 g/dL, at which time placebo administration resumed. Throughout the study, investigators could prescribe any concomitant medications or treatments (including red blood cell transfusions) deemed necessary to provide adequate supportive care, with the exception of commercial ESA (apart from investigational product). This study was an event-driven design, scheduled to conclude when approximately 1203 subjects had experienced a primary CV endpoint event (all-cause mortality and CV events, including myocardial ischemia, CHF, MI, and CVA). An external, unblinded, independent statistical analysis center performed safety and efficacy analyses in support of ongoing reviews by an external independent Data Safety Monitoring Committee (DSMC).

Number of Subjects Planned: Approximately 4000 subjects (approximately 2000 per treatment group)

Number of Subjects Enrolled: A total of 4047 subjects were enrolled in the study. One subject, incorrectly randomized twice into the trial, was analyzed as a single enrollment. Due to significant ICH GCP noncompliance at study center 0349 (6 subjects enrolled) that included falsification of data, and center 3209 (3 subjects) that included irregularities in procedures for subject informed consent, data obtained from the 9 subjects enrolled at these 2 centers were removed from the clinical database and therefore excluded from all efficacy and safety analyses; the decision to exclude these data was made prior to unblinding. Therefore, the number of subjects enrolled and randomized in this study is reported in this document as 4038 (2012 darbepoetin alfa, 2026 placebo).

Sex: 2312 (57.3%) women; 1726 (42.7%) men

Mean (standard deviation [SD]; range) Age: 67.4 ([10.6]; 27 to 99) years

Ethnicity (Race): 2570 (63.6 %) White or Caucasian; 815 (20.2 %) Black or African American, 538 (13.3%) Hispanic or Latino; 78 (1.9%) Asian; 11 (0.3%) Japanese, 5 (0.1%) American Indian or Alaska Native, 9 (0.2%) Native Hawaiian or Other Pacific Islander, 3 (0.1%) Aborigine, and 9 (0.2%) other races

Diagnosis and Main Criteria for Eligibility: Subjects eligible for the study were ≥ 18 years of age, with a diagnosis of CKD and type 2 DM, had a mean screening hemoglobin concentration ≤ 11.0 g/dL, eGFR within the range of ≥ 20 mL/min/1.73 m^2 and ≤ 60 mL/min/1.73 m^2, and a mean transferrin saturation ≥ 15%. Subjects excluded from participation were those who had a prior kidney transplant (or who anticipated or had scheduled a living related-donor kidney transplant), uncontrolled hypertension, the use of any erythropoietic protein within the 12 weeks prior to randomization, or a history of CV events within the 12 weeks prior to randomization (eg, myocardial ischemia, hospitalization for CHF, MI, CVA).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Darbepoetin alfa was provided as a clear, colorless protein solution in pre-filled syringes (PFS) contaning the following unit doses: 10, 15, 20, 30, 40, 50, 60, 80, 100, 150, 200, and 300 μg. The starting dose of investigational product was 0.75 μg/kg, calculated using the subject's body weight during screening and rounded to the nearest PFS. Darbepoetin alfa was administered by SC injection once every 2 weeks (Q2W) and adjusted to achieve a hemoglobin concentration of 13.0 g/dL. Subjects who achieved 2 consecutive hemoglobin concentrations between 12.0 and 13.5 g/dL, with no intervening dose change, had the frequency of darbepoetin alfa administration extended to once monthly (QM), with the initial QM dose being twice the previous Q2W dose. If a

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subject receiving the maximum QM dose (600 μg) of darbepoetin alfa had 3 consecutive monthly hemoglobin concentrations < 11.0 g/dL, the frequency of administration of investigational product was increased to Q2W and the dose reduced to half the initial QM dose. Manufacturing lot numbers of darbepoetin alfa used in this study are provided in Appendix 18.

