1. TITLE PAGE

Study Title:	A double-blind, randomized, placebo-controlled, multicenter study to assess the efficacy and safety of darbepoetin alfa treatment on mortality and morbidity in heart failure (HF) subjects with symptomatic left ventricular systolic dysfunction and anemia RED-HF Trial – Reduction of Events with Darbepoetin alfa in Heart Failure Trial
Investigational Product:	Darbepoetin alfa
Indication:	Subjects with heart failure who have symptomatic left ventricular systolic dysfunction and anemia
Brief Description:	An international study designed to assess the effect of the treatment of anemia with darbepoetin alfa on the composite of all-cause mortality or hospitalization for worsening heart failure in subjects with symptomatic left ventricular systolic dysfunction and anemia. The study also evaluated the effect of darbepoetin alfa on all-cause death, cardiovascular death or hospitalization for worsening heart failure, and health-related quality-of-life (HRQOL) outcomes.
Study Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 USA
Study No.:	20050222
IND No.:	10146
Study Phase:	3
Study Initiation Date:	13 June 2006 (first subject enrolled)
Study Completion Date:	11 October 2012 (last subject completed follow-up)
Principal Investigator(s):	This was a multicenter study conducted at 453 study centers in the United States, Australia, Canada, Latin America, Asia, Europe, Israel, South Africa, and Russia. Study centers and principal investigators are listed in Appendix 4.
Contact Person:	[redacted], MD [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:	19 July 2013

2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Aranesp®

Name of Active Ingredient: Darbepoetin alfa

Title of Study: A double-blind, randomized, placebo-controlled, multicenter study to assess the efficacy and safety of darbepoetin alfa treatment on mortality and morbidity in heart failure (HF) subjects with symptomatic left ventricular systolic dysfunction and anemia.

Investigator(s) and Study Center(s): This study was conducted at 453 study centers in the United States, Australia, Canada, Latin America, Asia, Israel, Europe, South Africa, and Russia. The study centers and principal investigators are listed in Appendix 4.

Publication(s): Swedberg K, Young JB, Anand IS, et al. Treatment of anemia with darbepoetin alfa in systolic HF. N Eng J Med 2013;368:1210-1219.

Study Period:

- First subject enrolled: 13 June 2006
- Study termination date: 01 September 2012
- Last subject completed follow-up: 11 October 2012

Development Phase: 3

Study Objectives:

Primary: To determine the efficacy of darbepoetin alfa compared with placebo on the composite of time to death from any cause or first hospital admission for worsening HF in subjects with symptomatic left ventricular systolic dysfunction and anemia.

Secondary:
To evaluate the effects of treatment with darbepoetin alfa on the

- time to death from any cause
- time to cardiovascular death or first hospital admission for worsening HF, whichever occurred first
- change from baseline to month 6 in Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score
- change from baseline to month 6 in KCCQ Symptom Frequency Score

Tertiary:
To evaluate the effects of treatment with darbepoetin alfa on the

- time to all-cause death or first non-fatal cardiovascular event, including acute coronary syndrome (myocardial infarction [MI], unstable angina), cerebrovascular accident, venous thromboembolism (deep vein thrombosis [DVT] or pulmonary embolism [PE]), resuscitated sudden death, hospitalization for worsening HF, and hospitalization where HF was a major component
- time to first hospital admission for worsening HF
- time to cardiovascular death
- time to new onset atrial fibrillation/flutter
- total number and duration of hospital admissions for worsening HF
- total number and duration of hospital admissions where HF was a major component
- health-related quality of life (HRQOL) as measured by the KCCQ, and the European Quality of Life – 5 Dimensions (EQ-5D) questionnaire
- NYHA class
- estimated glomerular filtration rate (eGFR)
- health resource utilization
- to compare the safety profile of darbepoetin alfa with that of placebo

Exploratory objectives are presented in Section 6.4.

Methodology:

This multicenter study utilized a randomized, double-blind, placebo-controlled, event-driven design.

