Statistical Analysis Plan

Protocol Title:	A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Darbepoetin alfa Administered at 500 µg Once-Every-3-Weeks in Anemic Subjects With Advanced Stage Non-small Cell Lung Cancer Receiving Multi-cycle Chemotherapy
Short Protocol Title:	Placebo-controlled Non-inferiority Study in CIA NSCLC Subjects
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Table of Contents

List of Table

List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
ATE	Arterial thromboembolic event
Baseline Value	The baseline value is the value measured on study day 1 before the first dose of investigational product. If such a measurement is not available, the closest value measured within 7 days before randomization**/study day 1** will be used as the baseline value. For assessments not scheduled to be performed on study day 1, the baseline value is the value from the screening period measured closest to study day 1. The definition above will be used to derive "baseline" hemoglobin but it should be noted that the "screening" hemoglobin is the value taken just prior to randomization to determine eligibility and randomization stratum; and the "pre-chemotherapy" hemoglobin is the value taken just prior to the start of first line chemotherapy for NSCLC. It should also be noted that "baseline" in terms of imaging studies will be defined as the imaging studies performed just prior to the start of first line chemotherapy for NSCLC.
CIA	Chemotherapy-induced anemia
CTCAE	Common Toxicity Criteria for Adverse Events
DMC	Data monitoring committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
End of the Efficacy Treatment Period	End of the efficacy treatment period is defined as 21 days after either the last dose of IP or the last dose of chemotherapy, whichever is later; the EOETP will be set to the EOTP if the EOETP exceeds the EOTP
End of Study (EOS)	The end of study is defined for a subject as either the date of death or the date when the long term follow-up period ends (i.e., when 2700 deaths have occurred) **or early study termination**, whichever comes first. For subjects lost to follow-up, this will be the date of last contact

Abbreviation or Term	Definition/Explanation
End of Treatment Period	The treatment period ends at the end of treatment period visit which is scheduled to occur at the next Q3W visit following disease progression. Subjects who are unable to continue Q3W visits and Q9W imaging studies until progression should complete EOTP procedures no later than their next Q3W visit (± 6 days). The date captured on the end of treatment period electronic case report form (eCRF) will not be used in determining time to disease progression; time to disease progression will be derived from the dates of imaging studies.
EOETP	End of the Efficacy Treatment Period
EOI	**Event of Interest**
EOS	End of Study
EOTP	End of Treatment Period
ESA	Erythropoiesis stimulating agent
First-line chemotherapy	**Initial (first) chemotherapy given for a disease.**
g/dL	Gram per deciliter
IBG	**Independent Biostatistics Group. This group provides statistical support to a data monitoring committee (DMC) but is not a voting member of the DMC.**
IP	Investigational Product
IVRS	Interactive Voice Response System
Kg	Kilogram
LTFU	Long term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
MOI	**Medication of Interest**
NSCLC	Non-small cell lung cancer
ORR	**Objective (tumor) response rate**
OS	Overall survival

Abbreviation or Term	Definition/Explanation
PFS	Progression-free survival
Pre-chemotherapy" Hemoglobin	The hemoglobin value taken just prior to the start of first-line chemotherapy for NSCLC
Q3W	Once-every-3-weeks
Randomization Day	This is the day subjects are randomized (enrolled) into the study through the interactive voice response system (IVRS). The randomization day may occur on the same day as the first dose of investigational product or it may occur up to 4 days before the first dose of investigational product.
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
Screening Hemoglobin	The local laboratory hemoglobin value obtained within 7 days prior to randomization; this is used to **confirm** eligibility and randomization stratum and will be used as a stratification factor for overall survival, progression-free survival, and incidence of transfusions from weeks 5 (ie, day 29) to end of treatment
Study Day 1.	This is the first day of investigational product administration. All laboratory assessments on study day 1 are to be completed before study drug administration and will be used as baseline measurements. The randomization day may occur on the same day as the first dose of investigational product or it may occur up to 4 days before the first dose of investigational product
Study Entry Hemoglobin	**The hemoglobin value obtained closest to the date when the subject signs and dates the informed consent form (ICF). This may be a central or local laboratory hemoglobin value.**

Abbreviation or Term	Definition/Explanation
Study Termination Date	The **planned** study termination date will be the date when the 2700th death is reported in the clinical trial database **or at an early termination date, if applicable**. Once this death is reported **or the early termination date is reached,** sites will be instructed to enter all outstanding data into the clinical trial database, the database will be cleaned, a snapshot will be taken, the database will be locked, and the primary analysis will be performed. Any additional deaths reported during the entry of outstanding data which occur **on or** prior to the termination date will be counted in the primary analysis.
Study Week 1	The 7-day period beginning with study day 1 is considered study week 1.
Treatment Period	The treatment period begins on study day 1 and ends at the next Q3W visit following disease progression. Subjects who are unable to continue Q3W visits and Q9W imaging studies until progression should complete EOTP procedures no later than their next Q3W visit (± 6 days).
TVE	Thrombovascular event
VTE	Venous thromboembolic event

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20070782, darbepoetin alfa dated 14 September 2017. The scope of this plan includes the **planned final** analysis and will be executed by the Amgen Global Biostatistics department unless otherwise specified.

This SAP does not cover the planned interim analyses; these are outlined in the Data Monitoring Committee charter and maintained by the Independent Biostatistics Group (IBG; PRA Health Sciences, Charlottesville, Virginia). The SAP also does not cover the unplanned interim analysis performed in Q4 2016.

The SAP was amended on 30 June 2017 to reflect a recommendation by the independent Data Monitoring Committee to terminate the study early and incorporates the current SAP Template and Tables, Figures, and Listing guidance.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate non-inferiority of overall survival (OS) when comparing subjects on darbepoetin alfa treated to a hemoglobin ceiling of 12.0 g/dL to subjects treated with placebo	• Overall survival
Secondary	
• To demonstrate non-inferiority of progression-free survival (PFS) when comparing subjects on darbepoetin alfa treated to a hemoglobin ceiling of 12.0 g/dL to subjects treated with placebo	• Progression-free survival
• To demonstrate superiority in reducing the incidence of red blood cell (RBC) transfusions when comparing subjects on darbepoetin alfa treated to a hemoglobin ceiling of 12.0 g/dL to subjects treated with placebo	• Incidence of at least 1 RBC transfusion or hemoglobin $\leq$ 8.0 g/dL from week 5 (day 29) to end of the efficacy treatment period (EOETP; defined as 21 days after either the last dose of IP or the last dose of chemotherapy, whichever is later; the EOETP will be set to the EOTP if the EOETP exceeds the EOTP)
• If non-inferiority hypotheses are confirmed for both OS and PFS and the superiority hypothesis is confirmed for the transfusion endpoint, a superiority hypothesis will then be tested for both OS and PFS.	Overall all and progression-free survival
Other Endpoints	
• To assess other safety and efficacy parameters in subjects on darbepoetin alfa treated to a hemoglobin ceiling of 12.0 g/dL compared to subjects treated with placebo	• Incidence of adverse events such as thrombovascular events (TVE), venous thromboembolic events (VTE), and AEs associated with RBC transfusions • Objective tumor response **rate** • Incidence of neutralizing antibody formation to darbepoetin alfa

	• Incidence of at least 1 RBC transfusion or hemoglobin ≤ 8.0 g/dL from study day 1 to EOETP • Change in hemoglobin from baseline to EOETP

2.2 Hypotheses and/or Estimations

The primary hypothesis to be tested is that the OS of subjects treated with darbepoetin alfa is not worse than the OS of subjects treated with placebo. The hypothesis for OS will be confirmed if the upper confidence limit for the hazard ratio (darbepoetin alfa to placebo) is less than 1.15 using a 1-sided significance level of 0.025.

If the primary hypothesis is confirmed, the secondary hypothesis that PFS is not worse in subjects treated with darbepoetin alfa than the PFS in subjects treated with placebo will be tested. The hypothesis for PFS will be confirmed if the upper confidence limit for the hazard ratio is less than 1.15 using a 1-sided significance level of 0.025.

If both the OS and PFS hypotheses are confirmed, the hypothesis that the incidence of RBC transfusions is less in subjects treated with darbepoetin alfa than in subjects treated with placebo will be tested. This hypothesis will be confirmed if the p-value is < 0.05 from a two-sided Cochran-Mantel-Haenszel test comparing darbepoetin alfa to placebo with respect to the incidence of at least 1 RBC transfusion or hemoglobin ≤ 8.0 g/dL from day 29 to EOETP.