Duration of Treatment: Subjects were to receive either darbepoetin alfa or placebo in a blinded fashion up to the final endpoint date. Subjects were removed from investigational product administration, but were to remain on study, if they required renal replacement therapy, developed cancer, or by subject/investigator request.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Placebo was provided as a clear, colorless solution in a PFS identical in appearance to those containing darbepoetin alfa. Using a dynamic dose-change schedule that imitated the active-group dose changes, subjects randomized to placebo had dose and schedule changes that mirrored those occurring for subjects randomized to the darbepoetin alfa treatment group. Subjects in the placebo qroup who required rescue therapy (hemoglobin concentration < 9 g/dL) received a single dose of darbepoetin alfa (0.45 μg/kg, rounded to the nearest PFS; described above under investigational product). Manufacturing lot numbers of placebo used in this study are provided in Appendix 18.

Study Endpoints

Primary

Cardiovascular Composite Endpoint: Time to the first confirmed composite event, comprising all-cause mortality and CV events including myocardial ischemia, CHF, MI, and CVA with overall alpha of 0.048.

Renal Composite Endpoint: Time to ESRD or all-cause mortality with overall alpha of 0.002.

Secondary Endpoints: Time to all-cause mortality; time to CV mortality; time to myocardial ischemia; time to MI; time to CVA; time to CHF; time to ESRD; rate of decline in eGFR relative to baseline; and change in subject-reported fatigue relative to baseline at week 25.

Other Endpoints of Interest: Time to cardiac revascularization; change in urine protein/urine creatinine ratio relative to baseline; change in patient-reported outcomes (PRO), other than fatigue, relative to baseline at week 25; change in physical and mental composite scores of the SF-36 relative to baseline; and health resource utilization (HRU) per subject follow-up time.

Safety Endpoints: Adverse events; changes in laboratory parameters and blood pressure; and anti-erythropoietic protein seroreactivity.

Functional Capacity Substudy Endpoint: change from baseline in distance walked in 6 minutes.

Statistical Methods

The primary analyses of primary and secondary time-to-event endpoints followed intent-to-treat principles. Subjects were analyzed as randomized using all available follow-up information.

Efficacy endpoints were analyzed according to a hierarchical procedure; to maintain the overall 5% significance level for the study after 4 planned interim analyses, the primary cardiovascular composite and renal composite endpoints were tested at the 0.04056 and 0.002 significance levels, respectively. Secondary endpoints (excluding PRO) were to be tested only if either of the cardiovascular and renal composite endpoints was statistically significant. The Holm adjustment was used as the primary multiplicity adjustment method to adjust for the multiple comparisons for

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the secondary endpoints in order to control the type 1 error. The Hochberg procedure was also planned per protocol.

All inferential statistical analyses were 2-sided. Continuous variables were summarized descriptively including the following: number of observations (n), mean, standard deviation (SD), standard error (SE), median, lower and upper 25th percentiles (Q1, Q3), minimum and maximum. Categorical variables were summarized using frequency (n) and percentage (%). For all time-to-event outcomes, there was no imputation of data.

The primary analysis of the time to event endpoints was a 2-sided log-rank test comparing the survival functions of the 2 groups stratified by baseline proteinuria and CV disease (CVD) history. Kaplan-Meier estimates of the 2 survival curves were presented. Treatment effect was estimated using a hazards ratio and 95% confidence interval (CI) obtained from a Cox proportional hazards model stratified by baseline proteinuria and CVD history. Decomposition of the events comprising the composite endpoint and adjudication criteria for the adjudicated events were summarized by treatment group. Poisson regression models were used to assess the treatment effect on the exposure-adjusted event rate per 100 subject-years, with or without adjusting for stratification factors, and 95% confidence intervals were calculated using Chi-square approximation to Poisson distribution.

Rate of decline in eGFR from baseline and change in urine protein/urine creatinine ratio were assessed using a linear mixed-effect model, adjusting for baseline measurement, stratification factors of proteinuria and CVD history to evaluate treatment effect.

For the change in patient-reported fatigue as measured by the FACT-fatigue scale from baseline to week 25, mean changes were compared across the 2 randomized treatment groups using a 2-sided t-test with a significance level of 0.05. Ninety-five percent CIs were calculated for the mean difference between the 2 groups. Analysis of covariance (ANCOVA) was also performed, adjusting for baseline FACT-fatigue scores and stratification factors of proteinuria and CVD history. Other endpoints of patient-reported outcomes were analyzed using the same method as that for FACT-fatigue scale.

