Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Long-term 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

Darbepoetin alfa
Amgen Protocol Number 20070782
BB-IND 8223
EudraCT number 2007-005792-34

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Date:	25 November 2008
Amendment 1	11 February 2009
Amendment 2	22 March 2009
Amendment 3	25 May 2010
Superseding Amendment 3	**13 November 2012**

Investigator's Agreement

I have read the attached protocol entitled, "A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Long-term 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" dated **13 November 2012**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub-investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Principal or Coordinating Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Long-term Safety and Efficacy of Darbepoetin Alfa Administered at 500 μg Once-Every-3-Weeks (Q3W) in Anemic Subjects With Advanced Stage Non-small Cell Lung Cancer Receiving Multi-cycle Chemotherapy

Study Phase: 3

Indication: Chemotherapy-induced Anemia (CIA)

Primary Objective

- 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

Secondary Objectives

- 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
- 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
- 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

Hypothesis

The primary hypothesis to be tested is that the OS of subjects with CIA with stage IV non-small cell lung cancer (NSCLC) receiving cyclic chemotherapy treated with darbepoetin alfa 500 μg Q3W to a hemoglobin ceiling of 12.0 g/dL will not be worse than the OS of anemic subjects treated with placebo.

Study Design

This is a double-blind, randomized, placebo-controlled phase 3 non-inferiority study in subjects with CIA receiving multi-cycle chemotherapy for the treatment of advanced stage NSCLC.

Approximately 3000 subjects with stage IV NSCLC will be randomized in a 2:1 allocation to Groups A and B:

- Group A: darbepoetin alfa 500 μg (Q3W) to a hemoglobin ceiling of 12.0 g/dL
- Group B: placebo Q3W

Section 6.1.2 describes the dosing algorithms.

Randomization will be stratified by geographic region, histology, and screening hemoglobin (local laboratory hemoglobin; sample obtained within 7 days prior to randomization).

The study consists of a screening period (up to 21 days), a treatment period, and a long-term follow up (LTFU) period. Investigational Product (IP) will be given 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 treatment period (EOTP) visit will occur at the next Q3W visit after disease progression has been determined. Subjects will then enter LTFU and will be followed with once-every-3-months (Q3M) study visits until death, or until approximately 2700 deaths have occurred (End of Study [EOS]). Adverse events and serious adverse events will be collected until 30 days after the last dose of IP. Based on the estimated recruitment rate and the projected survival rate of metastatic NSCLC, the study duration is anticipated to take approximately 7 years for enrollment and 3 years follow up for a total of 10 years from first subject enrolled into study to EOS.

Tumor Sample Banking: If available and upon the consent of the subjects, archived paraffin embedded tumor tissue blocks or unstained tumor slides (from primary tumor or metastasis) will be collected during screening and submitted upon enrollment for erythropoietin receptor (EpoR) testing, tumor mutation analysis, and other biomarker evaluation. There will not be an additional

procedure required but rather these tumor samples may be obtained from previous diagnostic biopsy.

Primary and Secondary Endpoints

Primary Endpoint

- Overall survival (OS)

Secondary Endpoints

- Progression-free survival (PFS)
- Incidence of at least 1 RBC transfusion or hemoglobin ≤ 8.0 g/dL from week 5 (day 29) to the 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)

Other Safety Endpoints

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

Other Efficacy Endpoints

- CCI [redacted]
- CCI [redacted]

Sample Size: Approximately 3000 subjects

Summary of Subject Eligibility Criteria

Inclusion Criteria

- Subjects with stage IV NSCLC (not recurrent or re-staged)
- Expected to receive at least 2 additional cycles (at least 6 total weeks) of first line myelosuppressive cyclic chemotherapy after randomization. Subjects should not be expected to receive only maintenance chemotherapy.
- Life expectancy > 6 months based on the judgment of the investigator and documented during screening
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 as assessed within 21 days prior to randomization
- 18 years of age or older at screening
- Hemoglobin level ≤ 11.0 g/dL as assessed by the local laboratory; sample obtained within 7 days prior to randomization (retest in screening is acceptable)
- Subjects must have had a baseline scan (CT, MRI, or PET/CT) of the chest to assess disease burden before starting on first line chemotherapy for NSCLC and those images must have been reviewed by the investigator prior to randomization. If the scan was performed more than 28 days prior to randomization, an additional scan must be performed and reviewed by the investigator to confirm that the patient has not progressed before randomization.
- Adequate serum folate (≥ 2 ng/mL) and vitamin B12 (≥ 200 pg/mL) levels assessed by the central laboratory during screening (supplementation and retest acceptable)
- Before any study specific procedure, the appropriate written informed consent must be obtained from the subject or legally accepted representative

Exclusion Criteria

- Known primary benign or malignant hematologic disorder which can cause anemia

- History of, or current active cancer other than NSCLC, with the exception of curatively resected non-melanomatous skin cancer, curatively treated cervical carcinoma in situ, or other primary solid tumors curatively treated with no known active disease present and no curative treatment administered for the last 3 years
- Received any prior adjuvant or neoadjuvant therapy for NSCLC
- Subjects with a history of brain metastasis
- Uncontrolled hypertension (systolic blood pressure [BP] > 160 mmHg or diastolic BP > 100 mmHg), or as determined by the investigator during screening
- History of neutralizing antibody activity to rHuEPO or darbepoetin alfa
- Uncontrolled angina, uncontrolled heart failure, or uncontrolled cardiac arrhythmia as determined by the investigator at screening. Subjects with known myocardial infarction within 6 months prior to randomization.
- Subjects with a history of seizure disorder taking anti-seizure medication within 30 days prior to randomization
- Clinically significant systemic infection or uncontrolled chronic inflammatory disease (eg, rheumatoid arthritis, inflammatory bowel disease) as determined by the investigator during screening
- Known seropositivity for human immunodeficiency virus (HIV) or diagnosis of acquired immunodeficiency syndrome (AIDS), positive for hepatitis B surface antigen, or seropositive for hepatitis C virus
- History of pure red cell aplasia
- History of deep venous thrombosis or embolic event (eg, pulmonary embolism) within 6 months prior to randomization
- Known previous treatment failure to ESAs (eg, rHuEPO, darbepoetin alfa)
- ESA therapy within the 28 days prior to randomization
- Known hypersensitivity to recombinant ESAs or the excipients contained within the investigational product
- Transferrin saturation < 20% and ferritin < 50 ng/mL as assessed by the central laboratory during screening. Subjects must have both to be excluded (supplementation and retest acceptable).
- Abnormal renal function (serum creatinine level > 2 times [X] the upper limit of normal [ULN]) as assessed by the central laboratory during screening
- Abnormal liver function (total bilirubin > 2X ULN or liver enzymes alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 2.5X ULN for subjects without liver metastasis or ≥ 5X ULN for subjects with liver metastasis) as assessed by the central laboratory during screening. Subjects with documented Gilbert's Disease may be eligible.
- Received any RBC transfusion within 28 days prior to randomization
- Plan to receive any RBC transfusion between randomization and study day 1
- Less than 30 days since receipt of any investigational product or device. Investigational use/receipt of a medicinal product or device that has been approved by the country's local regulatory authority for any indication is permitted
- Subjects of reproductive potential who are pregnant, breast feeding or not willing to use effective contraceptive precautions during the study and for at least one month after the last dose of investigational product in the judgment of the investigator (including females of childbearing potential who are partners of male subjects)
- Previously randomized to this study

- Investigator has concerns regarding the ability of the subject to give written informed consent and/or to comply with study procedures (including availability for follow-up visits)

Investigational Product Dosage and Administration

Investigational product will be initiated on study day 1 and administered subcutaneously Q3W. The first dose of IP may be administered no earlier than on the same day that first line myelosuppressive cyclic chemotherapy is initiated. Investigational product will be supplied in vials containing a human serum albumin free polysorbate formulation and darbepoetin alfa concentration of 500 μg, 300 μg, 200 μg or 100 μg per mL or placebo (without active drug). Each box will contain a single vial of IP. Investigational product will be blinded.

Control Group: Placebo Q3W

Procedures

See Section 7 and/or Appendix A (Schedule of Assessments) for a complete list of procedures.

Statistical Considerations

General Approach

The analyses will be based on all randomized and consented subjects who receive at least one dose of IP. Sensitivity analyses will be based on all randomized and consented subjects and on a prospectively defined per-protocol analysis set.

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 then 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.

Sample Size Considerations

A total of 2700 deaths will 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 will 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. This estimation assumes survival time is exponentially distributed which allows for a conversion from a hazard ratio to medians. A median survival of 12.3 months (Sandler et al, 2006) was assumed as the median survival in the placebo arm in order to derive the difference in medians that correspond to a hazard ratio of 1.15.

Analysis of Primary Endpoint

The analysis of OS will use a Cox proportional hazards model, stratified by the randomization factors, with treatment group as the only covariate (a sensitivity analysis will include additional covariates potentially predictive of OS to assess the robustness of the primary approach). 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 is less than 1.15 using a 1-sided significance level of 0.025.