If non-inferiority hypotheses are confirmed for both OS and PFS and the superiority hypothesis is confirmed for the transfusion endpoint, a superiority hypothesis will then be tested for both OS and PFS. These hypotheses will be confirmed by examining the p-values associated with hazard ratios from both OS and PFS; the Hochberg procedure will adjust for multiplicity and maintain an overall two-sided significance level of 0.05.

3. Study Overview

3.1 Study Design

This is a double-blind, randomized, placebo-controlled, phase 3 study in CIA subjects receiving multi-cycle chemotherapy for the treatment of advanced stage NSCLC cancer. Randomization will occur in a 2 to 1 ratio (darbepoetin alfa to placebo) and will be stratified by histology (squamous versus other), screening hemoglobin (< 10.0 g/dL versus ≥ 10.0 g/dL), and geographic region **(see Section 4.1 for regions).**

Subjects will receive IP Q3W during the treatment period. IP will be discontinued within 3 weeks after the completion of chemotherapy, or upon the determination of disease progression, whichever occurs first. Study visits Q3W and imaging studies Q9W will occur during the treatment period until disease progression.

An end of the treatment period visit will occur at the next Q3W visit after disease progression has been determined. **Hemoglobin and other hematology and chemistry values collected beyond this period (ie, beyond 3 weeks after disease progression) will be excluded from analysis.** Subjects will then enter long term follow-up and will be followed for survival until death, until approximately 2700 deaths have occurred **or until early study termination**.

3.2 Sample Size

A total of 2700 deaths **were planned to** be observed in order to exclude a hazard ratio (darbepoetin alfa to placebo) of 1.15 with a 1-sided significance level of 0.025. With 2700 deaths, the study is powered at just over 90% if the true hazard ratio is 1.0 (approximately 93%). To observe 2700 deaths, the study **planned to** randomize a total of 3000 subjects which assumes a 7-year enrollment period, a 3-year follow-up after last subject enrolled, a 1-year survival rate of 51% (Sandler et al, 2006), and a common exponential drop-out rate of 0.0511.

Excluding a hazard ratio of 1.15 corresponds to excluding a decrease in median survival of approximately 1.6 months in the darbepoetin alfa arm group compared to placebo. The estimated decrease in survival has equipoise with the decreased risk of the need for RBC transfusions. This estimation assumes survival time is exponentially distributed which allows for a conversion from a hazard ratio to medians (i.e., hazard ratio = $\text{median}_{\text{placebo}}/\text{median}_{\text{darbepoetin alfa}}$). A median survival of 12.3 months (Sandler et al, 2006) was assumed in the placebo arm in order to derive the difference in medians that corresponds to a hazard ratio of 1.15.

The study was terminated early based on a recommendation by the independent Data Monitoring Committee with a sample size of 2549 subjects. The study was closed to further

enrollment as of 8 May 2017 and the last data are anticipated to be collected as of 7 June 2017.

4. Covariates and Subgroups

4.1 Planned Covariates

- Stratification factors:
  - Geographic region **(some regions may be combined for analysis):**
    - **Region 1: Belgium, Germany, Israel, Italy, Luxembourg, Netherlands, Spain, Switzerland, South Africa, UK**
    - **Region 2: Bulgaria, Czech Republic, Greece, Poland, Romania, Russia, Serbia, Slovenia, Ukraine**
    - **Region 3: Argentina, Brazil, Chile, Hong Kong, South Korea, Malaysia, Mexico, Philippines, Taiwan**
    - **Region 4: India**
    - **Region 5: Canada, United States (reference group)**
    - **Region 6: China**
    - **Region 7: Japan (analyzed as part of Region 3)**
  - Histology: Squamous vs non-squamous cell (reference group)
  - Screening hemoglobin level: <10 g/dL vs >=10 g/dL (reference group)
- Potentially **clinically important** covariates:
  - NSCLC platinum-based chemotherapy vs. other chemotherapy (reference group)
  - NSCLC Targeted therapy (anti-EGFr or anti-angiogenic agents or other) vs. none (reference group)
  - Baseline serum erythropoietin: ≤100 mU/mL vs >100 mU/mL (reference group)
  - History of VTEs: yes vs. no (reference group)

Note that the reference group will be coded a "0" in any statistical modeling including stratification factors and/or covariates.

4.2 Subgroups

The subgroup of subjects who were not impacted by the early study closure to may be analyzed as a sensitivity analysis for the primary and secondary endpoints (overall survival, progression-free survival and incidence of transfusion or hemoglobin ≤ 8 g/dL) as well as the analyses of investigational product dosing and changes in dosing. For the analysis of overall survival, this would include subjects who were lost to follow-up or who died prior to 8 June 2017. For progression-free survival, this would include subjects who were withdrawn, lost to follow-up or who died or had radiographic progression prior to 8 June 2017. For incidence of transfusion or hemoglobin ≤ 8 g/dL, investigational product dosing and changes in dosing, this would include subjects who were withdrawn, lost to follow-up or completed chemotherapy prior to 8 June 2017.

These subgroups and planned covariates will be re-examined and appropriately re-categorized before the analysis. If a subgroup only contains less than 10% of the total study population, it will be combined with another subgroup in the analysis.

5. Definitions

Best Overall Response

A subject's best overall response during the study will be categorized in the following order: complete response, partial response, stable disease, disease progression, not evaluable, missing due to clinical progression, and missing for reasons other than clinical progression.

Change in hemoglobin from baseline to EOETP

The change score is the difference between the baseline hemoglobin value and the EOETP value (i.e., EOETP value – baseline value). Post-baseline hemoglobin values within 28 days after a RBC transfusion will not be used in the calculation of change. The last available post-baseline hemoglobin, not occurring in the 28 days after a RBC transfusion, will be used to calculate change in the event that the EOETP value is missing or occurred in the 28 days after a RBC transfusion. Subjects without a post-baseline value that did not occur in the 28 days after a RBC transfusion and subjects missing a baseline hemoglobin will be excluded from the analysis. Only central laboratory values will be used. Because the EOETP will vary by subject, the change in hemoglobin from baseline will also be summarized at specific time points of week 13 and week 16.

Events of Interest (EOI): EOIs for Aranesp are as follows:

Event of Interest	Search Strategy	Scope
Ischaemic Heart Disease, including MI	Ischaemic Heart Disease SMQ	Narrow
Mortality and/or Tumor Progression	Malignancies SMQ	Narrow
Cerebrovascular disorders	Central nervous system vascular disorders SMQ	Narrow
Hypertension	Hypertension SMQ	Narrow
Cardiac failure	Cardiac failure SMQ	Narrow
Thromboembolic events, venous	Embolic and thrombotic events, venous	Narrow
Convulsions	Convulsions SMQ	Narrow & Broad
Severe cutaneous reactions	Severe cutaneous reactions SMQ	Narrow & Broad
Hypersensitivity	Hypersensitivity SMQ	Narrow & Broad
PRCA	Antibody-mediated Pure Red Cell Aplasia AMQ	

Hemoglobin Threshold

A hemoglobin that increases to >12 g/dL at any time during the treatment period is considered to have exceeded the threshold. This increase will be summarized both by including and excluding hemoglobin values that occurred in the 28-day period following an RBC transfusion.

Medications of Interest (MOI): MOIs for Aranesp Oncology are as follows based on values as of **Q2 2017** or later:

Antihypertensives
Antimicrobials
Antithrombotic agents
Colony stimulating factors
Epoetins
Histone deacylating inhibitors
Hypomethylating agents
Iron
Iron chelating agents
Lenalidomide
Methotrexates
Platelets
Thalidomide
Thrombopoesis stimulating factors

Non-response (to investigational product)

A non-responder is a subject who, after study day 35, received two transfusions that are ≥21 days apart and ≤42 days apart.

Objective tumor response rate (ORR)

The incidence of a complete or partial response at any time during the study. Response will be determined by the investigator's assessment of the scans using the version of RECIST specified in the protocol at the time of subject enrollment.

Overall survival (OS)

Time from randomization to date of death. Subjects will be censored on the date of last contact (ie, the date the subject was last known to be alive) if they are not known to be dead.

Progression-free survival (PFS)

Time from randomization to date of radiographic disease progression or death from any cause, whichever event occurs first. Subjects without either event will be censored on the date of their last disease assessment. Disease progression will be based on the investigator's assessment of scans using the version of RECIST specified in the protocol at the time of subject enrollment.

Rate of rise in hemoglobin >1.5 g/dL in 21 days

The occurrence of a hemoglobin that increases by >1.5 g/dL in any 21-day period in the treatment

period. This will be summarized both by keeping a 21-day window after each RBC transfusion and **excluding** a 21-day window after each RBC transfusion.