Number of Subjects/Events:

- **Number of Subjects Planned:** Approximately 2600 subjects (1:1 darbepoetin alfa: placebo)
- **Number of Subjects Enrolled:** 2278 (1136 darbepoetin alfa, 1142 placebo)
- **Number of Events Planned:** Approximately 1150 subjects experiencing a primary endpoint event
- **Number of Events Observed:** 1141 subjects experiencing a primary endpoint event (576 darbepoetin alfa: 565 placebo)

Diagnosis and Main Criteria for Eligibility: Eligible subjects were adults who had HF of ≥ 3 months duration, with New York Heart Association (NYHA) classification of II, III, or IV and left ventricular ejection fraction (LVEF) ≤ 40% at the time of randomization, and who were anemic (hemoglobin 9 to 12 g/dL). Other requirements were: transferrin saturation (Tsat) ≥ 15%; blood pressure ≤ 160/100 mm Hg; and serum creatinine ≤ 3.0 mg/dL (≤ 265 μmol/L). Subjects should have been treated for HF with stable, optimal pharmacological therapy (guidance regarding stable, optimal treatment was provided in the protocol). A complete list of inclusion/exclusion criteria are provided in the protocol (Appendix 1).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Darbepoetin alfa was provided as a clear, colorless, sterile protein solution (1 mL) in single-use vials containing the following unit doses: 100, 200, 500, and 1000 μg. Darbepoetin alfa was administered in the following dose strengths: 20, 30, 40, 50, 60, 80, 100, 130, 150, 200, 250, 300, 400, 500, and 600 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 closest dose strength allowed per protocol. Darbepoetin alfa was administered by subcutaneous (SC) injection once every 2 weeks (Q2W) and adjusted to achieve and maintain a hemoglobin concentration of 13.0 g/dL, not to exceed 14.5 g/dL. Subjects who were receiving ≤ 300 μg Q2W and achieved 2 consecutive hemoglobin concentrations of at least 13.0 g/dL, with no 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, rounded to the closest available dose strength. If a subject receiving the maximum QM dose (600 μg) of darbepoetin alfa had 3 consecutive monthly hemoglobin concentrations < 12.5 g/dL, the frequency of administration of investigational product was increased to Q2W and the dose reduced to half the most recent QM dose. The subject remained on Q2W schedule for the remainder of the study, irrespective of hemoglobin concentration achieved. Manufacturing lot numbers of darbepoetin alfa used in this study are provided in Appendix 18.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Placebo was provided as a clear, colorless solution in a single-use vial 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 simulated those occurring for subjects randomized to the darbepoetin alfa treatment group. Manufacturing lot numbers of placebo 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 study termination date, which was expected to occur approximately 57 months after enrollment of the first subject. The actual enrollment period was approximately 71 months, and the duration of treatment for the last subject enrolled was approximately 4 months, for a total study duration of approximately 75 months.

Study Endpoints:

Efficacy Endpoints:

Primary Endpoint:

- Time to death from any cause or first hospital admission for worsening HF, whichever occurs first

Secondary Endpoints:

- time to death from any cause
- time to cardiovascular death or first hospital admission for worsening HF, whichever occurs first
- change from baseline to month 6 in KCCQ Overall Summary Score
- change from baseline to month 6 in KCCQ Symptom Frequency Score

Tertiary Endpoints:

- time to all-cause death or first non-fatal cardiovascular (CV) event composite endpoint, which includes acute coronary syndrome (MI, unstable angina), cerebrovascular accident (stroke), venous thromboembolism (DVT or PE), resuscitated sudden death, hospitalization for worsening HF, and hospitalization where HF was a major component (first HF during an ongoing hospitalization)
- time to first hospital admission for worsening HF
- time to cardiovascular death
- time to new onset atrial fibrillation/flutter
- total number and duration of hospital admissions for worsening HF
- total number and duration of hospital admissions where HF was a major component
- change from baseline at each time point in each KCCQ Score
- change from baseline at each time point in each EQ-5D Score
- change from baseline at each time point in NYHA class
- change from baseline at each time point in eGFR
- health resource utilization

Safety Endpoints:

- treatment-emergent adverse events
- change from baseline in laboratory measurements
- vital signs
- anti-erythropoietic protein antibodies (anti-darbepoetin alfa and anti-epoetin alfa antibodies)

Statistical Methods:

One primary composite endpoint (time to all-cause mortality or first hospitalization for worsening HF) was evaluated in this study.