Analysis of Secondary Endpoints

The same methods used to analyze OS will be used to analyze PFS. Progression-free survival 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 using investigator-assessed scans) or death from any cause; subjects without either event will be censored at the last disease assessment date. Non-inferiority will be declared if the upper confidence limit for the hazard ratio

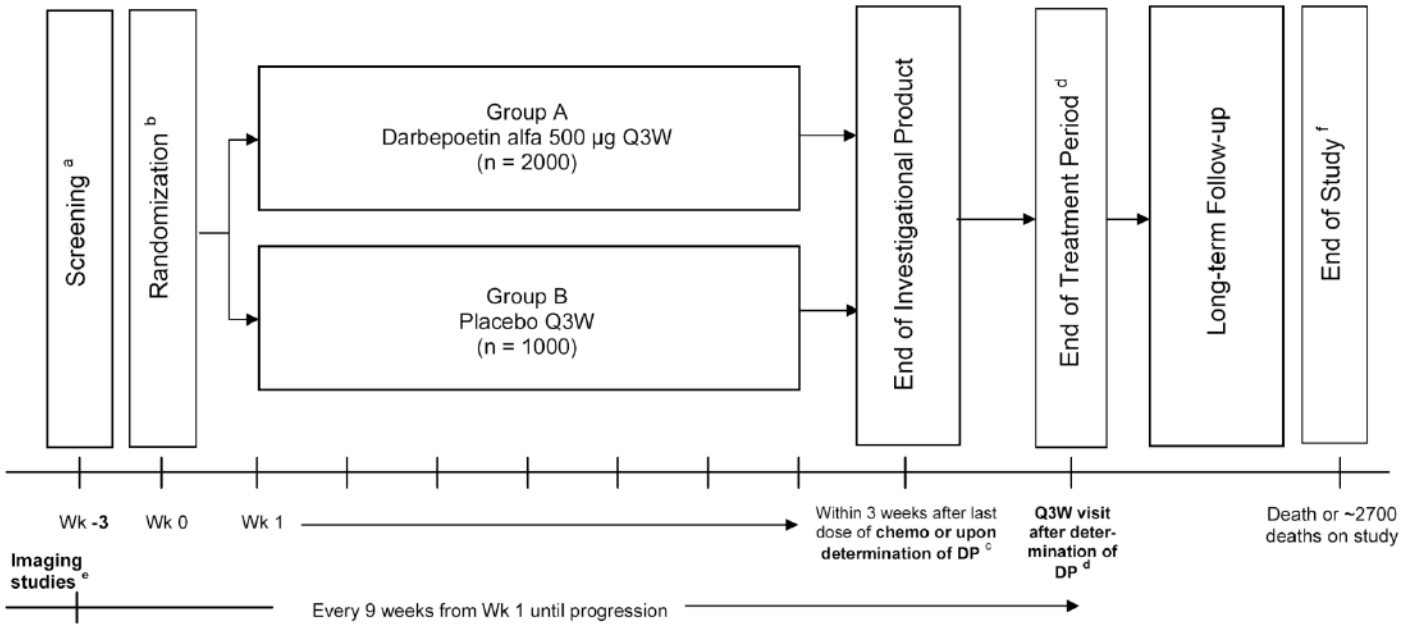
is less than 1.15 using a 1-sided significance level of 0.025. This analysis will be performed on all subjects in the primary analysis set who have not had disease progression prior to randomization.

To assess treatment group differences in the incidence of RBC transfusions or a hemoglobin ≤ 8.0 g/dL, the Cochran-Mantel-Haenszel method will be used which will adjust for the stratification factors at randomization. The incidence will be assessed from day 29 to the EOETP. This analysis will be performed on all subjects in the primary analysis set whose EOETP is ≥ day 29.

Interim Analysis and Early Stopping Guidelines

An independent Data Monitoring Committee (DMC) will assess safety on a regular basis throughout the duration of the study. The DMC will convene approximately once every 6 months for the first 2 years and once a year thereafter during the course of the trial. In addition, the DMC will oversee 5 formal interim analyses to assess harm (ie, inferiority of darbepoetin alfa), 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 evaluate changes in the practice of medicine to make recommendations regarding the ongoing feasibility of the trial. Prior to the completion of the recruitment period, the sponsor will re-assess the study assumptions (eg, recruitment rate and mortality rate) on a blinded basis, and may revise the sample size in order to ensure that the study completes.

Study Design and Treatment Schema



Q3W = once-every-3-weeks; Wk = Week; DP = disease progression

[a] Screening assessments will be performed within 21 days prior to randomization. The local laboratory hemoglobin sample to confirm eligibility must be obtained within 7 days prior to randomization.

[b] Subjects will be randomized in a 2:1 allocation (Group A:Group B), stratified by geographic region, histology, and screening hemoglobin (local laboratory hemoglobin; sample obtained within 7 days prior to randomization).

[c] Investigational product will be administered Q3W during the treatment period. IP will be discontinued within 3 weeks after the last dose of chemotherapy, or upon the determination of disease progression, whichever occurs first. For subjects who end IP without disease progression, imaging studies will continue every 9 weeks and study visits will continue Q3W until progression, at which time they will complete EOTP and enter LTFU. AEs and SAEs will be collected up to 30 days after the last dose of IP.

[d] EOTP visit will occur at the next Q3W visit after disease progression has been determined. Subjects who are unable to continue Q3W visits and Q9W imaging studies until disease progression should complete EOTP procedures at their next Q3W visit and will be asked to enter the LTFU period.

[e] Imaging studies (CT scans, MRI, or PET/CT) of the chest will be performed during screening (if needed for eligibility) and every 9 weeks (or sooner if clinically indicated) from Week 1 until disease progression. The same type of scan should be used throughout study. Subjects must have had a baseline image performed prior to starting first line chemotherapy for NSCLC. Bone scans, MRI, CT, PET, PET/CT, or X-ray should be performed when signs or symptoms suggestive of bone metastasis are present.

[f] Subjects will be followed for survival until death, or until approximately 2700 deaths have occurred on the study.

Study Glossary

Abbreviation or Term	Definition/Explanation
ACS	Acute coronary syndromes
AE	Adverse Event
AGO	Arbeitsgemeinschaft Gynaekologische Onkologie (German Gynecological Oncology Study Group)
AHRQ	Agency for Healthcare Research and Quality
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATE	Arterial thromboembolic event
Baseline Hemoglobin	Screening hemoglobin (ie, local laboratory hemoglobin; sample obtained within 7 days prior to randomization)
BEST	Breast Cancer Erythropoietin Survival Trial
BP	Blood pressure
BUN	Blood urea nitrogen
CA	Cancer
CBC	Complete blood count
CDM	Clinical Data Management
CI	Confidence interval
CIA	Chemotherapy-induced anemia
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
dL	Deciliter
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DP	Disease progression
DVT	Deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
Enroll, Enrolled, or Enrollment	Enrollment is defined as the point in time when all required screening procedures have been completed, all eligibility criteria are met, and IVR/IWR System has been accessed to randomize the subject.

Abbreviation or Term	Definition/Explanation
EOETP	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.
EOS	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 (ie, when 2700 deaths have occurred), whichever comes first.
EOTP	End of Treatment Period will occur at the next Q3W visit after disease progression has been determined.
EPO	Erythropoietin
EpoR	Erythropoietin receptor
ESA	Erythropoiesis stimulating agent
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-PET
g/dL	Gram per deciliter
GBG	German Breast Group
GGT	Gamma-glutamyltransferase
GOG	Gynecologic Oncology Group
HIV	Human immunodeficiency virus
HR	Hazard ratio
HSA-free	Human serum albumin-free
ICF	Informed consent form
ICH GCP	International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice
ID	Identification
IEC/IRB	Independent ethics committee/institutional review board
IP	Investigational product
IV	Intravenous
IVR/IWR System	Interactive Voice Response/Interactive Web Response System
PPD	[redacted]
kg	Kilogram
LDH	Lactate dehydrogenase
LTFU	Long-term follow-up
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndromes
mL	Milliliter
MRI	Magnetic resonance imaging

Abbreviation or Term	Definition/Explanation
NA	Not applicable
NE	Inevaluable
ng	Nanogram
NSCLC	Non-small cell lung cancer
ODAC	Oncologic Drug Advisory Committee
OR	Odds ratio
OS	Overall survival
PD	Progressive disease
PE	Physical examination or pulmonary embolism
PET	Positron emission tomography
PET-CT	Positron emission tomography-computer tomography
PFS	Progression-free survival
pg	Picogram
PICC	Peripherally-inserted central catheter
PIN	Personal identification number
PR	Partial response
Q3M	Once-every-3-months
Q3W	Once-every-3-weeks
Q9W	Once-every-9-weeks
QW	Once-weekly
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
rHuEPO	Recombinant human erythropoietin
SAE	Serious adverse events
SAER	Serious adverse event report
SCLC	Small cell lung cancer
Screening hemoglobin	Local laboratory hemoglobin; sample obtained within 7 days prior to randomization
Screening period	Starts when the subject signs and dates the informed consent form and ends when the subject is randomized or screen failed. Must not exceed 21 days.
SD	Stable disease
SUSAR	Suspected unexpected serious adverse reactions
TIA	Transient ischemic attack
TIBC	Total iron binding capacity
Tsat	Transferrin saturation