RBC transfusion or hemoglobin ≤8.0 g/dL from week 5 (day 29) to EOETP

Any RBC transfusion (packed RBCs or whole blood) given or a hemoglobin ≤8.0 g/dL on or after study day 29 until the EOETP, inclusive.

RBC transfusion or hemoglobin ≤8.0 g/dL from week 1 (day 1) to EOETP

Any RBC transfusion (packed RBCs or whole blood) given or a hemoglobin ≤8.0 g/dL on or after study day 1 until the EOETP, inclusive.

RBC transfusion from week 5 (Day 29) to EOETP

Any RBC transfusion (packed RBCs or whole blood) given on or after study day 29 until the EOETP, inclusive.

RBC transfusion from week 1 (Day 1) to EOETP

Any RBC transfusion (packed RBCs or whole blood) given on or after study day 1 until the EOETP, inclusive.

Thrombovascular event (TVE)

Thrombovascular events are adverse events that include arterial thromboembolic events (ATEs), venous thromboembolic events (VTEs), and unspecified/mixed thromboembolic events. These events will be coded using MedDRA version **20.0** (or higher) and identified using a Standardized MedDRA Query (SMQ 20000081, "embolic and thrombotic events") or more appropriate query available at the time of analysis. **Arterial thromboembolic event (**ATEs**)**, **Venous thromboembolic event (**VTEs**) and Unspecified/mixed thromboembolic events** are described below:

- **ATE**

  ATEs include stroke, transient ischemic attack (TIA), acute coronary syndromes (ACS), and other arterial thrombosis/embolism. These events will be coded using MedDRA version **20.0** (or higher) and identified using the sub-SMQ 20000082 ("embolic and thrombotic events, arterial") or more appropriate query available at the time of analysis.

- **VTE**

  VTEs include deep vein thrombosis (DVT), pulmonary embolism (PE), and other venous thrombosis excluding superficial venous thrombosis. These events will be coded using MedDRA version **20.0** (or higher) and identified using the sub-SMQ 20000084 ("embolic and thrombotic events, venus") or more appropriate query available at the time of analysis. In

addition, VTEs will be distinguished by whether or not they were confirmed by imaging. The primary analysis of VTEs will include fatal VTEs and VTEs confirmed by imaging; a sensitivity analysis will summarize all VTEs regardless of severity or confirmation.

- **Unspecified/mixed thromboembolic event**
  Unspecified/mixed thromboembolic events include thromboembolic events where the vessel type is either unspecified or a mix of arterial and venous. These events will be coded using MedDRA version **20.0** (or higher) and identified using the sub-SMQ 20000083 ("embolic and thrombotic events, vessel type unspecified and mixed arterial and venous") or more appropriate query available at the time of analysis.

Time to Progression (TTP)

Time from randomization to date of radiographic disease progression. Subjects without progression will be censored on the date of their last disease assessment. Disease progression will be based on the investigator's assessment of scans using the version of RECIST specified in the protocol at the time of subject enrollment.

Treatment Group

Subjects were randomized to 1 of 2 treatment groups: darbepoetin alfa (500 µg) Q3W or placebo Q3W in a 2:1 allocation.

Treatment-emergent Adverse Event

A treatment-emergent adverse event is an adverse reported via the adverse event summary eCRF with an onset date between study day 1 and 30 days after the last dose of IP, inclusive, with one exception: VTEs and adverse events associated with RBC transfusions can have an onset date of 30 days after the last dose of IP or the EOTP visit, whichever is later.

6. Analysis Sets

6.1 Primary Analysis Set

The primary analysis set will include all randomized and consented subjects **with non-small cell lung cancer** who receive at least one dose of investigational product. Subjects will be analyzed according to their randomized treatment group. The analysis of **overall survival, progression-free survival, time to progression, response-related endpoints, serious AEs, events of interest, VTE and all efficacy endpoints** (except for the endpoint of transfusion or hemoglobin ≤ 8.0 g/dL from day 29 to EOETP) will be performed using the primary analysis set.

6.1.1 Transfusion from Week 5 to EOETP Primary Analysis Set

The transfusion from week 5 to EOETP primary analysis set will include all subjects in the primary analysis set whose EOETP is ≥ day 29. The analysis of the endpoint of transfusion or hemoglobin ≤ 8.0 g/dL from day 29 to EOETP will be performed using this primary analysis set.

6.1.2 Full Analysis Set

The full analysis set will include all randomized and consented subjects. Subjects will be analyzed according to their randomized treatment group. A sensitivity analysis of overall survival will be performed using the full analysis set.

6.1.3 Radiographic Endpoint Primary Analysis Set

The radiographic endpoint primary analysis set will include all randomized and consented subjects who have not had disease progression prior to randomization and who received at least one dose of investigational product. Subjects will be analyzed according to their randomized treatment group.

6.1.4 Radiographic Endpoint Full Analysis Set

The radiographic endpoint full analysis set will include all randomized and consented subjects who have not had disease progression prior to randomization. Subjects will be analyzed according to their randomized treatment group. This data set will be used as a sensitivity analysis for progression-free survival.

6.2 Safety Analysis Set

The safety analysis set will include all randomized and consented subjects who receive at least one dose of investigational product. Subjects will be analyzed according to their actual treatment group. If a subject is randomized to placebo but receives at least 1 dose of darbepoetin alfa, then that subject will be analyzed as a darbepoetin alfa subject. If a subject

is randomized to darbepoetin alfa but only receives placebo, then that subject will be analyzed as a placebo subject. The safety analysis set will be used to analyze adverse events, VTEs, hematologies, chemistries, dosing, vital signs, and antibody data.

6.3 Per Protocol Sets

Since poor adherence to the protocol could have the potential to bias the results towards a conclusion of non-inferiority, a sensitivity analysis will be performed on a per protocol set to confirm results from the primary analysis set. The sensitivity analysis using this per protocol set will be performed for overall survival and **progression free survival.** The per protocol set will include subjects in the primary analysis set who meet all of the following additional criteria **(also see Appendix A):**

- had metastatic **(Stage IV)** or advanced stage IIIB with malignant pleural effusion **(prior to Amendment 3)** NSCLC
- **no disease progression prior to study day 1**
- **no history of or current cancer diagnosis other than NSCLC**
- **had baseline pre-chemo scan prior to randomization (for PFS only)**
- had an ECOG performance status of 0 or 1 at screening
- had a life expectancy > 6 months based on the judgment of the investigator at screening
- did not receive erythropoiesis stimulating agents within the 28 days prior to screening
- did not have a documented history of pure red cell aplasia
- dosed per protocol through week 7 with the correctly assigned investigational product (this includes receiving planned doses and dose adjustments per section 6.1.2 of the protocol)
- received first-line cyclic chemotherapy for NSCLC during the treatment period
- did not receive erythropoiesis stimulating agents, other than investigational product as defined in the protocol, during the treatment period.

6.4 Interim Analyses Set(s)

The interim analyses will be conducted on subjects in primary analysis set who are in the clinical trial database at the time of the interim analyses. **The interim analysis may include subjects with only partial data** (eg, a subject may have only been on study through week 3).

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

An Independent Biostatistics Group (IBG) will perform regular safety and interim analyses for an independent Data Monitoring Committee (DMC). The DMC will review all available safety data regularly; once every 6 months for the first 2 years and once a year thereafter. In addition, the IBG will conduct 5 formal interim analyses to assess harm (ie, inferiority of darbepoetin alfa relative to placebo) which will occur when approximately 10%, 20%, 30%, 40% and 60% of the planned total of 2700 deaths have been observed. If warranted from these reviews, the DMC may request additional safety data, recommend modifying or stopping the treatment, or recommend suspending randomization. In addition, the DMC will review enrollment status and assess changes in the practice of medicine to make recommendations regarding the ongoing feasibility of the trials.

The IBG and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and will not have any direct contact with study center personnel or subjects. The DMC will communicate major safety concerns and recommendations regarding study modification or termination based on the safety parameters to Amgen in accordance with the DMC charter.

Records of all meetings will be approved by the DMC and maintained by the IBG on behalf of the DMC Chair for the duration of the study. Records of all meetings will be transferred and archived in the eTMF (in accordance with SOP-024846) at the conclusion of the study. Further details are provided in the DMC charter.

7.2 Primary Analysis

The primary analysis will be triggered by the study termination date. The **planned** study termination date will be the date when the 2700th death is reported in the clinical trial database **or the study is otherwise stopped**. **The study was terminated early based on an independent Data Monitoring Committee recommendation. The study was closed to further enrollment as of 8 May 2017.** Sites **were** instructed to enter all outstanding data into the clinical trial database **as of 7 June2017**, the database will be cleaned, a snapshot will be taken, the database will be locked, and the primary analysis will be performed. Any additional deaths reported during the entry of outstanding data which occur on or prior to the termination date will be counted in the primary analysis. **The primary analysis will also serve as the final analysis for this study.**

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study uses the RAVE database.

