## 1. SYNOPSIS

**Name of Sponsor:** Amgen, Inc. Thousand Oaks, CA

**Name of Finished Product:** Aranesp®

**Name of Active Ingredient:** Darbepoetin alfa

**Title of Study:** A Multicenter, Double-blind, Placebo-controlled Rollover Study to Protocol 20010103 of Darbepoetin Alfa for the Treatment of Anemia of Cancer

**Investigator(s) and Study Center(s):** This study was conducted at 93 sites across multiple regions including Western Europe, North America, Australia, and Central and Eastern Europe.

**Publication(s):** None.

**Study Period:** 10 August 2004 (first subject enrolled) through 17 January 2007 (last subject completed end-of-study visit)

**Development Phase:** 3

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**Introduction and Objectives:**

Study 20010103 was the antecedent phase 3 pivotal study of darbepoetin alfa in anemic subjects with active nonmyeloid malignancies who were not receiving chemotherapy or radiotherapy. The primary objective was to evaluate the efficacy of darbepoetin alfa given Q4W for 16 weeks in reducing the total occurrences of red blood cell (RBC) transfusions. Due to the desirability of characterizing the safety profile of darbepoetin alfa over a longer period of time, the extension study 20020149 was designed to allow subjects completing study 20010103 to receive an additional 16 weeks of blinded treatment, with an emphasis on safety outcomes across a total of 32 weeks.

**Methodology:**

After 16 weeks of blinded treatment on study 20010103, subjects who completed the study were eligible to roll over into study 20020149, maintaining their blinded randomized treatment for an additional 16 weeks, or a total of up to 32 weeks.

Subjects received darbepoetin alfa at a dose of 6.75 µg/kg or placebo SC Q4W, ie, at weeks 1, 5, 9, and 13, with an end-of-treatment visit (week 17), an end-of-study visit (week 19) and follow-up for survival status (continuing for 2 years from the completion of study 20010103). Treatment was designed to maintain HGB at ≤ 12 g/dL; the dose of investigational product was withheld or reduced accordingly based on HGB monitoring throughout the study.

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| **Number of Subjects Planned:** | 750 estimated |
| **Number of Subjects Enrolled:** | 371 |
| **Number of Subjects Treated:** | 350 (all 371 were evaluable for safety) |
| **Sex:** | 171 males (46%), 200 females (54%) |
| **Age:** | Mean 65.3 (SD 11.1) years |
| **Ethnicity (Race):** | 95% white, 4% black, 1% other |

**Diagnosis and Main Criteria for Eligibility:**

Successful completion of study 20010103, informed consent signed for study 20020149

**Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:**

Darbepoetin alfa was administered by SC injection at a dose of 6.75 μg/kg Q4W. Darbepoetin alfa was provided at a concentration of 1000 μg/mL in vials containing approximately 1.0 mL of a human serum albumin-free polysorbate formulation.

**Duration of Treatment:** Darbepoetin alfa or placebo was administered once every 4 weeks for 4 doses.

**Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:**

Placebo was provided in containers identical to darbepoetin alfa and administered by SC injection on the same schedule (ie, Q4W).

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**Study Endpoints**

**Primary Safety Endpoint:** Incidence of adverse events

**Secondary Safety Endpoints:**

- Formation of antibodies to darbepoetin alfa
- Survival
- Laboratory parameters
- Vital signs

**Efficacy Endpoints:**

- RBC transfusions
- HGB concentration and HGB change from baseline

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**Statistical Methods:**

Standard tabulations were constructed for adverse events incidence, listing preferred terms grouped by MedDRA system organ class, and additionally tabulated in descending order of incidence. Standard summary statistics were generated for laboratory analytes, vital signs, and incidence of antibody formation, as well as demographics, baseline characteristics, study drug exposure, and other descriptive variables. Survival was analyzed using the Cox proportional hazards model either stratified or adjusted for the stratification factors used at randomization, and additionally including enrollment status into study 20020149 as a time-dependent covariate to adjust for possible bias. Median survival was estimated using Kaplan-Meier curves with supporting statistics.

Subject incidence of transfusions given any time during the 32-week treatment period was expressed as a simple proportion with summary statistics; no inferential testing was employed. Descriptive statistics were used to display HGB concentration and changes in HGB during the treatment period.

## Summary of Results

### Subject Disposition:

A total of 371 subjects were enrolled into the study: 173 previously randomized to placebo and 198 randomized to receive darbepoetin alfa. Of these, 350 subjects received study drug during study 20020149. The remaining 21 subjects were not dosed during extension treatment due to their HGB being above the target; these subjects were however followed for all observations and were evaluable for safety. Most subjects were white and there were slightly more females than males; median age was 67 years (range: 27, 89). The most common malignancies were non-small cell lung, breast, prostate, colorectal, and kidney cancers. Median duration on treatment was 33.0 weeks for both treatment groups. The most common reasons for premature study discontinuation were death, disease progression, and consent withdrawn.

### Safety Results:

The percent of subjects who experienced 1 or more adverse events in the darbepoetin alfa group vs placebo group was 78.9% vs 83.7%, respectively. The most common adverse events were fatigue, constipation, dyspnea, nausea, and anorexia. Three adverse events occurred with a between-group difference greater than 5%: fatigue, headache, and anemia—all occurring at a higher incidence in the placebo group.

Thirty-two subjects (16.1%) died on-study in the darbepoetin alfa group compared with 22 subjects (12.8%) in the placebo group. The majority of deaths on study were attributed by the investigator to the subjects' underlying neoplastic disease. Overall median survival time was shorter in the darbepoetin alfa group relative to the placebo group (37.1 weeks vs 47.0 weeks, respectively). The hazard ratio for death in the darbepoetin alfa group relative to placebo was 1.22 (95% CI: 1.03, 1.45; $p = 0.022$) based on Cox regression stratified for randomization factors but unadjusted for other covariates. Predictors for death included disease stage, gender, screening HGB, geographic region, recent RBC transfusion, tumor type, and ECOG score.

Serious adverse events were experienced by 30.7% of subjects in the darbepoetin alfa group vs 32% of subjects in the placebo group. The majority of serious adverse events were associated with the underlying neoplastic disease. Cardiovascular/thromboembolic events occurred at a low incidence overall, but were slightly higher in the darbepoetin alfa group relative to placebo (8.5% vs 7.6%, respectively). The low incidences of individual events preclude definitive conclusions. None of these adverse events of interest (including death) appeared to be associated with maximum HGB attained or with rate of HGB rise.

No notable blood chemistry or hematologic toxicities were detected. No subject in either treatment group developed neutralizing anti-erythropoietic antibodies.

### Efficacy Results:

Among subjects who continued into extension treatment, 1 or more transfusions were received by 15.2% of subjects receiving darbepoetin alfa during the entire 32-week treatment period vs 26.0% of subjects receiving placebo. HGB in the darbepoetin alfa group increased from a pretreatment median of 9.9 g/dL to an end-of-treatment median of 11.3 g/dL, a mean increase of 1.29 g/dL. In the placebo group, median HGB increased from 10.1 g/dL to 10.5 g/dL, a mean increase of 0.5 g/dL.