Abbreviation or Term	Definition/Explanation
Treatment period	Starts when the subject is randomized and ends at the next Q3W visit after disease progression has been determined (EOTP). Note that EOTP is based on disease progression, not IP dosing.
TVE	Thrombovascular event
μg	microgram
ULN	Upper limit of normal
US	Ultrasound
VTE	Venous thromboembolic event
WBC	White blood cell
Wk	Week

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1. OBJECTIVES

1.1 Primary

The primary objective is:

- 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

1.2 Secondary

The secondary objectives are:

- 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
- 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
- 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

2. BACKGROUND AND RATIONALE

2.1 Background

2.1.1 Anemia

Anemia frequently develops in patients with neoplastic disease and is associated with mild to moderate erythroid hypoplasia, reduction in RBC survival and abnormal ferrokinetics (Quirt et al, 2002). The etiology of anemia in cancer patients tends to be multifactorial including a direct inhibitory effect by various pro-inflammatory cytokines on the proliferation and differentiation of erythroid precursors within the bone marrow (Weiss and Goodnough, 2005) coupled with a blunted erythropoietic response to endogenous erythropoietin (Cazzola, 2000; Miller et al, 1990). Additional etiologies of cancer related anemia include bone marrow infiltration by tumor, poor nutritional status, tumor related hemorrhage and myelotoxicity from systemic chemotherapy and/or radiotherapy (Ray-Coquard et al, 1999).

The severity of cancer associated anemia depends in part on the extent of the underlying neoplastic disease as well as the regimen of cytotoxic treatments administered. In a state of persistent anemia, compensatory mechanisms for the reversal of tissue hypoxia are instigated including shunting of blood from non-vital areas to more essential oxygen-sensitive organs (Vatner, 1974) along with compensatory cardiopulmonary hyperactivities resulting in increased cardiac work load

(Metivier et al, 2000; Hébert et al, 2004). Symptoms of anemia may include fatigue, dyspnea on exertion, shortness of breath, decreased motivation, and impaired cognition and depression, with fatigue affecting greater than 65% of patients during their chemotherapy treatments. Fatigue is regarded by patients as a symptom that has a greater negative impact on their daily lives than many other cancer or treatment related complications (Harper and Littlewood, 2005).

2.1.2 Chemotherapy-induced Anemia

Myelosuppressive chemotherapy is a common cause of anemia in cancer patients with the degree of chemotherapy-induced anemia (CIA) dependent upon the type, schedule and intensity of the chemotherapy regimen. For patients with non-myeloid malignancy, the highest frequency of anemia occurs among those undergoing systemic therapies for lymphoma, lung carcinoma, ovarian carcinoma or urothelial carcinoma (Ludwig and Fritz, 1998; Tas et al, 2002; Skillings et al, 1993). In situations where rapid reversal of anemia is required RBC transfusion is indicated, although allogeneic blood product transfusion carries potential undesirable risks including subjecting the recipient to possible infection with viral agents such as hepatitis and human immunodeficiency virus (Barbara, 2004), acute hemolytic transfusion reaction (Sloop and Friedberg, 1995), transfusion-related acute lung injury (Looney et al, 2004), allergic reactions (Gilstad, 2003), iron overload (Franchini and Veneri, 2004) or hypervolemia-related exacerbation of congestive heart failure symptoms (Freudenberger and Carson, 2003). As an alternative to blood product transfusion, erythropoiesis stimulating agents (ESAs) have been employed as a pharmacological measure to palliate and/or reverse the anemia associated with chemotherapy in non-emergent settings, effectively reducing a patient's transfusion requirement as well as the number of RBC units required by those who do receive transfusions.

2.1.3 Darbepoetin alfa

Darbepoetin alfa, a novel glycoengineered analog of rHuEpo with 2 additional extra consensus N-linked carbohydrate addition sites, has a longer mean residence time and a 3-fold longer serum half-life than rHuEpo in both dialysis and cancer patients as well as demonstrating augmented *in vivo* activity (Egrie et al, 2003; Macdougall et al, 1999; Elliott et al, 2004; Jung and Schwartz, 2002). Darbepoetin alfa is manufactured by recombinant DNA technology using a Chinese hamster ovary mammalian cell line and is currently licensed in the United States, European Union, Australia, and Canada for the treatment of anemia associated with chronic renal failure (including patients who are and

are not on dialysis) and for the treatment of anemia in patients with non-myeloid malignancy where anemia is due to the effects of concomitantly administered chemotherapy.

Details of the chemistry, preclinical pharmacology, pharmacokinetics, and toxicology of darbepoetin alfa are contained in the current version of the Investigator's Brochure.

2.2 Safety Concerns of ESAs

In the CIA setting, an increased risk of thromboembolic events associated with the use of ESAs is well documented and reflected in the current ESA label. However, safety concerns regarding increased mortality or tumor progression with ESAs have also been raised by 8 of 59 studies conducted outside of the currently-approved treatment indication or recommended target hemoglobin range (Table 1). Data from randomized, controlled studies evaluating mortality in subjects treated with ESAs in accordance with current labeling are not available.

Table 1. Studies That Have Raised Safety Concerns for ESA Use

Study	Population	Primary endpoint	Hemoglobin target (g/dL)	Key results for survival and/or disease progression
Chemotherapy alone or chemoradiotherapy				
Leyland-Jones et al, 2005 (BEST trial)	Metastatic breast CA N = 939	12-month OS	12 – 14	Shortened overall survival and increased deaths attributed to disease progression at 4 months in ESA group Higher 12-month mortality in ESA group: HR 1.37 (95% CI: 1.07, 1.75, p = 0.012)[a] Long-term follow up OS similar between ESA and control groups: HR 1.04 (95% CI: 0.90, 1.20; p=0.6)[b]
Hedenus et al, 2003 Hedenus et al, 2005	Lymphoid malignancy N = 344	hemoglobin response	13 – 14 (women); 13-15 (men)	Higher mortality in ESA group: HR: 1.36 (95% CI: 1.02, 1.82)[a]
PREPARE (AGO/GBG)	Early breast cancer N = 733	Relapse-free survival and OS	12.5 – 13	No significant difference in pathologic complete remission (final data) Lower survival rate in the ESA group (interim data) (HR 1.42, 95% CI: 0.93, 2.18)[a] Lower relapse-free survival rate in the ESA group (interim data) (HR 1.33, 95% CI: 0.99, 1.79)[a]
Thomas et al, 2007 (GOG study)	Cervical cancer N = 114	PFS, OS and locoregional control	12 – 14	More frequent local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) in ESA group Lower 3-year OS in ESA group HR 1.28, 95% CI: 0.68, 2.42)[a] Lower 3-year PFS in ESA group HR 1.06, 95% CI: 0.58, 1.91)[a]

[a] Aranesp® Prescribing Information
[b] Data on file
[c] Cancer study 8 in Aranesp® Prescribing Information: Median survival was shorter in the ESA group (HR 1.30, 95% CI: 1.07, 1.57).

Table 1. Studies That Have Raised Safety Concerns for ESA Use

Study	Population	Primary endpoint	Hemoglobin target (g/dL)	Key results for survival and/or disease progression
No radiotherapy or chemotherapy				
Smith et al, 2008	Mixed tumors N = 989	RBC transfusions	12–13	Higher mortality in ESA group: HR 1.22 (95% CI: 1.03, 1.45) [c]
Wright et al, 2007	NSCLC N = 70	Quality of life	12–14	Shorter survival duration in the ESA group (HR 1.84; p = 0.04) [a] Deaths due to disease progression: 89% ESA, 91% control
Radiotherapy only				
Henke et al, 2003 (ENHANCE study)	Head and neck CA N = 351	Locoregional PFS	≥14 (women); ≥15 (men)	Shorter OS in ESA group: (HR 1.39, 95% CI: 1.05, 1.84; p = 0.02) [a] Locoregional PFS poorer in ESA group: HR 1.62 (95% CI: 1.22, 2.14; p = 0.0008) [a]
Overgaard et al, 2007 (interim data) (DAHANCA-10 study)	Head and neck CA N = 522	Locoregional disease control	14–15.5	Higher 5- year mortality in ESA group: RR 1.28 (95% CI: 0.98, 1.68; p = 0.08) [a] 5-year locoregional control poorer in ESA group: RR 1.44 (95% CI: 1.06, 1.96; p = 0.02) [a]

[a] Aranesp® Prescribing Information
[b] Data on file
[c] Cancer study 8 in Aranesp® Prescribing Information: Median survival was shorter in the ESA group (HR 1.30, 95% CI: 1.07, 1.57).