8.3 Handling of Missing and Incomplete Data

8.3.1 Missing Survival Data

Subjects who did not die on study and are lost to follow-up will be censored on the date last known to be alive.

8.3.2 Missing Progression Data

In order to minimize missing progression data, the study is designed to follow subjects until documented radiographic disease progression. If radiographic disease progression is not observed, the primary analysis **of progression-free survival and time to progression** will censor subjects at their last on-study disease assessment date.

8.3.3 Missing Transfusion Data

Subjects who withdraw from study prior to day 29 will have missing data for the secondary endpoint, "RBC transfusion or hemoglobin $\leq$ 8.0 g/dL from week 5 (day 29) to EOETP"; these subjects will be excluded from the analysis of this endpoint.

8.3.4 Missing Hemoglobin Data

For the endpoint "Change in hemoglobin from baseline to EOETP", the last available post-baseline hemoglobin, not occurring in the 28 days after a RBC transfusion, will be used to calculate change in the event that the EOETP value is missing or occurred within 28 days after a RBC transfusion. Subjects without a post-baseline value that did not occur in the 28 days after a RBC transfusion and subjects with a missing baseline hemoglobin will be excluded from the analysis of this endpoint.

8.3.5 Missing Adverse Event and Concomitant Medication Data

Missing data for adverse events and concomitant medication will not be imputed. Adverse event and concomitant medication data will be analyzed as observed with the exception of missing dates. Missing or incomplete dates for adverse event or concomitant medication data will be handled according to the following rules in order to estimate when the event occurred/medication was taken and the duration:

8.3.5.1 Imputing Partial or Missing Start Dates

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the month is unknown, then:
  - If the year matches the first dose date, then impute the month and day of the first dose date.
  - Otherwise, assign January.
- If the day is unknown, then:
  - If the month and year match the first dose date, then impute the day of the first dose date.
  - Otherwise, assign '01'.

8.3.5.2 Imputing Partial or Missing Stop Dates

- If the year is unknown or "ongoing" is indicated, then the date will not be imputed and will be assigned a missing value.
- If the month is unknown, then assign December.
- If the day is unknown, then assign the last day of the month.

In no case will the stop date be later than the EOS date

8.4 Detection of Bias

To check for the introduction of bias, the following analyses will be performed:

- Comparing the percentage of subjects between treatment groups who withdraw from the treatment prematurely (e.g., withdrawing before completion of chemotherapy or radiographic disease progression)
- Calculating the rate of cross-in (subjects randomized to placebo who receive erythropoiesis stimulating agents at any point after randomization) in the placebo arm **(if applicable)**
- Comparing the percentage of subjects between treatment groups who receive an RBC transfusion when the hemoglobin value at the time of transfusion was ≤8.0 g/dL **(number of subjects transfused is the denominator)**
- Cross-tabulating the values of the stratification factors recorded in the IVRS versus the case report forms to assess the degree of misspecifications of the stratification factors at randomization.

Analyses that examine the impact of these potential sources of bias will be described in the sections that describe the analyses for the primary and secondary endpoints; **however, these tables may not be included in the clinical study report.**

8.5 Outliers

Potential data outliers will be identified **during** the **analysis dataset programming process** and queried as appropriate. Any data points that are identified as possible outliers, but are subsequently verified through the query process, will be treated as valid data and analyzed accordingly.

8.6 Distributional Characteristics

The statistical assumptions for each method of inferential testing or estimation will be assessed. If the assumptions for the distributional characteristics of endpoints are not met, these will be described and further analyses may be carried out using transformations of endpoint values or alternative inferential or estimation methods. The use of transformations or alternative analysis methods will be fully justified in the final study report.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment **for statistical analyses** consists of Amgen-supported versions of **statistical analysis** software; **for example, the** SAS **System version 9.4** or later **or using R.**

9. Statistical Methods of Analysis

9.1 General Considerations

- Continuous variables will be summarized by the mean, standard deviation, median, and range. The confidence interval and standard error for the mean will also be summarized for efficacy variables that are continuous.
- Categorical variables will be summarized by the number and percentage in each category.
- Time to event variables will be summarized with hazard ratios, Kaplan-Meier curves, Kaplan-Meier quartiles, the number of subjects per treatment group, the number of subjects censored, and the number & percent of subjects with events.
- For stratified analyses, the value for the stratification factors will be taken from IVRS rather than the case report forms; a cross-tabulation of the values recorded in the IVRS versus the case report forms will be generated to assess degree of misspecifications of the stratification factors at randomization.
- To preserve the overall significance level for the study, statistical testing of the primary and secondary endpoints will follow a hierarchical structure. First, the primary endpoint of OS will be tested. If darbepoetin alfa is demonstrated to be non- inferior to placebo with respect to OS, PFS will be formally tested. If darbepoetin alfa is demonstrated to be non-inferior to placebo with respect to PFS then the incidence of RBC transfusions or a hemoglobin ≤ 8.0 g/dL will be formally tested. If non- inferiority is demonstrated for both OS and PFS and superiority is demonstrated for the transfusion endpoint, superiority will then be tested for both OS and PFS using the Hochberg procedure to adjust for multiplicity. For endpoints that are not designated as primary or secondary, statistical testing will be considered descriptive and no adjustments will be made for multiplicity.
- Where confidence intervals are provided, these will be 2-sided at the 95% level, unless otherwise specified

9.2 Subject Accountability

The number and percentage of subjects screened, randomized, and who received at least one dose of investigational product will be presented (a footnote will include the date of first subject randomized and the end of study date). The number and percentage of subjects who withdrew prematurely will be tabulated by the reason for withdrawal. **Since the study was terminated early,**

the number of subjects who were still on-study as of the termination date (dosing terminated 8 May 2017; data collection terminated 7 June 2017) will be tabulated by treatment group.

The number and percentage of subjects in the primary analysis set, the radiographic endpoint primary analysis set, the transfusion from week 5 to EOETP primary analysis set, full analysis set, **and the safety analysis set** will be presented. The number and percentage excluded from the analysis sets will be tabulated by the reason for exclusion.

A cumulative distribution plot will depict subject randomization over time; this will include a footnote of the number of subjects randomized but not dosed. In addition, the number and percentage of subjects randomized will be tabulated by study site and by the stratification factors **(ie, geographic region, tumor histology and screening hemoglobin value)**.

A cumulative distribution plot will depict subject discontinuation from the treatment period over time. Each reason for ending the treatment period will be depicted by a line with separate plots for each treatment group

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol. The final IPD list is used to produce the Summary of IPDs table and the List of Subjects with IPDs.

9.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized by treatment group and for both treatment groups combined:

- Age, age group (**18-64, 65-74, 75-84, ≥85 as well as ≥65 and ≥75),** sex, and race
- Weight**, height** and body mass index (BMI)
- **Stratification factors (geographic region, tumor histology, screening hemoglobin). A cross tabulation of stratification factors according to the IVRS compared to the case report form values will be generated. If there are major differences between the IVRS and case report form stratification factors, then a sensitivity analysis of the primary and secondary endpoints (overall survival, progression-free survival and incidence of transfusion or hemoglobin ≤8 g/dL) may be done.**
- ECOG performance status, **tumor** histology, and presence of measurable disease

- Smoking status and significant medical history including hypertension, prior VTEs, prior ATEs, and diabetes
- Type of therapy for NSCLC used prior to randomization (chemotherapy, targeted therapy and/or radiotherapy) and on study day 1 (eg, chemotherapy with or without any anti-EGFr or anti-angiogenic agents)
- Baseline hematology values for hemoglobin level (at start of chemotherapy, at screening/randomization and at baseline), platelet count, absolute neutrophil count, white blood cell count, and baseline laboratory values for serum iron, serum ferritin, transferrin saturation (TSAT), total iron binding capacity, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and serum erythropoietin (EPO) level.

These characteristics will be summarized for the primary analysis set.