Safety analyses of adverse events, hospitalization, red blood cell transfusion and anti-erythropoietic protein seroreactivity were performed using the safety analysis set. Summaries of laboratory data (including hemoglobin summaries) and vital signs were completed using the safety analysis set, limited to values obtained while the subject was receiving the investigational product. Safety data were summarized descriptively. No statistical testing was performed.

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Summary of Results

Subject Disposition: A total of 4038 subjects were enrolled into the study, with 2012 subjects randomized to the darbepoetin alfa group and 2026 subjects randomized to the placebo group. Randomization was stratified by baseline proteinuria, < 1g/g (62% of subjects enrolled), ≥ 1 g/g (38%), and by history of CVD, yes (63%) or no (37%); randomization was well-balanced between treatment groups within the strata. Of the randomized subjects, 4023 received ≥ 1 dose of investigational product (2004 darbepoetin alfa, 2019 placebo). Sixty-seven percent of the enrolled subjects completed end of study assessments (67% darbepoetin alfa, 67% placebo), and 45.86% of enrolled subjects completed investigational product (46% darbepoetin alfa, 45% placebo).

Efficacy Results

A total of 1234 cardiovascular composite endpoint events occurred: 632 events (31%) among the 2012 subjects in the darbepoetin alfa group and 602 (30%) among the 2026 subjects in the placebo group (hazard ratio darbepoetin alfa/placebo: 1.05 [95% CI: 0.94, 1.17]; p = 0.411). Annualized event rates (95% CI) were 13.0% (12.0, 13.9) in the darbepoetin alfa group and 12.5% (11.6, 13.5) in the placebo group. In a homogeneity analysis, a nominally statistical

significant result (p = 0.002) was observed due to the result for the composite endpoint event of time to CVA compared with the other time to event endpoints of death, MI, CHF, and myocardial ischemia. No nominally statistically significant quantitative interactions were detected in subgroup analyses (level of proteinuria, history of CVD, age, race, geographic region and baseline eGFR).

A total of 1270 renal composite endpoint events occurred: 652 events (32%) among the 2012 subjects in the darbepoetin alfa group and 618 (31%) among the 2026 subjects in the placebo group (hazard ratio [95% CI] of 1.06 [0.95, 1.19]; p = 0.287). The annualized event rate (95% CI) was 13.2% (12.3, 14.2) in the darbepoetin alfa group and 12.6% (11.6, 13.5) in the placebo group. Results were consistent with the overall results when analyzed by subgroups, with the exception of race subgroups (interaction p = 0.030): white (hazard ratio: 1.06 [95% CI 0.92, 1.21; p = 0.450), black (hazard ratio: 0.869 [95% CI 0.69, 1.10; p =0.247), other (hazard ratio: 1.46 [95% CI 1.10, 1.95; p =0.0095).

No difference was observed between the darbepoetin alfa and placebo groups for the secondary endpoints of time to all-cause mortality (hazard ratio: 1.05 [95% CI 0.92, 1.21]; nominal p = 0.479), time to CV mortality (hazard ratio: 1.05 [95% CI: 0.87, 1.23]; nominal p = 0.606), time to myocardial ischemia (hazard ratio: 0.84 [95% CI: 0.55, 1.27]; nominal p = 0.396), time to fatal or non-fatal MI (hazard ratio: 0.98 [95% CI: 0.76, 1.26]; nominal p = 0.867), time to fatal or non-fatal CHF (hazard ratio: 0.89 [95% CI: 0.74, 1.08]; nominal p = 0.236), and time to ESRD (hazard ratio: 1.016 [95% CI: 0.87, 1.18]; nominal p = 0.834). Differences in cause of deaths between the darbepoetin alfa and placebo groups were observed in the categories of presumed CV death (8.5% darbepoetin alfa, 5.8% placebo), fatal stroke (6.6%, 3.8%), and malignancy (9.5% [39 subjects], 6.3% [25 subjects]).