The secondary endpoints were to be tested only if the primary endpoint reached statistical significance. The 4 secondary endpoints were to be split into 2 parallel groups with unequal allocation of significance levels for testing. The 2 time-to-event endpoints (death, and cardiovascular death or first hospital admission for worsening HF) were tested at an overall significance level of 0.045 applying the Holm procedure (Holm, 1979). The 2 KCCQ endpoints (change in KCCQ overall summary and symptom frequency scores) were tested at an overall significance level of 0.005 while also applying the Holm procedure.

The principal analyses of time to event endpoints (primary, secondary and tertiary endpoints) employed the intent-to-treat (ITT) method and included all randomized subjects according to their randomly assigned treatment group. For the primary endpoint, Kaplan-Meier estimates were computed and graphically displayed. The difference between treatment groups was analyzed using a 2-sided log-rank test stratified by region and device at baseline. The treatment effect was evaluated in a Cox proportional hazards regression model stratified by region and device. As secondary analyses of the primary endpoint, treatment effect was evaluated with multivariate and univariate adjustment of baseline covariates. The hazard ratio (HR) and its 95% confidence interval (CI) for darbepoetin alfa versus placebo were estimated. The primary analysis of the KCCQ secondary endpoints used the mixed effects model adjusted for the stratification factors and baseline KCCQ score.

Safety endpoints were analyzed using the safety analysis set, which included all randomized subjects who received ≥ 1 dose of investigational product. The subject incidence of each adverse event was tabulated by system organ class (SOC), preferred term, severity, seriousness, and relationship to treatment. The following adverse events, as current identified or potential risks of darbepoetin alfa, were summarized separately: hypertension, embolic/thromboembolic events, convulsions, hypersensitivity reactions, antibody mediated pure red cell aplasia, cerebrovascular disorders, dialysis vascular access thrombosis, ischemic heart disease, cardiac failure, and malignancies. Clinical laboratory parameters and vital signs were summarized using descriptive statistics and/or shift tables.

Summary of Results:

Subject Disposition: A total of 2278 subjects were enrolled into the study, with 1136 subjects randomized to the darbepoetin alfa group and 1142 subjects randomized to the placebo group. Randomization was stratified by region (North America [28.3%]; Latin America/Asia [25.1%]; Western Europe/Israel/South Africa/Australia [26.7%]; Eastern Europe/Russia [19.9%]) and usage of ICD/CRT device (none [76.6%]; CRT [with or without ICD] [12.6%]; ICD without CRT [10.8%]). Of the randomized subjects, 2273 received ≥ 1 dose of investigational product (1133 darbepoetin alfa, 1140 placebo). Fifty-two percent of the enrolled subjects completed end of study assessments (51% darbepoetin alfa, 52% placebo), and 41.6% of enrolled subjects completed investigational product (43% darbepoetin alfa, 41% placebo).

Baseline Demographics:

Sex: 944 (41.4%) women; 1334 (58.6%) men

Age: Mean (range) 69.8 (24, 97) years

Ethnicity/Race: 1549 (68.0%) white or Caucasian, 324 (14.2%) Asian, 202 (8.9%) black or African American, 182 (8.0%) Hispanic or Latino, 4 (0.2%) American Indian or Alaska native, 1 (0.0%) Japanese, 1 (0.0%) native Hawaiian or other Pacific Islander, 15 (0.7%) other

Efficacy Results:

Primary Endpoint:

The study did not meet statistical significance on the primary endpoint of time to death from any cause or first hospital admission for worsening HF, whichever occurs first, in the ITT analysis (HR 1.01; 95% CI: 0.90, 1.13; stratified log-rank test p = 0.871).

A total of 1141 subjects experienced primary composite endpoint events:
576 (50.7%) darbepoetin alfa subjects and 565 (49.5%) placebo subjects. Annualized event rates (95% CI) were 19.5% (18.1, 21.0) in the darbepoetin alfa group and 19.2% (17.8, 20.6) in the placebo group.