Several study-level meta-analyses have been performed to examine the relationship of ESAs and overall mortality in patients with cancer (Table 2). In addition, the EPO Individual Patient Data Meta-analysis Collaborative Group, a working group of the Cochrane Hematological Malignancies Group has recently completed and presented an analysis of overall mortality using patient-level data provided by ESA study sponsors and independent investigators (Bohlius et al, 2008). It is important to note that these meta-analyses are comprised of studies that did not use ESAs in accordance with current FDA label, as they included patients without chemotherapy-induced anemia and/or treated to higher hemoglobin targets. The results of these meta-analyses differ somewhat based on differences in the studies included and exact methodology used.

However, the hazard ratio estimates for meta-analyses limited to studies where patients are receiving chemotherapy are similar and do not indicate a statistically significant increase in mortality risk. Although these results may be viewed as reassuring, well-designed, randomized, controlled clinical trials are needed to completely characterize the effects of ESAs on survival and tumor progression in chemotherapy-induced anemia.

Table 2. Comparison of Meta-analyses of Overall Mortality

	All Studies				Chemotherapy Studies			
	n (studies)	Events	Risk Estimate	Survival 95% CI	n (studies)	Events	Risk Estimate*	Survival 95% CI
Cochrane (Bohlius et al 2006)	8167[a] (42)	2234[a]	1.08	0.99, 1.18	6282 (30)	1743	1.02	0.90, 1.15
AHRQ (Seidenfeld et al 2006)	7891 (39)	2202	1.08	0.98, 1.18	6704[b] (32)	1759[b]	1.03	0.92, 1.15
Bennett et al, 2008	>13122 (51)	>2632[c]	1.10	1.01, 1.20	>7670 (41)	>1940[c]	1.03	0.94, 1.13
ODAC 2008 (Amgen)	15249 (59)	5340	1.05	0.97, 1.14	12034 (46)[d]	4009	1.02	0.93, 1.13
Cochrane (Bohlius et al 2008)	13933 (53)	4993	1.06[e]	1.00, 1.12	10441 (38)[e]	3555	1.04[e]	0.97, 1.11

* Estimated by Amgen based on the reported original classification of studies
[a] Cochrane included 1 MDS study (3 events/66 subjects); Chemotherapy excluded 5 CTxRTx studies and 2 studies classified as "Unclear"; 3 chemotherapy studies had no deaths in either arm
[b] Assume same classification as Cochrane since same studies and events were used but added in 2 studies classified as "Unclear" in Cochrane
[c] Bennett did not report the number of events for 9 studies (7 chemotherapy studies)
[d] Chemotherapy studies included studies where both chemotherapy and radiotherapy could be given concomitantly or sequentially
[e] Patient-level meta-analysis; estimates based on Cox proportional hazards model stratified by study; Chemotherapy studies included were those where at least 70% of study subjects received myelosuppressive chemotherapy

2.2.1 Non-small Cell Lung Cancer

In the setting of lung cancer, only the EPO-CAN-20 study has raised concerns regarding the effect of ESAs on overall survival. The EPO-CAN-20 study (Wright et al, 2007) was a 12-week, randomized, double-blind, placebo-controlled study that was initially designed to examine the effect of epoetin alfa 40000 U once-weekly (QW) on

quality-of-life in subjects with advanced NSCLC and hemoglobin level ≤ 12.0 g/dL who neither received chemotherapy 2 months prior to the study nor were expected to receive chemotherapy during the study. Study drug was withheld if hemoglobin level exceeded 14.0 g/dL.

Due to concerns regarding thromboembolic events in other ESA trials, an unplanned safety analysis of this study was conducted after the first 70 subjects (of a planned 300 subjects) were randomized (33 epoetin alfa group, 37 placebo group). In this analysis, OS in the subjects receiving epoetin alfa was worse than the subjects who received placebo (63 versus 129 days, p=0.04), leading to termination of the study.

The majority of deaths in this study, 66 of 70 enrolled subjects, was reported to be due to underlying lung cancer; 28 of 32 subjects (87.5%) in the epoetin alfa group and 31 of 34 subjects (91.2%) in the placebo group died. Tumor progression was not assessed in this study. Furthermore, the study was conducted in subjects not receiving chemotherapy and who were treated to higher hemoglobin levels than those recommended in the prescribing information. Consequently no conclusions can be drawn regarding the safety of ESAs in lung cancer patients within the labeled indication of CIA when ESAs are used in accordance with current labeling.

2.2.2 Combined Analysis of Safety of ESAs in Lung Cancer

Five randomized, controlled lung cancer studies in CIA (representing 1943 subjects) have collected long-term follow-up information [Pirker et al, 2007; Grote et al, 2005; Vansteenkiste et al, 2002; Milroy et al, 2003; and EPO-GER-22 (ODAC 2008)]. An additional two studies [EPO-CAN-15 (ODAC 2008) and Thatcher et al, 1999] reported deaths on study but did not collect long-term follow-up information. In all studies in CIA, ESAs had a neutral effect on survival relative to the control group. These studies, along with study EPO-CAN-20 which did not involve chemotherapy, are summarized in Table 3.

Table 3. Summary of Overall or On-study Death or Progression in Lung Cancer Studies

	Tumor type	HR or OR for OS (95% CI)	Progression endpoints (95% CI)
Study with negative signal (subjects not receiving chemotherapy)			
Wright et al, 2007 (EPO-CAN-20)	Advanced NSCLC	HR[b]: 1.54 (0.94, 2.53)	OR[a] death due to disease progression: 1.08 (0.30, 3.95)
Studies with neutral signal (subjects receiving chemotherapy)			
Pirker et al, 2007	Extensive stage SCLC	HR: 0.93 (0.78, 1.11)	HR: 1.02 (0.86, 1.21)
Vansteenkiste et al, 2002	NSCLC + SCLC NSCLC SCLC	HR: 0.78 (0.59, 1.01) HR: 0.85 (0.62, 1.17) HR: 0.63 (0.38, 1.04)	HR: 0.77 (0.60, 0.99) HR: 0.91 (0.68, 1.23) HR: 0.55 (0.34, 0.88)
EPO-GER-22 (ODAC 2008)	NSCLC (stage 3, inoperable)	HR[b]: 0.81 (0.64, 1.02)	N/A
Grote et al, 2005 (N93-004)	SCLC (all stages)	HR[b]: 1.17 (0.89, 1.54)	OR[a] (PD/EOS Tumor Response): 0.85 (0.50, 1.44)
Milroy et al, 2003 (EPO-INT-49)	NSCLC (stage 3B and 4)	HR[b]: 1.13 (0.89, 1.44)	OR[a] (PD/EOS Tumor Response): 0.90 (0.57, 1.41)
EPO-CAN-15 (ODAC 2008)	Limited stage SCLC	OR[a,c]: 0.93 (0.43, 2.00)	N/A
Thatcher et al, 1999	SCLC (all stages)	OR[a,c]: 1.21 (0.30, 4.93)	N/A

[a] Calculated by Amgen for ODAC 2008
[b]: Calculated by J&JPRD for ODAC 2008
[c]: Based on reported deaths on-study; long-term (>6 months after ESA use) was not evaluated
HR: hazard ratio; J&JPRD: Johnson & Johnson Pharmaceutical Research & Development; OR: odds ratio; SCLC: small-cell lung cancer; N/A: not available

When the study-level data from all controlled CIA studies in subjects with lung cancer (including those without long-term follow up) were meta-analyzed, the OR (ESA versus control; random effects model) for mortality was 0.85 (95% CI: 0.66, 1.04). Given this continued uncertainty as to whether ESAs affect OS or PFS in NSCLC, particularly at a hemoglobin ceiling of 12.0 g/dL, this study is designed to address these questions.

2.3 Rationale

The 20070782 study is a large, multi-national study intended to provide safety and efficacy data that are applicable to all regions where ESAs are approved for the treatment of chemotherapy-induced anemia.

The study design, including hemoglobin initiation and ceiling levels, and non-responder and dose reduction algorithms will allow sufficient exposure to study drug to evaluate safety outcomes while ensuring consistent dosing, minimizing risks and maintaining potential benefits to subjects. While some design parameters are not consistent with the United States and other regional labels, Amgen intends for the results of this study to be directly extrapolated to corresponding product labeling and to risk: benefit decisions about the use of ESA in the oncology setting.

The definition of non-inferiority in this study will be the exclusion of a hazard ratio (darbepoetin alfa to placebo) of 1.15 with a 1-sided significance level of 0.025 (ie, the upper limit of the 95% confidence interval is < 1.15). This definition is derived from a benefit:risk assessment. 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.

2.4 Hypothesis

The primary hypothesis to be tested is that the OS of subjects with CIA with stage IV NSCLC receiving cyclic chemotherapy treated with darbepoetin alfa 500 μg Q3W to a hemoglobin ceiling of 12.0 g/dL will not be worse than the OS of anemic subjects treated with placebo.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a double-blind, randomized, placebo-controlled phase 3 non-inferiority study in subjects with CIA receiving multi-cycle chemotherapy for the treatment of stage IV NSCLC. Approximately 3000 subjects with stage IV NSCLC receiving or about to receive first line chemotherapy will be enrolled into the study. Subjects will be randomized in a 2:1 allocation (Group A: Group B):

- Group A: darbepoetin alfa 500 μg Q3W to a hemoglobin ceiling of 12.0 g/dL
- Group B: placebo Q3W

Section 6.1.2 describes the dosing adjustment algorithms.