A higher number of CVA events were observed in the darbepoetin alfa group compared with placebo: 101 (5%) subjects in the darbepoetin alfa group and 53 (3%) in the placebo group had a CVA event (hazard ratio: 1.92 [95% CI: 1.38, 2.68]; nominal p < 0.0001). Annualized subject incidence event rates (95% CI) were 2.1% (1.7, 2.6) and 1.1% (0.8, 1.5) in the darbepoetin alfa and placebo groups, respectively. The majority of stroke events were nonhemorrhagic in both treatment groups; however, both hemorrhagic and nonhemorrhagic events were higher in the darbepoetin alfa group.

Fewer endpoint events of cardiac revascularization were observed in the darbepoetin alfa group compared with the placebo group (hazard ratio: 0.71 [95% CI: 0.54, 0.94]; nominal p = 0.016).

During the study, the rate of decline in eGFR from baseline using a mixed effect model was -1.37 mL/min/1.73 m2 per year in darbepoetin alfa group and -1.25 mL/min/1.73m^2 per year in placebo group, with an estimated difference in rate of decline (SE) of -0.12 (0.20) mL/min/1.73 m^2 per year (95% CI: -0.51, 0.26; nominal p = 0.536). The least square mean change in eGFR from baseline to end of study was -3.26 mL/min/1.73m^2 in the darbepoetin alfa group and -4.06 mL/min/1.73m^2 in the placebo group, with an estimated difference in decline (SE) of 0.80 (0.31) mL/min/1.73m^2 (95% CI: 0.20, 1.41; nominal p = 0.009).

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A nominally statistically significant treatment effect was detected in favor of placebo in proteinuria change from baseline when evaluated by a linear mixed effect model, adjusting for stratification factors (interaction term of time and treatment $p < 0.0001$). Median (Q1, Q3) proteinuria values at baseline were 0.38 g/g creatinine (0.13, 2.01) in the darbepoetin alfa group and 0.41 g/g creatinine (0.14, 1.76) in the placebo group. Median (Q1, Q3) change in proteinuria from baseline to each time point (24 week intervals) during the study ranged from 0.029 (-0.078, 0.345) to 0.055 (-0.029, 0.415) g/g creatinine for the darbepoetin alfa group and from 0.003 (-0.174, 0.162) to 0.052 (-0.014, 0.390) g/g creatinine for the placebo group.

The difference between the darbepoetin alfa and placebo groups in the change in Functional Assessment of Cancer Therapy (FACT)-Fatigue subscale score from baseline to week 25 was 1.33 (95% CI: 0.64, 2.02; $p < 0.0001$ using a 2-sided t-test), indicating greater improvement for the darbepoetin alfa group. The difference in the change in EQ-5D VAS scores from baseline to week 25 was 1.62 (0.38, 2.86) $p = 0.011$), also indicating greater improvement for the darbepoetin alfa group compared with placebo. However, the clinical significance of this modest improvement is unclear. No statistically significant differences were observed between treatment groups in the other PRO assessments evaluated (EuroQol-5 Dimensions [EQ-5D] Health State Index and Short Form-36 [SF-36]), or for Health Resource Utilization (HRU).

In the Functional Capacity Substudy (n = 600), no statistically significant difference between treatment groups was observed in the mean distance traveled within 6-minutes at each time point tested.

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Safety Results

A total of 1880 (93.8%) subjects in the darbepoetin alfa group and 1878 (93.0%) subjects in the placebo group had $\geq$ 1 treatment-emergent adverse event. The most frequently reported adverse events in both treatment groups (exposure-adjusted subject incidence > 10 per 100 subject-years in either group) were peripheral oedema (12.1 darbepoetin alfa, 12.9 placebo), hypertension (10.4, 9.7), and fatigue (9.1, 10.6). Adverse events reported by the investigator as being related to investigational product occurred in 303 (15.1%) subjects in the darbepoetin alfa group and 244 (12.1%) subjects in the placebo group. The most frequent treatment-related adverse events (> 0.5 per 100 subject-years in either group) were hypertension (2.7 darbepoetin alfa, 1.8 placebo), increased blood pressure (0.9, 0.4), and peripheral oedema (0.4, 0.5). The exposure-adjusted subject incidence per 100 subject-years of withdrawals due to adverse events was similar between treatment groups (8.4 darbepoetin alfa, 8.5 placebo).