Secondary multivariate analyses of the primary endpoint were performed to estimate adjusted treatment effects. Results from these analyses were consistent with the primary analysis. Subgroup analyses were also performed by age, sex, race, region, ICD/CRT usage, and eGFR category; in no subgroup was a treatment effect demonstrated. The results in the eGFR < 60 mL/min/1.73m2 subgroup were consistent with the overall results.

The following sensitivity analyses were conducted for the primary composite endpoint:

- For approximately 5.3% of subjects, incorrect device usage data (ie. the usage of ICD and/or CRT devices) was entered into IVRS for randomization. A sensitivity analysis was conducted using corrected device data from the clinical database to evaluate the potential impact of this discrepancy on the primary endpoint:
  HR 1.01; 95% CI 0.90, 1.14; stratified log-rank test p = 0.865
- heart transplants classified as CV death at the time of transplant:
  HR 1.02; 95% CI 0.91, 1.15; stratified log-rank test p = 0.739
- assessment of trend and consistency of treatment effect in the individual components of the primary composite endpoint
  - Time to any cause death:
    HR of 1.04; 95% CI 0.92, 1.19

- Time to first hospital admission for worsening HF:
  HR of 0.99; 95% CI 0.85, 1.16
- Homogeneity test: p = 0.522

- unadjusted stratification factors for treatment comparisons:
  HR 1.02; 95% CI 0.91, 1.15; log rank test p = 0.731
- on-treatment analysis: HR 0.98; 95% CI 0.86, 1.13; stratified log-rank test p = 0.815
- analysis that included all endpoints collected in the database, including the 19 events that occurred after the study termination date:
  HR 1.01; 95% CI 0.90, 1.14; stratified log-rank test p = 0.841

Secondary Endpoints:
Since the primary endpoint was not statistically significant, reported p-values for the secondary endpoints should be considered nominal.

- time to death from any cause:
  HR 1.04; 95% CI 0.92, 1.19; stratified log-rank test p = 0.512
- time to cardiovascular death or hospitalization for worsening HF:
  HR 1.01; 95% CI 0.89, 1.14; stratified log-rank test p = 0.922
- change from baseline to month 6 in KCCQ Overall Summary score:
  greater improvement with darbepoetin alfa compared with placebo at 6 months (least squares [LS] mean [standard error, SE] treatment difference, 2.20 [0.79] units, p = 0.005)
- change from baseline to month 6 in KCCQ Symptom Frequency score:
  greater improvement with darbepoetin alfa compared with placebo at 6 months (LS mean [SE] treatment difference, 2.29 [0.90] units, p = 0.011)

Subgroup analyses were also performed by age, sex, race, region, ICD/CRT usage, and eGFR category; in no subgroup was a treatment effect demonstrated. The results in the eGFR < 60 mL/min/1.73m2 subgroup were consistent with the overall results.

Tertiary Endpoints:

- Time to Event Tertiary Endpoints

  All time to event endpoints except new onset of atrial fibrillation/flutter were adjudicated. No difference was observed between treatment groups for any of the time to event endpoints (nominal p-values from stratified log rank test):

  - time to all-cause death or first non-fatal CV event composite endpoint:
    607 (53.4%) darbepoetin alfa subjects vs. 589 (51.6%) placebo subjects
    HR: 1.04 (95% CI: 0.93, 1.17), p = 0.487

    Assessment of individual components of composite endpoint:

    - time to first MI:
      64 (5.6%) darbepoetin alfa subjects vs. 74 (6.5%) placebo subjects
      HR: 0.84 (95% CI: 0.60, 1.18), p = 0.316
    - time to first unstable angina:
      18 (1.6%) darbepoetin alfa subjects vs. 12 (1.1%) placebo subjects
      HR: 1.49 (95% CI: 0.72, 3.09), p = 0.284
    - time to first cardiovascular accident (stroke):
      42 (3.7%) darbepoetin alfa subjects vs. 31 (2.7%) placebo subjects
      HR: 1.33 (95% CI: 0.83, 2.12), p = 0.229
    - time to first DVT:
      10 (0.9%) darbepoetin alfa subjects vs. 10 (0.9%) placebo subjects
      HR: 1.01 (95% CI: 0.42, 2.43), p = 0.979
    - time to first PE:
      6 (0.5%) darbepoetin alfa subjects vs. 2 (0.2%) placebo subjects
      HR: 3.20 (95% CI: 0.64, 15.90), p = 0.133