9.5 Efficacy Analyses

The following table summarizes the planned efficacy analyses:

Table 9-1. Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set)	Sensitivity Analysis
Primary Efficacy Endpoint – n/a (primary endpoint is a safety endpoint)		
Secondary Efficacy Endpoints		

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set)	Sensitivity Analysis
Transfusion or Hemoglobin ≤ 8.0 g/dL from Week 5 (day 29) to EOTP– Transfusion from Week 5 to EOETP	Summarize the number and percent of subjects who are transfused or have hemoglobin ≤ 8.0 g/dL, the difference in percent transfused between treatment groups; the common odds ratio; and the Cochran-Mantel-Haenszel statistic and p-value in the primary analysis set; calculate odds ratio of the treatment effect Dataset: Transfusion from Week 5 to EOETP Primary Analysis Set	• Transfusion from Week 5 (day 29) to EOETP Dataset: Transfusion from Week 5 to EOETP • Transfusion or Hemoglobin ≤ 8.0 g/dL from Week 5 (day 29) to EOETP by stratification factors Dataset: Transfusion from Week 5 to EOETP • Transfusion or Hemoglobin ≤ 8.0 g/dL from Week 5 (day 29) to EOETP adjusted for stratification factors [logistic regression model(s)] Dataset: Transfusion from Week 5 to EOETP • **Repeat analysis for subjects impacted vs not impacted by early study termination** Dataset: Transfusion from Week 5 to EOETP • **Repeat analysis for targeted study day 1 for subjects who delayed start of investigational product** Dataset: Week 5 to EOETP using the Full Analysis Set (starting from targeted day 1)
Transfusion from Week 5 (day 29) to EOETP when Hemoglobin is ≤ 8.0 g/dL at the Time of Transfusion	Summarize the number and percent of subjects with a transfusion when the hemoglobin is ≤ 8.0 g/dL at the time of transfusion by treatment group; the common odds ratio; and the Cochran-Mantel-Haenszel statistic and p-value in the primary analysis set; calculate odds ratio of the treatment effect Dataset: Transfusion from Week 5 to EOETP Primary Analysis Set	N/A

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set)	Sensitivity Analysis
Transfusion or Hemoglobin ≤ 8.0 g/dL from Week 1 (day 1) to EOETP	Summarize the number and percent of subjects with a transfusion or hgb≤ 8.0 g/dL by treatment group by treatment group; the difference in percent transfused between treatment groups; the common odds ratio; and the Cochran-Mantel-Haenszel statistic and p-value Dataset: Primary Analysis Set	• Transfusion from Week 1 (day 1) to EOETP Dataset: Primary Analysis Set • Transfusion from Week 1 (day 1) to EOETP when hemoglobin is ≤ 8.0 g/dL at the Time of Transfusion Dataset: Primary Analysis Set
Change in Hemoglobin from Baseline	Summarize the change in hemoglobin from baseline to Week 13, Week 16 and EOETP by treatment group and provide t-test p-value. Dataset: Primary Analysis set; use central laboratory hemoglobin values	• Box plot of median, mean 25th and 75th percentiles, minimum and maximum over time by randomized treatment group Dataset: Primary Analysis set; use central laboratory hemoglobin values • Plot change in hemoglobin values from baseline over time by randomized treatment group Dataset: Primary Analysis set; use central laboratory hemoglobin values • **Repeat analysis for targeted study day 1 for subjects who delayed start of investigational product** Dataset: Full analysis set using targeted day 1 as the baseline use central laboratory hemoglobin values

9.5.1 Analyses of Primary Efficacy Endpoint(s)

Not applicable

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

The primary analysis of the incidence of a transfusion or hemoglobin ≤ 8.0 g/dL from day 29 to EOETP will be based on the Cochran-Mantel-Haenszel method which will test for treatment group differences while adjusting for the stratification factors at randomization. In addition, the Mantel-

Haenszel estimate of the common odds ratio across strata will be estimated with a 95% confidence interval. This analysis will be performed on all subjects in the transfusion from week 5 to EOETP primary analysis set. If non-inferiority has been declared for OS and PFS, superiority will be declared for the transfusion endpoint if the p-value from a two-sided test of significance using the Cochran-Mantel-Haenszel method is less than 0.05 in favor of the darbepoetin alfa group.

The following sensitivity analyses will be performed:

- An analysis will be performed that removes the "hemoglobin ≤ 8.0 g/dL" from the definition of the endpoint in order to examine the treatment effect on the incidence of transfusion only from day 29 to EOETP.
- An analysis of transfusions when "hemoglobin ≤ 8.0 g/dL".
- **To assess the impact of the early termination of the study, the analysis will be repeated for subjects who were still on-study or in long-term follow-up as of June 7 and for subjects who were not impacted by the early study termination.**

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

An analysis similar to the analysis for transfusion or hemoglobin ≤ 8.0 g/dL from week 5 to EOETP will be done for transfusion or hemoglobin ≤ 8.0 g/dL from day 1 to EOETP (with a sensitivity analysis of incidence of a transfusion from day 1 to EOETP). These will be based on the Primary Analysis Set.

Descriptive statistics for change in hemoglobin from baseline will be provided at weeks 13 and 16 and graphs will be provided for hemoglobin over time (box plot) and change in hemoglobin from baseline over time (line plot) by treatment group. These will all be based on the Primary Analysis Set.

9.6 Safety Analyses

The following table summarizes the safety endpoints in this study, including the primary endpoint, overall survival, and the key secondary endpoint, progression-free survival.

Table 9-1. Safety Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
• Primary Safety Endpoint (primary endpoint of the study)		
Overall Survival	Summarize the number of subjects with events and numbers of subjects censored, Kaplan-Meier quartiles, KM estimates of 1-year, 2-year, and 3-year	• Overall survival using: Full Analysis Set • Overall survival using: Per-protocol Analysis Set

	survival by treatment group. Present the hazard ratio with 95% confidence interval Dataset: Primary Analysis Set	• KM time-to-event plots using the Primary Analysis Set, Full Analysis Set and Per-protocol Analysis Set • Repeat analysis by stratification factors Dataset: Primary Analysis Set • **Repeat analysis for subjects impacted vs not impacted by early study termination** Dataset: Primary Analysis Set • **Repeat analysis based on study day 1 rather than date of randomization** Dataset: Full analysis set using targeted day 1 as the baseline use central laboratory hemoglobin values
Overall Survival	Cox proportional hazards regression modelling with treatment group in the model, stratified by the stratification factors. This will include the p-value testing for an interaction between treatment group and each stratification factor Dataset: Primary Analysis Set	• Cox proportional hazards regression modelling including treatment group only. Dataset: Primary Analysis Set • Cox proportional hazards regression modelling including the stratification factors and other clinically important covariates Dataset: Primary Analysis Set • Results for stratification factors and covariates may be provided as a forest plot. Dataset: Primary Analysis Set
Overall Survival	Overall Survival with Adjustment for Cross-in using a Cox regression that estimates the hazard ratio with treatment group treated as a time-dependent covariate to account for cross-in of erythropoietic agent use by placebo Dataset: Primary Analysis Set	
• Secondary Safety Endpoint		
Progression-free Survival	Summarize the number of subjects with events and numbers of subjects censored, Kaplan-Meier quartiles, KM estimates of 1-year, 2-year, and 3-year survival by treatment group. Present the hazard ratio with 95% confidence interval Dataset: Radiographic Endpoint Primary Analysis Set	• KM time-to-event plots using the Radiographic Endpoint Dataset: Radiographic Endpoint Primary Analysis Set • Repeat analysis by stratification factors Dataset: Radiographic Endpoint Primary Analysis Set

		• **Repeat analysis using Radiographic Endpoint Full Analysis set** • **Repeat analysis using Per Protocol Analysis set** • **Repeat analysis for subjects impacted vs not impacted by early study termination** Dataset: Radiographic Endpoint Primary Analysis Set
Progression-free Survival	Cox proportional hazards regression modelling with treatment group in the model, stratified by the stratification factors. This will include the p-value testing for an interaction between treatment group and each stratification factor Dataset: Radiographic Endpoint Primary Analysis Set	• Cox proportional hazards regression modelling including treatment group only. Dataset: Radiographic Endpoint Primary Analysis Set • Cox proportional hazards regression modelling including the stratification factors and other clinically important covariates Dataset: Radiographic Endpoint Primary Analysis Set
Progression-free Survival with Adjustment for Cross-in	Summarize the results of a Cox regression that estimates the hazard ratio with treatment group treated as a time-dependent covariate to account for cross-in of erythropoietic agent use by placebo Dataset: Radiographic Endpoint Primary Analysis Set	
Progression-free Survival to account for RECIST version	Summarize the results of a Cox regression that estimates the hazard ratio with treatment group treated and RECIST version as covariates Dataset: Radiographic Endpoint Primary Analysis Set	
Other Safety Endpoint		
Time to disease progression	Summarize the number of subjects with events and numbers of subjects censored, Kaplan-Meier quartiles, KM estimates of 1-year, 2-year, and 3-year survival by treatment group. Present the hazard ratio with 95% confidence interval. Dataset: Radiographic Endpoint Primary Analysis Set	• Repeat analysis by stratification factors Dataset: Radiographic Endpoint Primary Analysis Set • KM time-to-event plots using the Radiographic Endpoint Dataset: Radiographic Endpoint Primary Analysis Set
Summary of Objective Tumor	Summarize the number and percent of subjects with an objective tumor response by treatment group; the	• Repeat analysis stratified by RECIST version