Randomization for NSCLC will be stratified by geographic region, histology, and screening hemoglobin (local laboratory hemoglobin; sample obtained within 7 days prior to randomization).

The study consists of a screening period (up to 21 days), a treatment period, and a long-term follow up (LTFU) period. IP will be administered Q3W during the treatment period. IP will be discontinued within 3 weeks after the last dose 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. Once disease progression has been determined, subjects will complete the EOTP visit and then enter LTFU and will be followed for survival until death, or until approximately 2700 deaths have occurred in the study (End of Study [EOS]).

Investigational product vials and boxes will be packaged in a blinded manner and identified by a unique box number for assignment via Interactive Voice Response/ Interactive Web System (IVR/IWR). Darbepoetin alfa and placebo will be administered subcutaneously by a trained healthcare professional at the site.

The overall study design is described in a study schema at the end of the protocol synopsis section and the Schedule of Assessments (Appendix A).

The study endpoints are defined in Section 10.2.

3.2 Number of Centers

Approximately 500 sites will participate in this study across the world (eg, North America, Europe, Asia, Africa, Australia, and Latin America). Subject enrollment will be competitive and sites that do not enroll subjects within 6 months of site initiation may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects.” This study will randomize approximately 3000 subjects with stage IV NSCLC in order to observe 2700 death events. For additional information on the sample size justification, please see Section 10.3.

3.4 Estimated Study Duration

3.4.1 Study Duration for Subjects

Subject enrollment may occur over approximately a 7-year period. The study will consist of a screening period (up to 21 days), a treatment period in which Q3W study visits and Q9W radiological assessments will continue until disease progression, the EOTP visit, and the LTFU period. Once disease progression has been determined, subjects will complete the EOTP visit at their next Q3W visit and then enter the LTFU and will be followed for survival status every 3 months until their death or until approximately 2700

deaths have occurred. Based on estimated recruitment rate and the estimated OS rate of patients with NSCLC, it is anticipated that the study duration may take approximately 10 years from the first subject enrolled into study to EOS.

3.4.2 End of Study

Since this is an event driven protocol, this study will end when approximately 2700 deaths have occurred.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (ie, age, sex, race), date and outcome of the screening (eg, enrolled into study, reason for ineligibility, or refused to participate).

4.1 Inclusion Criteria

4.1.1 Disease Related

- Subjects with stage IV NSCLC (not recurrent or re-staged)
- Expected to receive at least 2 additional cycles (at least 6 total weeks) of first line myelosuppressive cyclic chemotherapy after randomization. Subjects should not be expected to receive only maintenance chemotherapy.

4.1.2 Demographic

- Eastern Cooperative Oncology Group performance status of 0 or 1 as assessed within 21 days prior to randomization
- 18 years of age or older at screening
- Life expectancy > 6 months based on the judgment of the investigator and documented during screening

4.1.3 Laboratory

- Hemoglobin level ≤ 11.0 g/dL as assessed by the local laboratory; sample obtained within 7 days prior to randomization (retest in screening is acceptable)
- Adequate serum folate (≥ 2 ng/mL) and vitamin B_{12} (≥ 200 pg/mL) levels assessed by central laboratory (supplementation and retest acceptable) during screening

4.1.4 Imaging

- Subjects must have had a baseline scan (CT, MRI, or PET/CT) of the chest to assess disease burden before starting on first line chemotherapy for NSCLC and those images must have been reviewed by the investigator prior to randomization. If the scan was performed more than 28 days prior to randomization, an additional scan must be performed and reviewed by the investigator to confirm that the patient has not progressed before randomization.

4.1.5 Ethical

- Before any study-specific procedure, the appropriate written informed consent must be obtained from the subject or a legally accepted representative (see Section 12.1)

4.2 Exclusion Criteria

4.2.1 Disease Related

- Known primary benign or malignant hematologic disorder which can cause anemia
- History of, or current active cancer other than NSCLC, with the exception of curatively resected non-melanomatous skin cancer, curatively treated cervical carcinoma in situ, or other primary solid tumors curatively treated with no known active disease present and no curative treatment administered for the last 3 years
- Received any prior adjuvant or neoadjuvant therapy for NSCLC
- Subjects with a history of brain metastasis
- Uncontrolled hypertension (systolic BP > 160 mmHg or diastolic BP > 100 mmHg), or as determined by the investigator during screening
- History of neutralizing antibody activity to rHuEPO or darbepoetin alfa
- Uncontrolled angina, uncontrolled heart failure, or uncontrolled cardiac arrhythmia as determined by the investigator at screening. Subjects with known myocardial infarction within 6 months prior to randomization.
- Subjects with a history of seizure disorder taking anti-seizure medication within 30 days prior to randomization
- Clinically significant systemic infection or uncontrolled chronic inflammatory disease (eg, rheumatoid arthritis, inflammatory bowel disease) as determined by the investigator during screening
- Known seropositivity for HIV or diagnosis of AIDS, positive for hepatitis B surface antigen, or seropositive for hepatitis C virus
- History of pure red cell aplasia
- History of deep venous thrombosis or embolic event (eg, pulmonary embolism) within 6 months prior to randomization

4.2.2 Laboratory

- Transferrin saturation < 20% and ferritin < 50 ng/mL as assessed by the central laboratory during screening. Subjects must have both to be excluded (supplementation and retest acceptable).
- Abnormal renal function (serum creatinine level > 2X ULN) as assessed by the central laboratory during screening
- Abnormal liver function (total bilirubin > 2X ULN or liver enzymes ALT or AST > 2.5X ULN for subjects without liver metastasis or ≥ 5X ULN for subjects with liver metastasis) as assessed by the central laboratory during screening. Subjects with documented Gilbert's Disease may be eligible**.**

4.2.3 Medications

- Received any RBC transfusion within 28 days prior to randomization.
- Plan to receive any RBC transfusion between randomization and study day 1
- Known previous treatment failure to ESAs (eg, rHuEPO, darbepoetin alfa)
- ESA therapy within the 28 days prior to randomization

- Known hypersensitivity to recombinant ESAs or the excipients contained within the investigational product

4.2.4 General

- Less than 30 days since receipt of any investigational product or device. Investigational use/receipt of a medicinal product or device that has been approved by the country's local regulatory authority for any indication is permitted
- Subjects of reproductive potential who are pregnant, breast feeding or not willing to use effective contraceptive precautions during the study and for at least one month after the last dose of investigational product in the judgment of the investigator (including females of childbearing potential who are partners of male subjects)
- Previously randomized to this study
- Investigator has concerns regarding the ability of the subject to give written informed consent and/or to comply with study procedures (including availability for follow-up visits)

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable, and that the site undergoes a formal site initiation visit (see Section 12.3). The written informed consent form (ICF) must be signed and personally dated by the subject or legally acceptable representatives and by the person who conducted the informed consent discussion before any study specific procedures are performed.

5.1 Screening

The screening period, which starts when the subject signs and dates the ICF and ends when the subject is randomized or screen failed, must not exceed 21 days. All subjects who enter into the screening period will receive a unique subject identification (ID) number, assigned by IVR/IWR System before any study procedures are performed. The unique subject ID will be comprised of 9 digits (eg, 82-3456-789). The first 2 digits represent the study code (82), 3 to 6 are for the site number, and 7 to 9 are for the subject number at the site. This number will be used to identify the subject throughout the study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed at the time of re-screening (if required) or randomization. The subject identification number is not the same as the randomization number assigned for the study. The randomization number will be assigned by the IVR/IWR System at the time of randomization.

Subjects determined to be screen failures (based on laboratory or any other assessment) will not be eligible for immediate participation and must be registered as a screen failure in IVR/IWR System. Laboratory assessments used to determine subject eligibility may be repeated during the screening period before the subject is considered a screen failure. Screen-failed subjects may be re-screened at the investigator's discretion (the subject will maintain the same subject ID number provided at the initial screening). Subjects who are determined not eligible after re-screen must be registered as a screen fail in IVR/IWR System. Subjects must be re-consented if more than 30 days have elapsed between date of informed consent and date of randomization.

5.2 Treatment Assignment

The site will obtain the subject's treatment group randomization prior to or at the first dosing visit via IVR/IWR System. At each dosing visit the site will access IVR/IWR System and enter the last hemoglobin value and, if applicable, any transfusion information in order to obtain the appropriate treatment assignment for each subject. The appropriate volume and box number of the vial of IP to be administered to each subject will be provided by IVR/IWR System.

5.3 Randomization

Randomization may occur on the same day as the first dose of IP (ie, study day 1), or it may occur up to 4 days prior to study day 1.