- time to first resuscitated sudden death:
  12 (1.1%) darbepoetin alfa subjects vs. 15 (1.3%) placebo subjects
  HR: 0.77 (95% CI: 0.36, 1.65), p = 0.502
- time to first HF during on ongoing hospitalization:
  25 (2.2%) darbepoetin alfa subjects vs. 22 (1.9%) placebo subjects
  HR: 1.08 (95% CI: 0.61, 1.93), p = 0.782

- time to first hospitalization for worsening HF:
  314 (27.6%) darbepoetin alfa subjects vs. 311 (27.2%) placebo subjects
  HR: 0.99 (95% CI: 0.85, 1.16), p = 0.915
- time to cardiovascular (CV) death:
  388 (34.2%) darbepoetin alfa subjects vs. 376 (32.9%) placebo subjects
  HR: 1.04 (95% CI: 0.91, 1.20), p = 0.556
- time to new onset atrial fibrillation/flutter (not adjudicated):
  52 (4.6%) darbepoetin alfa subjects vs. 57 (5.0%) placebo alfa subjects
  HR: 0.93 (95% CI: 0.63, 1.35), p = 0.686

Subgroup analyses were also performed by age, sex, race, region, ICD/CRT usage, and eGFR category; in no subgroup was a treatment effect demonstrated. The results in the eGFR < 60 mL/min/1.73m2 subgroup were consistent with the overall results.

No effect of treatment was observed for the remaining tertiary endpoints: number of hospital admissions for worsening HF, number of events of HF during an ongoing hospitalization, number of days hospitalized for worsening HF, number of days hospitalized for HF during an ongoing hospitalization, and change in NYHA class or eGFR over time.

Additional Analyses:

Major Adverse Cardiac Events (MACE) Endpoints:

During the course of the trial, MACE endpoints were added to the analysis plan to further inform the safety profile of ESA therapy. No difference was observed between treatment groups for any of the MACE endpoints (nominal p-values from stratified log rank test):

- first all-cause death, MI, or stroke (ITT analysis set):
  HR: 1.03 (95% CI: 0.91, 1.17), p = 0.589
- first CV death, MI, or stroke (ITT analysis set):
  HR: 1.05 (95% CI: 0.92, 1.20), p = 0.495

Safety Results:

Adverse events that occurred during the study are provided in the table below for the safety analysis set.

	Darbepoetin alfa (N = 1133)		Placebo (N = 1140)	
Adverse Events	n (%)	Exposure-adjusted subject incidence [a]	n (%)	Exposure-adjusted subject incidence [a]
All adverse events	1041 (91.9)	173.3	1049 (92.0)	187.1
Treatment-related adverse events	122 (10.8)	5.3	114 (10.0)	5.0
Fatal adverse events	432 (38.1)	16.3	408 (35.8)	16.0
Serious adverse events	781 (68.9)	46.7	741 (65.0)	44.7
Adverse events leading to IP withdrawal	221 (19.5)	8.9	229 (20.1)	9.5
Events of Interest				
Cardiac failure	438 (38.7)	21.1	459 (40.3)	23.5
Ischaemic heart disease	155 (13.7)	6.7	164 (14.4)	7.4
Embolic and thrombolic events	153 (13.5)	6.5	114 (10.0)	4.9
Hypersensitivity	99 (8.7)	4.3	96 (8.4)	4.2
Hypertension	81 (7.1)	3.5	69 (6.1)	3.0
Malignancies	69 (6.1)	2.8	68 (6.0)	2.8
Cerebrovascular disorders	61 (5.4)	2.5	45 (3.9)	1.9
Convulsions	4 (0.4)	0.2	5 (0.4)	0.2
Dialysis vascular access thrombosis	1 (0.1)	0.0	0 (0)	0.0
Antibody-mediated PRCA	0 (0)	0.0	0 (0)	0.0
Lack of efficacy-effect	0 (0)	0.0	0 (0)	0.0