Response **Rate**	difference in percent between treatment groups; the common odds ratio; and the Cochran-Mantel-Haenszel statistic and p-value Dataset: Radiographic Endpoint Primary Analysis Set	
Summary of Best Overall Objective Tumor Response	Summarize the number and percentage of subjects whose best overall response during the treatment period falls into each of the following categories: complete response, partial response, stable disease, disease progression, not evaluable, missing due to clinical progression, and missing for reasons other than clinical progression by treatment group Dataset: Radiographic Endpoint Primary Analysis set,	• Repeat analysis stratified by RECIST version • **Stratified by non-response to investigation product category** **Dataset: Safety Analysis Set**
Product Dosing and Medications		
Exposure to Investigational Product	Summarize the number and percent of subjects exposed to investigational product, and the dose and duration measures described. Dataset: Safety Analysis Set	• **Subgroup of subjects impacted or not impacted by early study termination**
Dose Changes to Investigational Product	Summarize the number and percent of subjects with dose reductions, dose withholdings, dose discontinuations, and switches to placebo for non-response Dataset: Safety Analysis Set	• **Subgroup of subjects impacted or not impacted by early study termination**
Summary of Concomitant Medications	Tabulation of subjects receiving concomitant medication by WHODRUG preferred term by treatment group Dataset: Safety Analysis Set	• Repeat for MOIs
Summary of Treatment for NSCLC	Summarize the type and exposure NSCLC treatment by treatment group Dataset: Safety Analysis Set	• Dataset: Primary Analysis Set
Summary of Erythropoiesis Stimulating Agents use Outside of Investigational Product	Summarize the amount of exposure to erythropoiesis stimulating agent use outside of investigational product by treatment group Dataset: Safety Analysis Set	
Adverse Events		
Overall Summary of Treatment-emergent	Tabulation of subjects experiencing the following types of summary of treatment-emergent adverse events: all, serious, those leading to withdrawal	

Adverse Events	of investigational product, and fatal by treatment group in the primary analysis set. Safety Analysis Set	
Treatment-emergent Adverse Events by SOC and Preferred Term	Tabulation of subjects experiencing any treatment-emergent adverse events by system organ class and preferred term in alphabetical order by treatment group Dataset: Safety Analysis Set	.
Serious Treatment-emergent Adverse Events by SOC and Preferred Term	Tabulation of subjects experiencing serious treatment-emergent adverse events by system organ class and preferred term in alphabetical order by treatment group Dataset: Safety Analysis Set	• Dataset: Primary Analysis Set
Summary of Treatment-emergent Adverse Events Leading to Withdrawal of Investigational Product by SOC and Preferred Term	Tabulation of subjects experiencing treatment-emergent adverse events leading to withdrawal of investigational product by system organ class and preferred term by treatment group in alphabetical order Dataset: Safety Analysis Set	
Summary of Fatal Treatment-emergent Adverse Events by SOC and Preferred Term	Tabulation of subjects experiencing fatal treatment-emergent adverse events by system organ class and preferred term by treatment group in alphabetical order Dataset: Safety Analysis Set	.
Treatment-emergent Adverse Events of Interest by Category	Tabulation of subjects experiencing treatment-emergent adverse events of special interest by category (which include TVEs, VTEs and AEs associated with RBC transfusions) by treatment group in alphabetical order Dataset: Safety Analysis Set	• Dataset: Primary Analysis Set
Treatment-emergent Serious	Tabulation of subjects experiencing treatment-emergent serious adverse events of special interest by category	• Dataset: Primary Analysis Set

Adverse Events of Interest by Category	(which include TVEs, VTEs and AEs associated with RBC transfusions) by treatment group in alphabetical order Dataset: Safety Analysis Set	
Treatment-emergent Adverse Events of Interest by Category and Preferred Term	Tabulation of subjects experiencing treatment-emergent adverse events of special interest by category (which include TVEs, VTEs and AEs associated with RBC transfusions) and preferred term by treatment group in descending order of frequency Dataset: Safety Analysis Set	.
Treatment-emergent Serious Adverse Events of Interest by Category and Preferred Term	Tabulation of subjects experiencing treatment-emergent adverse events of special interest by category (which include TVEs, VTEs and AEs associated with RBC transfusions) and preferred term by treatment group in alphabetical order Dataset: Safety Analysis Set	
Treatment emergent VTEs	**VTEs confirmed and not confirmed by imaging, including fatal and non-fatal VTEs. Subjects with or without a history of VTE will also be included** **Dataset: Safety Analysis Set**	• **Dataset: Primary Analysis Set**
Treatment emergent Serious VTEs	**Serious VTEs confirmed and not confirmed by imaging, including fatal and non-fatal VTEs. Subjects with or without a history of VTE will also be included** **Dataset: Safety Analysis Set**	• **Dataset: Primary Analysis Set**
Treatment-emergent Adverse Events Occurring in ≥ 5% of All Subjects in Descending Order of Frequency	Tabulation of subjects experiencing any treatment-emergent adverse events by treatment group in descending order of frequency in the total column and coded by preferred term Dataset: Safety Analysis Set	
Treatment-emergent Serious Adverse Events Occurring in ≥ 5% in Descending	Tabulation of subjects experiencing any treatment-emergent adverse events by treatment group in descending order of frequency in the total column and coded by preferred term Dataset: Safety Analysis Set	

Order of Frequency		
Treatment-emergent Adverse Events in Descending Order of Frequency by SOC, Preferred Term and Grade	Tabulation of subjects experiencing any treatment-emergent adverse events by treatment group in descending order of frequency and coded by preferred term and grade Dataset: Safety Analysis Set	.
Treatment-emergent Serious Adverse Events in Descending Order of Frequency by SOC, Preferred Term and Grade	Tabulation of subjects experiencing any treatment-emergent adverse events by treatment group in descending order of frequency and coded by preferred term and grade Dataset: Safety Analysis Set	.
Laboratory Results		
Clinical Laboratory	Summary statistics for baseline, minimum on study, maximum on study, EOTP, and change from baseline to EOTP by treatment group will be provided for: • Hemoglobin • Platelets • White blood cell count • Serum ferritin • Serum iron • Transferrin saturation level (TSAT) • Total iron binding capacity • Creatinine • Total bilirubin • Alanine aminotransferase (ALT), and • Aspartate aminotransferase (AST) Dataset: Safety Analysis Set	N/A Note: data for all other analytes will be provided in an electronic format
Summary of Hemoglobin	Summarize the number and percent of subjects who had hemoglobin > 12.0	

Threshold – Primary Analysis Set	g/dL at any time in the treatment period (both adjusting and not adjusting for RBC transfusions) by treatment group Dataset: Safety Analysis Set	
Summary of Rapid Rate of Rise in Hemoglobin – Primary Analysis Set	Summarize the number and percent of subjects who had a rapid rate of rise in hemoglobin (> 1.5 g/dL in 21 days) at any time in the treatment period (both adjusting and not adjusting for RBC transfusions) by treatment group Dataset: Safety Analysis Set	
Summary of Non-response to Investigational Product – Primary Analysis Set	Summarize the number and percent of subjects who were non-responders by treatment group Dataset: Safety Analysis Set	.
Antibody Results, Vital Signs, ECOG		
Summary of Antibody Results –	Summarize antibody results for darbepoetin alfa by treatment group Dataset: Safety Analysis Set	• Summarize antibody results for erythropoetin by treatment group Dataset: Safety Analysis Set
Summary of Vital Signs	Summarize weight, systolic blood pressure, diastolic blood pressure, pulse by treatment group Dataset: Safety Analysis Set	.
Summary of ECOG Performance Status	Summarize ECOG by treatment group Dataset: Safety Analysis Set	.

9.6.1 Primary Safety Endpoints

The primary analysis of OS will be based on the primary analysis set and will use a Cox regression model, stratified by the randomization factors, with treatment group as the only covariate. Subjects last known to be alive will be censored on date of last contact. Non-inferiority will be declared if the upper confidence limit for the hazard ratio (darbepoetin alfa to placebo) is less than 1.15 using a 1-sided significance level of 0.025.

The following sensitivity analyses will be performed as further exploratory analyses for the primary endpoint:

- To provide a completely unadjusted analysis, a hazard ratio with 95% confidence interval will be estimated from an unstratified Cox regression with treatment group as the only covariate.
- To support the results obtained from the primary analysis set, analyses will be performed using the overall survival per protocol set.