Eligible subjects will be randomized in a 2:1 allocation (Group A: Group B):

- Group A: darbepoetin alfa 500 μg Q3W to a hemoglobin ceiling of 12.0 g/dL
- Group B: placebo Q3W

Randomization will be stratified by:

- Histology (squamous versus other)
- Screening hemoglobin (local laboratory hemoglobin value; sample obtained within 7 days prior to randomization) (< 10.0 g/dL versus ≥ 10.0 g/dL)
- Geographic region

Randomization will be based on a schedule generated by Amgen before the start of the study and will be centrally executed using IVR/IWR System. The subject, site personnel, and Amgen study personnel and designees will be blinded to the randomization treatment group assignment, with the exception of those circumstances where the investigator deems it necessary to break the blind in order to provide appropriate medical treatment for the subject. Refer to Section 10.4 for details on when and how the randomization code may be broken.

6. TREATMENT PROCEDURES

Darbepoetin alfa and placebo will be considered investigational products for the purposes of maintaining the blind to treatment groups in this study.

6.1 Investigational Product Dosage, Administration, and Schedule

Investigational product will be provided as a human serum albumin free polysorbate formulation that is a clear, colorless, sterile, preservative-free protein solution containing 500 μg, 300 μg, 200 μg, and 100 μg of darbepoetin alfa per mL or placebo (without the active drug). For dose adjustment and stopping rules, refer to Section 6.1.2. Investigational product administration including date of dosing will be recorded on the case report forms (CRFs).

The day of the first dose of IP (darbepoetin alfa or placebo) will be considered study day 1 and may occur up to 4 days after randomization. The first dose of IP must be administered no earlier than on the same day that first line myelosuppressive cyclic chemotherapy is initiated. Investigational product should be administered subcutaneously by the appropriately trained and designated study personnel at the dosing schedule outlined in the Schedule of Assessment (Appendix A). The correct box number of IP to be administered will be assigned via IVR/IWR System. It is important that the correct hemoglobin value and transfusion information are entered into IVR/IWR System for each dosing visit. Failure to comply with IVR/IWR System dosing instructions may result in the removal of the subject from the study and possible suspension of further enrollment activities at the site.

Investigational product should be stored, prepared and administered according to the instructions in the Pharmacy Guide (**Appendix E**).

6.1.1 Dose Escalation

No dose escalation will be allowed in this study.

6.1.2 Dosage Adjustments and Stopping Rules

Dose adjustments will be based on the most recent local laboratory hemoglobin value (obtained on the day of the dosing visit or 1 day prior to the dosing visit), incidence of RBC transfusion in the last 21 days prior to the dosing visit, disease and chemotherapy status. An RBC transfusion includes either whole blood or packed RBC transfusion. Before the subject can be dosed, the site personnel will enter the relevant information into IVR/IWR System during a medication assignment call.

Automated programming in IVR/IWR System will determine if dose adjustment or withholding is required based on the dosing rules listed below. If dose adjustment occurs, all subsequent adjustments will be relative to the new dose. Rate of rise calculations will be based on the subject's hemoglobin value at the time of the last dose or for the last 3 weeks of study if more than 3 weeks have passed since the last dose.

If a subject stops myelosuppressive chemotherapy completely, IP will be discontinued within 3 weeks after the last dose of chemotherapy.

At any time during the study, the investigator may withhold or discontinue IP administration for any subject who experiences a severe or life-threatening adverse event reported by the investigator to be related to IP. The Common Toxicity Criteria for Adverse Events (CTCAE) grading scale will be used as a guide for grading the adverse events. Refer to Section 9 for more detail on adverse event reporting. If an investigator decides to discontinue IP (regardless of whether the subject will continue in the study), the site personnel are to enter this information into the IVR/IWR System.

IVR/IWR System will instruct investigators to withhold IP or to reduce the dose of IP according to the following criteria, which include non-responsiveness, rapid rate of rise of hemoglobin, and high hemoglobin value. These criteria are described as follows:

- A non-responder is defined as a subject who, after study day 35, receives 2 or more transfusions that are ≥ 21 days apart and ≤ 42 days apart. Non-responders will be discontinued from darbepoetin alfa if they are on the darbepoetin alfa treatment arm and will be switched to placebo (by IVR/IWR System).
- If hemoglobin increases by > 1.5 g/dL in any 21 day period in the absence of RBC transfusion, the IVR/IWR System will reduce the dose of IP by approximately 40% of the previous dose (ie, 500 μg to 300 μg; 300 μg to 200 μg, 200 μg to 100 μg) for a maximum of 3 dose reductions. Investigational product will be discontinued after 3 dose reductions.
- If hemoglobin > 12.0 g/dL, the IVR/IWR System will instruct the investigator that IP will be temporarily withheld until hemoglobin falls to ≤ 12.0 g/dL at which time treatment will be restarted at a dose which is reduced by approximately 40% of the previous dose (ie, 500 μg to 300 μg; 300 μg to 200 μg, 200 μg to 100 μg) for a maximum of 3 dose reductions. Investigational product will be discontinued after 3 dose reductions.

6.1.3 Missed or Delayed Doses

Investigational product should be administered on the same day Q3W throughout the study. However, if IP cannot be administered as scheduled, every attempt should be made to administer the IP within ± 6 days of the Q3W schedule. If a dosing visit does not occur within this window, then it is considered a missed dose. No 2 separate IP administrations should occur within a 14-day interval. After a missed or delayed dose,

every attempt should be made to resume dosing according to the original dosing schedule.

6.2 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except for those listed in Section 6.3. Selected medications administered while the subject is on study must be recorded on the CRF.

6.2.1 RBC Transfusion

Subjects may receive RBC (whole blood or packed red blood cell) transfusion if medically indicated. Documentation of RBC transfusions received while on study will include date of transfusion and number of units and volume, reason for transfusion, any associated AEs including VTE, the associated pre-transfusion hemoglobin value and any AEs as a result of the transfusion. Red blood cell transfusion is recommended when hemoglobin level decreases to $\leq$ 8.0 g/dL. Subjects may also require a RBC transfusion when hemoglobin level is > 8.0 g/dL if clinically indicated (eg, subject is symptomatic). Administration of a RBC transfusion when the hemoglobin level is > 8.0 g/dL, in the absence of accompanying signs and/or symptoms, is not recommended.

6.2.2 Chemotherapy

Subjects should be expected to receive at least 2 additional cycles (at least 6 total weeks) of first line myelosuppressive cyclic chemotherapy (eg, standard doublet chemotherapy) after randomization. Subjects should not be expected to receive only maintenance chemotherapy. First line chemotherapy in combination with other targeted therapy (eg, biologics) that is considered acceptable standard for first line treatment of NSCLC is allowed. Chemotherapy regimens or combination therapies including chemotherapy will be dependent upon local standard and practices, however, chemotherapy regimens containing investigational agents (ie, not approved for any indication by the applicable regulatory authority) will not be allowed. If the first line chemotherapy regimen changes at any time during the study (eg, due to toxicity) or if optional myelosuppressive maintenance therapy is initiated, then the subject may receive IP as scheduled as long as the subject continues to receive myelosuppressive chemotherapy and does not have disease progression. If a subject stops myelosuppressive chemotherapy completely, IP will be discontinued within 3 weeks after the last dose of chemotherapy.

Chemotherapy regimen including date of administration will be recorded in the subject's CRF.

6.2.3 Supplementation

Iron supplementation is recommended for subjects with transferrin saturation < 20% at any point during the study. Iron supplementation may be administered according to the local practice or institution guidelines.

Folate and vitamin B_{12} supplementation are recommended if vitamin B_{12} is < 200 pg/mL or serum folate is < 2 ng/mL. Supplementation should be administered in accordance with local practice or institution guidelines.

6.3 Proscribed Therapy During the Treatment Period

During the treatment period of the study and prior to EOTP, subjects should not receive an ESA (other than IP as defined in this protocol), or any investigational agents/devices not currently approved by the country's regulatory authority for any indication. The dose and date of dosing information will be collected on the CRFs for any extra darbepoetin alfa or ESA administration during the study. Subjects who receive additional IP or other ESA therapy during the treatment period may be discontinued from IP at Amgen's discretion, but will be followed for progression and survival.

There is no proscribed therapy during the LTFU period.

7. STUDY PROCEDURES

Refer to the Schedule of Assessments (Appendix A) for an outline of the procedures required at each study visit. The investigator at each site is responsible for ensuring that all study procedures are performed as specified in the protocol.

For each study visit, all assessments should be performed prior to the administration of IP or chemotherapy.

Sites must utilize local laboratory hemoglobin for subject eligibility and for dosing decisions/adjustments during the treatment period on study. A central laboratory will be utilized for parameters detailed in Section 7.1.12.

7.1 General Study Procedures

All subjects or the legally authorized representative must personally sign and date the Amgen/IEC/IRB approved ICF before any study specific procedures are performed. All study procedures should be performed prior to the administration of IP, chemotherapy and prior to initiation of intravenous hydration for chemotherapy. Please refer to the

Schedule of Assessments (Appendix A) for details on study procedures and on-study visit schedule.

7.1.1 Medical and Medication History

A review of targeted medical history, including tumor details (primary malignancy type, tumor staging, metastasis), RBC transfusion, anti-cancer therapy, radiotherapy, anti-cancer surgery, medication, including ESA use will be performed by the investigator **during** screening.