IP = investigational product; PRCA = pure red cell aplasia.
[a] per 100 subject years

In subjects with a history of malignancy, the exposure-adjusted subject incidence rate (per 100 subject-years) for malignancies was 5.8 in the darbepoetin alfa group compared with 7.3 in the placebo group. Among subjects with no history of malignancy, the exposure-adjusted subject incidence rate for malignancies was 2.6 for the darbepoetin alfa group and 2.5 for the placebo group.

For serious adverse events, the risk difference between treatment groups of each preferred term was graphically presented with nominal p-values from Fisher's exact test (Figure 14-6.2.2). In this analysis, 5 serious adverse events (sudden cardiac death, cardiopulmonary failure, cerebrovascular accident, septic shock, and cholelithiasis) were reported at a higher incidence in the darbepoetin group than the placebo group with a nominal p-value of < 0.05. These differences were not supported by higher incidences of corresponding adverse events of interest, where available, or by higher incidences of high level terms in cases with no corresponding adverse event of interest.

- sudden cardiac death: The subject incidence of serious adverse events with the preferred term 'sudden cardiac death' was higher with darbepoetin alfa (exposure-adjusted rate per 100 subject year of 0.8) compared with placebo (0.3). However, high level term "death and sudden death" adverse event exposure-adjusted subject incidence rates (per 100 subject-year) were the same (0.3 for both groups) (Table 14 6.2.2).
- cardiopulmonary failure: The subject incidence of serious adverse events with the preferred term 'cardiopulmonary failure' was more frequent with darbepoetin alfa (exposure-adjusted rate per 100 subject year of 0.2) compared with placebo (0.0). However, the exposure-adjusted subject incidence rate per 100 subject years for cardiac failure, the corresponding adverse event of interest, was similar between treatment groups (21.1 and 23.5 for darbepoetin alfa and placebo, respectively).
- cerebrovascular accident: The subject incidence of serious adverse events with the preferred term 'cerebrovascular accident' was more frequent with darbepoetin alfa (exposure-adjusted rate per 100 subject year of 1.1) compared with placebo (0.6). The

preferred term of cerebrovascular accident has the corresponding adverse event of interest of cerebrovascular disorders; the exposure-adjusted subject incidence rate per 100 subject years for cerebrovascular disorders was similar between treatment groups (2.5 and 1.9 for darbepoetin alfa and placebo, respectively).

- septic shock: The incidence of serious adverse events with the preferred term 'septic shock' was more frequent with darbepoetin alfa (exposure-adjusted subject incidence of 0.8 per 100 subject year) compared with placebo (0.3). However, high level term "sepsis, bacteremia, viremia, and fungemia" exposure-adjusted subject incidence rates were similar (darbepoetin alfa 2.1; placebo 1.8).
- cholelithiasis: The incidence of serious adverse events with the preferred term of 'cholelithiasis' were more frequent with darbepoetin alfa (exposure-adjusted subject incidence of 0.4 per 100 subject year) compared with placebo (0.1). However, high level term 'cholecystitis and cholelithiasis' exposure-adjusted subject incidence rates were the same (darbepoetin alfa 0.8; placebo 0.8).

In the darbepoetin alfa treatment group, mean hemoglobin concentrations increased until reaching a plateau at approximately week 16. From week 17 until the end of study, the mean (standard error [SE]) achieved hemoglobin concentration based on a standardized AUC analysis was higher in the darbepoetin alfa group (12.81 [0.03] g/dL) than the placebo group (11.50 [0.04] g/dL).