The exposure-adjusted subject incidence (per 100 subject-years) of serious adverse events was similar between treatment groups (45.5 darbepoetin alfa, 46.5 placebo). The most common serious adverse events in both treatment groups (> 0.3 per 100 subject-years) were chronic renal failure (5.7, 4.8), congestive cardiac failure (4.6, 5.9), and pneumonia (2.3, 3.2). The exposure-adjusted subject incidence of treatment-related serious adverse events was also similar between treatment groups (1.3 darbepoetin alfa, 1.2 placebo).

A total of 395 subjects (19.7%) in the darbepoetin alfa group and 386 subjects (19.1%) in the placebo group had fatal adverse events during the study. The exposure-adjusted subject incidence (per 100 subject-years) of fatal adverse events was similar between treatment groups (9.9 darbepoetin alfa, 10.1 placebo). The most common preferred terms for fatal adverse events in both treatment groups were death (1.0 darbepoetin alfa, 1.0 placebo), cardiac arrest (0.7, 0.5),

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cerebrovascular accident (0.7, 0.3), myocardial infarction (0.6, 0.5), and congestive cardiac failure (0.5, 0.9).

The overall exposure-adjusted subject incidence (per 100 subject-years) of the 7 pre-defined adverse events of interest was similar for both treatment groups (29.0 darbepoetin alfa, 28.5 placebo). The exposure-adjusted subject incidence rates (per 100 subject-years) for these individual events of interest (darbepoetin alfa and placebo) were 14.8 and 13.7 for hypertension, 3.3 and 2.9 for myocardial infarction, 7.8 and 9.3 fir cardiac failure, 4.2 and 2.7 for cerebrovascular disorders, 0.2 and 0.1 for convulsions, and 5.8 and 4.6 for all thromboembolic events. No subject had antibody-mediated pure red cell aplasia (PRCA).

Within the cerbrovascular disorders Standardised MedDRA Query (SMQ), adverse events within the hemorrhagic and ischemic cerbrovascular disorders SMQs were reported (darbepoetin alfa vs placebo) with an exposure-adjusted subject incidence of 2.3 vs 1.3 and 3.9 vs 2.6 per 100 subject-years, respectively. This is consistent with the analyses of the CVA component of the primary composite endpoint. Within the thromboembolic events SMQ, these events included (per 100 subject-years) venous thromboembolic events (1.0 darbepoetin alfa, 0.6 placebo) and arterial thromboembolic events (4.6, 3.9), and vascular access thrombosis (0.1, 0.1).

Adverse event rates occurring within 28 days of a hemoglobin excursion (> 14 g/dL) and of a hemoglobin rate-of-rise (ROR) > 2.0 g/dL/4 wk were also reviewed in subjects in the darbepoetin alfa group. Adverse events of hypertension occurred more frequently in subjects with hemoglobin excursions (24.4 per 100 subject-years) than in the hemoglobin comparison group (subjects who reached 12.0 to 13.5 g/dL with no excursions) (13.3 per 100 subject-years). Among subjects with a serial hemoglobin ROR > 2.0 g/dL/4 wk, adverse events of hypertension and cardiac failure were reported more frequently compared with subjects with no hemoglobin ROR of > 2.0 g/dL/4 wk (33.2 vs 10.2 and 9.6 vs 4.6 , respectively, per 100 subject-years).