- To explore the consistency of the treatment effect, Cox regression **models** will be generated including the stratification variables and covariates listed in Section 4.1. These models will include any interaction terms with treatment group where nominal p-values of <0.10.
- In addition, a hazard ratio with 95% confidence interval will be generated from an unstratified Cox regression for each stratum formed from the combination of randomization factors (e.g., subjects from North America with squamous cell and who have a screening hemoglobin < 10.0 g/dL) and for each level of a given stratification factor (e.g., subjects from North America).
- To explore the impact of cross-in (placebo subjects who begin erythropoiesis stimulating agents at any point after randomization), an analysis will be performed that models erythropoiesis stimulating agent use as a time-dependent covariate in the stratified Cox regression. For subjects randomized to the darbepoetin alfa arm, the time-dependent covariate will be coded "1" throughout the time course (with the exception of subjects randomized to darbepoetin alfa who mistakenly receive placebo; they will be coded "0" throughout the time course unless they begin use of any erythropoiesis stimulating agent). For subjects randomized to the placebo arm, the time-dependent covariate will initially be coded "0" and change to "1" if and when they begin use of any erythropoiesis stimulating agent. Because the time-dependent covariate is based on information post-randomization, the results of this analysis will be interpreted with caution.
- To assess the impact of misspecifications of the stratification factors at randomization, a hazard ratio with 95% confidence interval will be estimated from an unstratified Cox regression with treatment group as a covariate along with covariates that represent the stratification factors. The values of the stratification factors will be determined from the case report forms rather than the IVRS. **This analysis will only be done if there is evidence that there were errors in the IVRS stratification factors.**
- **To assess the impact of the early termination of the study, the primary analysis will be repeated for subjects who were still on-study or in long-term follow-up**

as of June 7 and for subjects who were not impacted by the early study termination.

9.6.2 Secondary Safety Endpoint

The primary analysis of PFS will be based on the radiographic endpoint primary analysis set and will use a Cox regression model, stratified by the randomization factors, with treatment group as the only covariate. PFS will be measured from randomization to disease progression (as defined by the version of RECIST specified in the protocol at the time of subject enrollment) or death from any cause; subjects without either event will be censored at the last disease assessment date. If non-inferiority has been declared for OS, non-inferiority will be declared for PFS if the upper confidence limit for the hazard ratio is less than 1.15 using a 1-sided significance level of 0.025.

Sensitivity analyses for PFS will be done similar to those for the primary endpoint, OS, as further exploratory analyses for the secondary endpoint: **However, the sensitivity analyses will be largely limited to the Radiographic Endpoint Primary Analysis Set (ie, few sensitivity analyses using the Per Protocol Analysis Set or any other data set are planned).** In addition, a sensitivity analysis may be performed that examines the treatment effect by subgroups formed on the basis of which version of RECIST was used to evaluate the subject. If this analysis is performed, however, the results will need to be interpreted cautiously since the version of RECIST will be confounded with time of enrollment (RECIST 1.0 subjects will be enrolled first, RECIST 1.1 subjects second) and it is anticipated that less than 10% of the subjects will be evaluated with RECIST 1.0.

9.6.3 Other Safety Endpoints

The number and percentage of subjects with a confirmed objective tumor response **rate** (as defined by the version of RECIST specified in the protocol at the time of subject enrollment) will be presented by treatment group. Subjects without any post-baseline tumor assessments will be considered non-responders. Subjects without measurable disease at baseline will be excluded from the analysis. To assess treatment group differences, the Cochran-Mantel-Haenszel method will be used which will adjust for the stratification factors at randomization.

In addition, a more detailed classification of response will be presented by summarizing the number and percentage of subjects whose best overall response during the study falls into each of the following categories: complete response, partial response, stable disease, disease progression, not evaluable, missing due to clinical progression, and missing for reasons other than clinical progression. **Non-response will also be summarized.** These analyses will be performed for the **radiographic endpoint** primary analysis set.

9.6.4 Adverse Events and Disease-related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version **20.0** or later will be used to code all adverse events to a system organ class and a preferred term. **Treatment-emergent adverse events are events with an onset after the administration of the first dose of investigational product.** The subject incidence of adverse events will be summarized for all treatment emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, fatal adverse events and adverse events of interest **using the safety analysis set. Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in alphabetical order.**

Subject incidence of events of interest will also be summarized according to their categories and preferred term within category**.** Special interest adverse events include TVEs, VTEs and AEs associated with RBC transfusions. All three sub-categories of TVEs (VTEs, ATEs, and unspecified/mixed thromboembolic events)

will be summarized in order to present the complete decomposition of TVEs. However, ATEs alone are not of special interest. The primary analysis of VTEs will include fatal VTEs and VTEs confirmed by imaging; a sensitivity analysis will summarize all VTEs regardless of severity or confirmation.

In addition, **summaries of treatment emergent and serious adverse events occurring in at least 5% of the subjects by preferred term in any treatment arm** will be provided in descending order of frequency **in the darbepoetin alfa arm. Summaries of treatment-emergent and serious adverse events will also be tabulated by system organ class, preferred term and grade. All adverse event tables will be summarized by treatment group using the safety analysis set. In addition, serious adverse events, events of interest and VTE data will be analyzed using the primary analysis set.**

9.6.5 Laboratory Test Results

Summary statistics for baseline, minimum on study, maximum on study, EOTP, and change from baseline to EOTP by treatment group will be provided for:

- Hemoglobin
- Platelets
- White blood cell count
- Serum ferritin
- Serum iron
- Transferrin saturation level (TSAT)
- Total iron binding capacity
- Creatinine
- Total bilirubin
- Alanine aminotransferase (ALT), and
- Aspartate aminotransferase (AST).

Summary statistics will not be **generated for** the other hematology or analytes reported by the central laboratory but the data will be captured in the electronic line listings.

In addition, summary statistics for the average of all post-baseline hemoglobin values will be provided by treatment group (summarized both by keeping and **excluding** hemoglobin values that occurred within 28 days **following** a RBC transfusion).

9.6.6 Vital Signs

Summary statistics for baseline, minimum on study, maximum on study, EOTP, and change from baseline to EOTP by treatment group will be limited to:

- Systolic blood pressure,
- Diastolic blood pressure, and;
- Pulse

No other vital signs data will be summarized but the data will be captured in the electronic line listings.

Eastern Cooperative Oncology Group (ECOG) performance status scores will be summarized for each treatment group at baseline, EOTP and change from baseline to EOTP.

9.6.7 Physical Measurements

Summary statistics for baseline, minimum on study, maximum on study, EOTP, and change from baseline to EOTP by treatment group will be provided for:

- Weight

No other physical measurements will be summarized but the data will be captured in the electronic line listings.

9.6.8 Electrocardiogram

The electrocardiogram (ECG) measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QT interval corrected (QTc) effect. Because these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; neither summaries nor statistical analyses will be provided, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.6.9 Antibody Formation

The number and percentage of subjects with confirmed neutralizing antibody formation to darbepoetin alfa **and erythropoietin** will be presented.

9.6.10 Exposure to Investigational Product

Exposure to investigational product endpoints will include dose duration in weeks (the study week of last dose plus 3), the number of doses, the cumulative dose

administered (μg), the weight-adjusted cumulative dose administered (cumulative dose divided by the baseline weight), the average weekly dose (cumulative dose divided by the dose duration), the average dose administered (cumulative dose divided by the number of doses), the weight-adjusted average weekly dose (weight-adjusted cumulative dose divided by the dose duration), and the weight-adjusted average dose administered (weight-adjusted cumulative dose divided by the number of doses).

Change in dosing will include the number and percent of subjects who had a dose reduction because of a **fast** rate of **hemoglobin** rise, had a dose withheld because the hemoglobin threshold was surpassed, had dose discontinued because of a severe or life-threatening adverse event reported by the investigator to be related to investigational product, and **subjects** switched to placebo because of non-response (darbepoetin alfa group only).

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group (only the dose duration and the numbers doses will be summarized for the placebo group).

- **To assess the impact of the early termination of the study, the analysis of exposure to investigational product endpoints and change in dosing will be repeated for subjects who were still on-study or in long-term follow-up as of June 7 and for subjects who were not impacted by the early study termination.**

9.6.11 Exposure to Other Protocol-specified Treatment

Not applicable

9.6.12 Exposure to Concomitant Medication

Medications of Interest

The concomitant medications of interest will be summarized by preferred term for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary **as of Q2 2017**. **The number and proportion of subjects receiving therapies of interest, including erythropoiesis stimulating agents other than investigational product (as defined in the protocol), will be summarized by preferred term or category for each treatment group as coded by the WHODRUG dictionary**. For erythropoiesis stimulating agents, summary statistics will be provided to

describe the amount of exposure **received by treatment group. See Appendix B for a list of selected medications and their groupings**.