7.1.2 Physical Examination

A complete physical examination (PE) including weight and height will be performed on all subjects within 21 days prior to randomization. The subject's weight will be collected Q3W during the treatment period.

7.1.3 Venous Catheter

The presence of an existing central venous line, peripherally-inserted central catheter (PICC), or mid-line venous catheter will be reported at baseline; the presence of new / replaced central or mid-line venous catheters will be reported on the CRF at subsequent study visits during the treatment period.

7.1.4 Vital Signs

Vital signs will include pulse, temperature and resting blood pressure (systolic and diastolic blood pressures in mmHg).

7.1.5 ECOG Performance Status

Subject's Eastern Cooperative Oncology Group (ECOG) performance status will be assessed within 21 days prior to randomization and Q3W during the treatment period. Subjects must have ECOG of 0 or 1 to be eligible for the study. The subject's ECOG performance status will be assessed by the investigator. See Appendix D for a complete description of the scale.

7.1.6 Imaging Studies

Subjects must have had a pre-chemotherapy scan (computed tomography [CT], magnetic resonance imaging [MRI] or positron emission tomography-computer tomography [PET/CT with diagnostic quality CT]) of the chest to assess disease burden at baseline. The scan must include the chest and is expected to include the adrenal glands. The scan(s) must be reviewed by the investigator prior to randomization. If the scan was performed more than 28 days prior to randomization, an additional scan must be performed and reviewed by the investigator to confirm that the patient has not

progressed before randomization. Subjects who have progressed are not eligible for randomization.

Throughout the study, a subject will be followed by the same method of assessment that was used at baseline to ensure consistency and comparability of images. When possible, similar scanning techniques and equipment, including level and thickness should be used as at baseline for a subject. Tumor assessments will be performed according to the modified RECIST 1.1 criteria (Appendix H) and must be conducted according to protocol specified techniques.

After randomization, imaging studies will be performed every 9 weeks (± 7 days) from study day 1/week 1 or sooner if clinically indicated until disease progression as defined by modified RECIST 1.1 criteria. Once disease progression has been determined, imaging studies are no longer required.

Additional CT scans of other body regions (eg, brain, bone) may be acquired in the event of a suspected metastasis as clinically appropriate for evaluation and management. If there are signs or symptoms suggestive of bone metastasis, a bone scan, MRI, CT, PET, PET/CT, or X-ray will be performed. For subjects with a positive bone scan or PET scan, the bone metastasis must be confirmed with another method of imaging (ie, X-ray, CT or MRI). Evidence of suspected disease progression must be recorded in source documents at the site.

Images from the imaging studies will be collected and stored in a central location by the imaging vendor. Refer to the imaging manual for additional information and instructions on the handling and shipping of the images to the imaging vendor.

7.1.7 Disease Progression

Disease progression will be based on imaging studies assessed by the investigator using modified RECIST 1.1; if imaging cannot be performed, disease progression should be based on clinical signs and symptoms. Imaging studies to evaluate disease progression will be performed within 7 days of the study-specified visit and 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.

7.1.8 Thrombovascular Events

All subjects will be monitored closely for clinical signs and symptoms of thrombovascular events (TVE) (arterial thromboembolic events [ATE]: stroke, transient ischemic attack

[TIA], acute coronary syndromes [ACS], other arterial thrombosis/embolism; venous thromboembolic events [VTE]: deep vein thrombosis [DVT], pulmonary embolism [PE], other venous thrombosis excluding superficial venous thrombosis). If any signs or symptoms are present, the subject will undergo specific laboratory and medical imaging studies to confirm VTEs. The medical imaging study or studies selected will depend on the anatomic site of the suspected VTE or organ of involvement (eg, Doppler ultrasound, venography, ventilation perfusion lung scan, angiography, MRI). If a VTE is confirmed, appropriate medical care according to standard local clinical practice should be initiated immediately.

TVEs will be documented in the CRF through the EOTP or 30 days after the last dose of IP, whichever occurs later.

7.1.9 Concomitant Medication and Red Blood Cell Transfusion

Concomitant medications, procedures of interests (eg, radiotherapy, anti-cancer surgery), and RBC transfusion details will be collected from screening to EOTP. The reason for the RBC transfusion and any adverse events (including VTE) associated with RBC transfusion will be recorded on the CRFs. Concomitant medications include, but are not limited to, the use of any prohibited ESA or non-protocol specified dose of IP, hematopoietic growth factor, iron supplement, anti-hypertensive agent, anti-cancer therapy including chemotherapeutic agents, and anticoagulation therapy. Collection of information on ESA usage and anti-cancer therapy will be continued at pre-specified intervals during the LTFU period.

7.1.10 Adverse Events Reporting

Adverse events starting at randomization through 30 days after last dose of IP will be reported to Amgen. All serious adverse events (SAEs) occurring from the date the subject signs the ICF through 30 days after the last dose of IP will be reported to Amgen. All TVEs, and adverse events associated with RBC transfusions administered during the treatment period, will be reported through the EOTP or 30 days after the last dose of IP, whichever occurs later. Refer to Section 9 for more detail on adverse events reporting.

7.1.11 Survival Status

Survival status will be assessed by the investigator or qualified site personnel at the pre-specified intervals throughout the study. If the subject has died, the date of death and the primary cause of death will be collected on the CRF. If available, death certificates may be used by the monitors to confirm the date and cause of death. **Site**

staff can access publicly available records to determine survival status where permitted by law.

7.1.12 Central Laboratory Assessments

Laboratory data from the central laboratory will be used for analysis purposes and for determination of eligibility within 21 days prior to randomization. (Exception: The hemoglobin sample obtained within 7 days prior to randomization to confirm eligibility must be assessed by a local laboratory.) During the treatment period, the sample may be obtained on the day of IP dosing or up to 1 day prior to the day of IP dosing. Laboratory samples during the screening and treatment periods will be processed and sent to the central laboratory which is responsible for either completing the assessment or shipping the samples to Amgen for assay depending on the assessment. The central laboratory will be utilized for parameters such as: complete blood count (CBC) with differential (including hemoglobin for statistical analyses), serum chemistry, serum pregnancy test (for female subjects of reproductive potential), vitamin B_{12}, serum folate, C-reactive protein (CRP), reticulocyte count**,** soluble transferrin receptor, iron, ferritin, Tsat, and TIBC. Samples for darbepoetin alfa antibody and endogenous EPO testing will be sent to the central laboratory and the central laboratory will forward the samples to Amgen (or designee) for analyses.

The central laboratory will analyze the following list of analytes with the exception of the darbepoetin alfa antibody and endogenous EPO:

Chemistry	**CBC**	**Folate and Vitamin B12**	**Iron Studies**	**Other Labs**
Total bilirubin	Hemoglobin	Serum folate	Iron	Darbepoetin alfa antibody
Direct bilirubin	Hematocrit	Vitamin B_{12}	Ferritin	Serum pregnancy
Alkaline	RBC		TIBC	Endogenous EPO
Phosphatase	MCV		Tsat	**CRP**
ALT(SGPT)	MCH		**Soluble transferrin receptor**	Reticulocyte count
AST (SGOT)	MCHC			
GGT	RBC morphology			
LDH	WBC			
BUN	Neutrophils			
Creatinine	Lymphocytes			
Glucose	Monocytes			
Uric Acid	Eosinophils			
Sodium	Basophils			
Potassium	Platelets			
Chloride				
Bicarbonate				
Calcium				
Phosphorus				
Total protein				
Albumin				

7.1.13 Local Laboratory Assessment

Sites will utilize a local laboratory for assessing a subject's hemoglobin level to confirm eligibility (the sample must be obtained within 7 days prior to randomization) and for dosing decisions / adjustments during the treatment period (the sample may be obtained on the day of IP dosing or up to 1 day prior to the day of IP dosing).

7.1.14 Tumor Sample Banking (Optional)

If available, archived paraffin embedded tumor tissue blocks or unstained tumor slides (from primary tumor or metastasis) will be collected during screening and submitted upon enrollment to the central lab, along with the associated pathology report for erythropoietin receptor (EpoR) testing, tumor mutation analysis, and other biomarker evaluation. There will not be an additional procedure required but rather these tumor samples may be obtained from previous diagnostic biopsy.

Tumor sample blocks may be returned to an investigational site upon request by the investigator.

7.2 Screening

The screening period, which starts when the subject signs and dates the ICF and ends when the subject is randomized or screen failed, must not exceed 21 days. Study-specific screening tests and procedures must be performed and results obtained within the screening period. Certain procedures that are considered by the investigational site to be standard of care, such as imaging studies, the complete physical exam, local laboratory hemoglobin testing, and ECOG performance status assessment, may be performed prior to the start of screening.

Laboratory assessments used to determine subject eligibility may be repeated during the screening period before the subject is considered a screen failure. Subjects determined to be screen failures (based on laboratory or any other assessment) will not be eligible for immediate participation and must be registered as a screen failure in IVR/IWR System, but may be re-screened at the investigator's discretion (the subject will maintain the same subject ID number provided at the initial registration). Subjects who are determined not eligible after re-screen must be screen failed through IVR/IWR System. Subjects must be re-consented if more than 30 days have elapsed between date of informed consent and date of randomization.