In the darbepoetin alfa-treated group, 637 (56.2%) subjects had at least 1 hemoglobin excursion (> 14.5 g/dL) during the study, 334 (29.4%) subjects reached the hemoglobin target of ≥ 13.0 g/dL with no hemoglobin excursions, and an additional 151 (13.3%) subjects never achieved target (≥ 13.0 g/dL) hemoglobin levels. An ad hoc time-dependent analysis was conducted using the Anderson-Gill model (which takes into account recurrent events) to evaluate the potential association of hemoglobin excursions (> 14.5 g/dL) with an increased risk of adverse events of interest. This analysis compared the risk of adverse events of interest when a hemoglobin excursion occurred within 28 days prior to an event versus when no hemoglobin excursion occurred within 28 days prior to an event. Event times were censored at the last darbepoetin alfa dose date plus 30 days; events that occurred after this date or 28 days before starting investigational product were not included in the analysis. The results of this analysis did not demonstrate an increased risk of adverse events of interest with hemoglobin excursions > 14.5 g/dL.

More subjects in the darbepoetin alfa-treated group (900 [79.4%] subjects) had a serial hemoglobin rate of rise (ROR) > 1.0 g/dL/2 weeks during the study compared with the placebo-treated group (609 [53.4%] subjects). For the darbepoetin alfa treatment group, an ad hoc time-dependent analysis was conducted using the Anderson-Gill model (as described above) to evaluate the potential association of serial hemoglobin ROR > 1.0 g/dL/2 weeks with an increased risk of adverse events of interest. The results of this analysis did not demonstrate an increased risk of adverse events of interest with serial hemoglobin ROR > 1.0 g/dL/2 weeks.

Mean red blood cell (RBC) counts were higher from baseline to the end of study for the darbepoetin alfa group, with little change observed over time in the placebo group. No notable changes occurred during the study for mean white blood cell (WBC) counts in either treatment group. Mean reticulocyte and platelet count were lower at the end of the study than at baseline, with greater decreases observed in the darbepoetin alfa group compared with placebo. Transferrin saturation values for subjects in the darbepoetin alfa group increased relative to those in the placebo group beginning at week 6 and remained higher throughout the study. Serum ferritin values increased in both groups over time. There was a decrease in mean eGFR values from baseline in both treatment groups (-7.4 [3.0] mL/min/1.73m^2 darbepoetin alfa; -6.7 [3.2] mL/min/1.73m^2 placebo at month 66) that occurred in the context of increases in mean BUN (10.23 [3.81] mg/dL darbepoetin alfa; 5.48 [3.16] mg/dL placebo at month 66) and creatinine concentrations (0.26 [0.10] mg/dL darbepoetin alfa; 0.34 [0.11] mg/dL placebo at month 66). The mean (SE) systolic/diastolic blood pressure based on a standardized AUC analysis was 119.7 (0.5)/69.5 (0.3) mm Hg for the darbepoetin alfa treatment group and 118.8 (0.4)/68.7 (0.2) mm Hg for the placebo group. Neutralizing antibodies to erythropoietic protein were not detected in any subject tested.

Iron medications, were used by a similar proportion of subjects in both treatment groups at baseline and the proportion of subjects using these medications during the treatment period remained similar to baseline and was consistent between the groups. Fewer darbepoetin alfa subjects received ≥ 1 RBC transfusions (123 [10.9%]) compared with the placebo group (188 [16.5%]).

Conclusions:

The use of darbepoetin alfa targeting a hemoglobin concentration of 13 g/dL in subjects with HF and anemia (9 to 12 g/dL), did not reduce the risk of the primary composite outcome (time to all-cause death or first hospitalization for worsening HF) compared with placebo. In no subgroup was a treatment effect demonstrated, including subjects with eGFR <60 mL/min/1.73m^2. The overall subject incidence for adverse events, adverse events leading to withdrawal of investigational product, serious adverse events, and fatal adverse events were similar for both treatment groups. Of the adverse events of interest, the exposure-adjusted subject incidence rate was higher in the darbepoetin arm for hypertension, embolic and thrombotic events, and cerebrovascular disorders. The trend for greater occurrence of cerebrovascular disorder events in the darbepoetin alfa group was consistent with the adjudicated stroke results. The exposure-adjusted subject incidence rate for malignancies was not higher for the overall darbepoetin alfa cohort or for darbepoetin alfa subjects with a history of malignancy. No new safety findings for darbepoetin alfa were identified in this study.