Concomitant Chemotherapy

Treatment**(s)** for NSCLC (including chemotherapy, anti-EGF-R, anti-angiogenic agents, or other anti-cancer treatments) both during the treatment period and **until the first disease progression will be summarized, including the amount of exposure received by treatment group.**

10. Changes From Protocol-specified Analyses

The following changes to the analysis will be done due to changes in analysis practices during the study duration but are not specified in the protocol:

Summarization of demographic and baseline characteristics will be limited to the primary analysis set; analysis of these data using the radiographic endpoint primary analysis set, transfusion from week 5 to EOTP primary analysis set, full analysis and radiographic endpoint full analysis set will not be done

Sensitivity analyses are limited to the primary and secondary safety and efficacy endpoints

Stratified analyses are reduced to only the primary dataset per current practice

Subset analyses were limited per current practice

Analysis of safety data (adverse events, vital signs, hematology and chemistry data, study drug dosing, other medications, concomitant medications of interest, and antibodies) using a Safety Set and subjects as treated (rather than as randomized) replaced the analysis in the primary data set by randomized treatment group for consistency with the analyses for other clinical trials in the darbepoetin alfa program.

Analysis of adverse events is limited to current Amgen standard adverse events tables (eg, summaries of treatment-related adverse events and treatment-related serious adverse events have been excluded)

Changes from the protocol will also be documented in the Clinical Study Report.

11. Literature Citations / References

Sandler A, Gray, R, et al. Paclitaxel-Carboplatin Alone or with Bevacizumab for Non-Small Cell Lung Cancer. *N Engl J Med 2006*; 355:2542-50.

12. Prioritization of Analyses

First priority analyses (due within 2-3 business days following database lock):

- **Demographics, baseline characteristics, baseline disease characteristics, subject disposition, IPDs (to assess imbalances between treatment groups); cross tabulation of stratification factors in IVRS vs reported using case report forms**
- **Overall Survival (primary analysis set by randomized treatment group; all subjects and stratified by geographic region, histology and screening hemoglobin) including Kaplan-Meier plot**
- **Progression-free survival (all subjects in the primary analysis set by randomized treatment group) including Kaplan-Meier plot**
- **Objective response rate (all subjects in the primary analysis set by randomized treatment group)**
- **Incidence of RBC transfusions from Week 5 to EOTP or hemoglobin ≤ 8 g/dL (all subjects in the primary analysis set by randomized treatment group)**
- **Adverse Events (AEs; safety analysis set by actual treatment group; all subjects)**
- **Serious AEs (AEs; safety analysis set by actual treatment group; all subjects)**
- **Events of interest (AEs; safety analysis set by actual treatment group; all subjects)**
- **AEs leading to study drug discontinuation (AEs; safety analysis set by actual treatment group; all subjects)**
- **Fatal AEs (AEs; safety analysis set by actual treatment group; all subjects)**
- **VTEs (AEs; safety analysis set by actual treatment group and primary analysis set by randomized treatment group; all subjects)**
- **Line graph of mean (with 95% confidence limits) hemoglobin values over time (all subjects in the primary analysis set by randomized treatment group)**
- **Box plot of median hemoglobin values (with 25th and 75th percentiles, minimum and maximum) over time (all subjects in the primary analysis set by randomized treatment group)**

13. Data Not Covered by This Plan

Paraffin embedded tumor tissue blocks or unstained tumor slides collected in this study will not be described or analyzed directly and are not included in this plan.

Details of analyses provided to the Data Monitoring Committee, including the planned interim analyses, are not described or analyzed directly under this plan. These analyses were generated by PRA Health Sciences, Charlottesville, Virginia. An unplanned interim analysis conducted by an independent group at Amgen in Q4 2016 is also not covered in this plan.

14. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

Visit	***Study day(s)***	***Window Definition***	***Interval (days)***
Screening period	"-1"	Evaluation(s) within 21 days prior to the randomization date Note: these should be on or after the date of consent, and should include history, vital sign, ECOG and other protocol specified measurements	21 to day -1
Randomization	-4 to 1	Randomization may occur on study day 1 or up to 4 day prior to study day 1. Note: Adverse events will be reported beginning from the data of randomization Note: Subjects who progressed in the screening period (or prior to the screening period) are not eligible for randomization (protocol Section 7.1.6)	1 day
Baseline/Study Day 1	1	Evaluation on Study Day 1 or last evaluation prior to Study Day 1 (if no value is available on Study Day 1). The first dose of study drug should be given on study day 1 Note: Baseline hemoglobin value should be a central laboratory value. Note that a local laboratory hemoglobin value may be present in the database; this is used to confirm study eligibility and should not be used a the baseline hemoglobin value	1
Treatment Period (Q3W visits)	Every 21 days (+/- 6 days)	Dose 1: study day 1 (1-7) Dose 2: study day 22 (15-27) Dose 3: study day 43 (37-49) Dose 4: study day 64 (58-70) Dose 5: study day 85 (79-91) Dose 6: study day 106 (100-112) Dose 7: study day 127 (121-133) Dose 8: study day 141 (135-147) Dose 9: study day 162 (156-168) Dose 10: study day 183 (177-189)	Every 21 days(15-27 days); duration is n/d

		etc Note: The treatment period, including study drug administration should last until disease progression Note: Per protocol, study procedures (eg, ECOG, laboratory sample draws) may be performed up to 1 day prior to IP dosing	
		Imaging studies will be performed every 9 weeks (± 7 days) or at any time symptoms suggestive of disease progression occur. Subjects who discontinue chemotherapy or IP should continue to be evaluated radiographically Q9W until disease progression.	Every 8-10 weeks until progression
EOTP		The EOTP visit is the next Q3W visit (± 6 days) after disease progression	n/d
Long-term follow-up (LTFU)	…	LTFU begins after disease progression. Visits should occur at 3-month intervals (± 2 weeks). and	n/d
EOS		EOS is when a subject dies or is lost to follow-up or withdrawal or until 22 June 2017	n/d

n/d Not determinable – since many of these are event driven, the period for an individual subject cannot be determined apriori

Additional description of per protocol analysis

- **Exclude subjects with EN 111 or EN 101 or OT 903**
  This excludes:
  a) subjects that did not have NSCLC (OT 903)
  b) subjects that did not have metastatic (Stage IV) or advanced stage IIIB with malignant pleural effusion NSCLC (prior to Amendment 3) (ie, subjects that had a lower grade tumor)
- **Exclude subjects with EN 117A**

  This excludes subjects with disease progression prior to study day 1
- **Exclude subjects with EN 202**

  This excludes subjects with a history of or current cancer diagnosis of a cancer type other than NSCLC
- **Exclude subjects with EN 109 or EN 117 B**

  This excludes subject who did not have a baseline pre-chemo scan prior to randomization
- **Exclude subjects with an ECOG performance status > 1 at screening (EN 113 or EN 103)**
- **Exclude subjects with EN 114 or EN 105**

This should exclude subjects that had a life expectancy < 6 months based on the judgment of the investigator at screening

- **Exclude subjects who received any erythropoiesis stimulating agents within the 28 days prior to screening (EN 223 or 218)**

- **Exclude subjects with EN 210**
  This should exclude subjects with a documented history of pure red cell aplasia

- **Exclude subjects who are not dosed per protocol through week 7 (however, include subjects who received a planned dose adjustment per section 6.1.2 of the protocol)**

- **Exclude subjects who did not receive first line chemotherapy with an initial start date on or before Study day 1 and an end date after Study day 1**

- **Exclude subjects who received ≥ 1 dose of an erythropoiesis stimulating agent(s) other than investigational product as defined in the protocol [eg, epoetin alfa (Procrit, Eprex or Epogen), epoetin beta (Micera), epoetin zeta (Retacrit)] during the treatment period (TA 507)**

- **Exclude subjects who received the incorrect investigational product (ie, randomized to placebo and received ≥ 1 dose of darbepoetin alfa; or, randomized to darbepoetin alfa and received ≥ 1 dose of placebo**

Appendix B. Concomitant Medications

The following are the Concomitant Medications of Interest for this study:

- Antihypertensives
- Antimicrobials
- Antithrombotic agents
- Colony stimulating factors
- Epoetins
- Histone deacylating inhibitors
- Hypomethylating agents
- Iron
- Iron chelating agents
- Lenalidomide
- Methotrexates
- Platelets
- Thalidomide
- Thrombopoesis stimulating factors

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