Following the observation of a difference between treatment groups in adjudicated deaths due to malignancy (39 darbepoetin alfa, 25 placebo), post-hoc analyses were conducted to further understand the association between malignancy incidence, malignancy outcomes, and darbepoetin alfa treatment. There was no significant between-group difference in the number of subjects reporting an adverse event within the malignancy SMQ (139 [6.9%] darbepoetin alfa-treated subjects, 130 [6.4%] placebo-treated subjects). Among subjects who reported adverse events within the malignancy SMQ, adjudicated deaths due to any cause were balanced (53 darbepoetin alfa, 50 placebo). Among subjects with a baseline history of malignancy (188 darbepoetin alfa, 160 placebo), there were 60 deaths from any cause in the darbepoetin alfa group and 37 in the placebo group. The largest imbalance in cause of death among subjects with a baseline history of malignancy was death due to malignancy (14 darbepoetin alfa, 1 placebo). However, no single cause of death accounted for the full imbalance.

Hemoglobin concentrations progressively increased during the first 3 months in the darbepoetin alfa group. From 3 months until the end of treatment, the median achieved hemoglobin level based on a standardized daily hemoglobin AUC analysis was significantly higher in the darbepoetin alfa group (12.3 g/dL) than the placebo group (10.6 g/dL) ($p < 0.0001$).

Transferrin saturation values for subjects in the darbepoetin alfa group increased relative to those in the placebo group between weeks 13 and 25 and remained higher throughout the study. Serum ferritin values decreased during the first 13 weeks in the darbepoetin group, then progressively increased and were similar to the values in the placebo group at week 49 and after. Mean percent reticulocyte and platelet count were lower at the end of the study than at baseline and mean white blood cell counts were higher at the end of study than at baseline for both treatment groups. There were no notable changes or differences between treatment groups in serum chemistry or lipid values. Vital signs did not change notably over the study with the exception of diastolic blood pressure, which in a post-hoc analysis was significantly higher in the darbepoetin alfa group (median = 72.7 mmHg) than the placebo group (71.5 mmHg) ($p < 0.0001$). A low prevalence of binding antibodies for darbepoetin alfa and/or epoetin alfa was observed for

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both treatment groups at baseline (11.68% darbepoetin alfa, 12.04% placebo), and after treatment with investigational product (9.38% darbepoetin alfa, 11.00% placebo). All subjects tested in the bioassay were negative for neutralizing antibodies.

Significantly fewer subjects received ≥ 1 red blood cell transfusion in the darbepoetin alfa group compared with the placebo group (297 [15 %] and 496 [24%], respectively). Post-hoc analyses using the efficacy analysis set demonstrated similar results (hazard ratio for time to first transfusion 0.56 [95% CI, 0.49 to 0.65]; $p < 0.0001$). The exposure-adjusted event incidence was significantly lower in the darbepoetin alfa group (13.1 days of transfusion per 100 subject-years, annualized; 95% CI: 12.2, 14.1) compared with the placebo group (22.8 days of transfusion per 100 subject-years, annualized; 95% CI: 21.7, 23.9). Subjects in the darbepoetin alfa group also had a lower incidence rate (exposure-adjusted event rates per 100 subject-years) of adverse events (3.3 darbepoetin alfa, 6.8 placebo), serious adverse events (2.7, 4.9), and treatment-related adverse events (0.1, 0.3), that resulted in transfusion compared with subjects in the placebo group.

In the Functional Capacity Substudy, the incidence of adverse events during the 6-minute walk test was similar for the darbepoetin alfa group (126 subjects) and the placebo group (125 subjects).

Conclusions: In conclusion, use of darbepoetin alfa targeting a hemoglobin concentration of 13 g/dL in subjects with type 2 DM, CKD, and anemia (≤ 11 g/dL), who were not undergoing dialysis did not reduce the risk of either of the 2 primary composite outcomes (death or a cardiovascular event, or death or ESRD) and was associated with an approximately 2-fold increased risk of stroke, compared with the placebo group which included rescue therapy with darbepoetin alfa when the hemoglobin concentration was < 9 g/dL. In post-hoc analyses, an increased rate of death in subjects who reported a baseline history of malignancy was observed in the darbepoetin alfa group. Although not an endpoint in this study, subjects receiving darbepoetin alfa had a significantly lower incidence of red blood cell transfusions than placebo.

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