The following assessments will be completed as part of screening:

- Informed consent (marks the beginning of the screening period)
- Access IVR/IWR System to obtain subject ID number
- Medical history including tumor diagnosis and staging, and pre-chemotherapy tumor evaluation
- Complete physical examination including height and weight (exam may be performed up to 21 days prior to randomization)
- Vital signs
- ECOG performance status (assessment may be performed up to 21 days prior to randomization)
- The presence of a central or mid-line venous catheter
- Imaging studies (if required; see Section 7.1.6)
- Serious Adverse Events (collected beginning from the date informed consent is signed)
- Concomitant medications, radiotherapy and RBC transfusion history
- Central laboratory tests: serum chemistries, CBC with differential (including hemoglobin), reticulocyte count, serum folate, vitamin B_{12}, and iron studies
- Central laboratory serum pregnancy testing for women of child bearing potential according to investigator's judgment

- Local laboratory hemoglobin to determine eligibility (sample may be obtained up to 7 days prior to randomization)
- If available, paraffin embedded tumor tissue blocks or unstained tumor slides will be submitted along with associated pathology report

7.3 Randomization

Once all screening procedures are complete and all eligibility criteria have been met, the subject may be randomized into the study by calling IVR/IWR system. Before randomizing a subject, site staff should prospectively assess scheduling conflicts with the subject for the study from screening through EOTP.

Randomization may occur on the same day as the first dose of IP (ie, study day 1) or it may occur up to 4 days prior to the first dose of IP. Adverse events will be reported beginning from the date of randomization.

7.4 Study Day 1/Week 1

Study day 1 (ie, week 1) is the first day IP (darbepoetin alfa or placebo) is administered.

The day 1 / week 1 study procedures (eg, ECOG, laboratory sample draws) may be performed up to 1 day prior to IP dosing.

The following assessments and procedures will be completed on study day 1 (week 1):

- Vital signs and weight
- The presence of a central or mid-line venous catheter
- ECOG performance status
- Assess for signs and symptoms of clinically relevant TVE. If present, perform appropriate laboratory, diagnostic, and medical imaging for suspected TVE
- Darbepoetin alfa antibody collection
- Endogenous EPO level
- Adverse events
- Concomitant medications, radiotherapy, anti-cancer therapy, anti-cancer surgery, and RBC transfusions
- Central laboratory tests: clinical chemistries and CBC with differential (including hemoglobin for statistical analyses)**, CRP, and soluble transferrin receptor**
- Local laboratory hemoglobin for dosing determination
- Access IVR/IWR system for medication assignment
- Subcutaneous administration of IP

7.5 Treatment Period (Q3W Visits)

Study visits will occur every 3 weeks ± 6 days with subcutaneous IP administration Q3W during the treatment period. IP will be discontinued within 3 weeks after the last dose of chemotherapy, or upon the determination of disease progression, whichever occurs first.

For all study visits during the treatment period, study procedures (eg, ECOG, laboratory sample draws) may be performed up to 1 day prior to IP dosing.

The following assessments and procedures will be performed during the treatment period:

- Vital signs and weight
- The presence of a central or mid-line venous catheter
- ECOG performance status
- Assessment of disease progression
- Assess for signs and symptoms of clinically relevant TVE. If present, perform appropriate laboratory, diagnostic, and medical imaging for suspected TVE
- Imaging studies Q9W (or earlier if clinically indicated) until documented disease progression (see Section 7.1.6)
- Central laboratory tests: clinical chemistries and CBC with differential (including hemoglobin for statistical analyses), Tsat, ferritin, iron, and TIBC. Central laboratory tests will continue until the next Q3W study visit that occurs after the last dose of IP
- Local laboratory hemoglobin for IP dosing determination. Local laboratory hemoglobin testing will continue until the next Q3W study visit that occurs after the last dose of IP
- Access IVR/IWR system for medication assignment or to register a subject's discontinuation from IP (if applicable)
- Subcutaneous Q3W administration of IP
- Subjects who discontinued IP but have not had disease progression will continue Q3W visits and Q9W imaging studies until disease progression has been determined. Subjects who are unable to continue Q3W visits and Q9W imaging studies until disease progression should complete EOTP procedures at no later than their next Q3W visit and will be asked to enter the LTFU period

Concomitant medications, radiotherapy, anti-cancer therapy, anti-cancer surgery, and RBC transfusion information will be collected throughout the treatment period. AEs and SAEs will be collected up to 30 days after the last dose of IP.

7.6 End of Treatment Period

Subjects will complete the EOTP visit at the next Q3W visit (± 6 days) after disease progression has been determined either by imaging studies or by clinical assessments in the absence of imaging confirmation. Subjects who are unable to continue Q3W visits and Q9W imaging studies until disease progression should complete EOTP procedures

at no later than their next Q3W visit (± 6 days). At the time of the EOTP visit, any subject who has experienced a serious and treatment related adverse event during the study, as determined by the investigator, will continue to be followed for that event, until the event is resolved or considered stable; all EOTP visit procedures may still be conducted prior to resolution.

The following EOTP assessments and procedures will be required for all subjects:

- Vital signs and weight
- The presence of a central or mid-line venous catheter
- ECOG performance status
- Assess for signs and symptoms of clinically relevant TVE. If present, perform appropriate laboratory, diagnostic, and medical imaging for suspected TVE
- Adverse events, concomitant medications, radiotherapy, anti-cancer therapy, anti-cancer surgery, and RBC transfusions
- Central laboratory serum chemistries and CBC with differential (including hemoglobin for statistical analyses) (except if EOTP visit occurs following the Q3W visit after the last dose of IP)
- Local laboratory hemoglobin (except if EOTP visit occurs following the Q3W visit after the last dose of IP)
- Darbepoetin alfa antibody

7.7 Long-term Follow-up Period

After the EOTP visit, subjects will enter the LTFU period and will visit the clinic at 3-month intervals (± 2 weeks). For subjects who are unable to come to the clinic, site staff should contact the subjects by phone to ascertain survival status.

The following data will be collected by the investigator or site personnel and forwarded to Amgen or designee:

- Overall survival status
- ESA administration (eg, date of administration, type, and dose)
- Anti-cancer therapy (eg, date of administration, type and dose)
- Anti-cancer surgery
- Radiotherapy

7.8 End of Study

The EOS for a subject is when the subject has died or when approximately 2700 deaths have occurred. For any subjects still receiving IP when the 2700th death occurs, these subjects may continue to receive IP per protocol.

7.9 Tumor Sample for Future Biomarker Evaluation (Optional)

CCI

[redacted]

CCI [redacted]

Tumor Sample Storage and Destruction

CCI [redacted]

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

Subjects have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject the most appropriate way to withdraw to ensure the subject's health.

Withdrawal of partial consent means that the subject does not wish to take IP any longer but is still willing to collaborate in providing further data by continuing on study (eg, participate in all subsequent imaging visits until disease progression and/or to be followed during the LTFU period). Withdrawal of partial consent also means that the subject, although having completed IP or stopped receiving IP for other reasons, is still willing to collaborate in providing further data by continuing on study (eg, participate in all subsequent imaging visits until disease progression and/or to be followed during the LTFU period).

Reasons for discontinuation of IP or study visits or procedures might include:

- withdrawal of full consent
- withdrawal of partial consent
- administrative decision by the investigator or Amgen
- pregnancy (report on Pregnancy Notification Worksheet, see **Appendix F**)
- ineligibility
- lost to follow up
- significant protocol deviation
- subject non-compliance
- adverse event

8.2 Replacement of Subjects

Subjects who prematurely discontinue following randomization will not be replaced.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Event

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject occurring from the time that the subject has signed informed consent through 30 days after last dose of IP and does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record. These records are the source documents from which data are extracted and reported to Amgen per the reporting procedures (Section 9.1.2).

The definition of adverse event includes worsening of a pre-existing medical condition. Worsening indicates the pre-existing medical condition (eg, cancer, diabetes, migraine headache, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study, but involves an intervention such as elective cosmetic surgery or a routine standard of care medical procedure while on study, is not considered an adverse event.

Disease progression (ie, progression of cancer) will not be considered an adverse event, nor a serious adverse event if International Conference for Harmonization (ICH) criteria for seriousness are met. Disease progression will instead be documented on a specific case report form and analyzed separately as a key secondary study endpoint. Similarly,

disease progression as a cause of death will be captured on a Death Summary case report form.

There are several well documented adverse events in oncology subjects that are known to occur during chemotherapy treatment such as nausea, vomiting, diarrhea, constipation, anorexia, and fatigue. These symptoms should not be considered adverse events, unless:

- Severity, frequency, or duration of the symptom(s) has increased from baseline
- Symptom(s) meets a serious criterion (report as AE and SAE)
- Symptom(s) is considered possibly related to investigational product

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from the subject's baseline values. In general, an abnormal laboratory finding without clinical significance (based on the investigator's judgment) should not be considered adverse events. However, a laboratory value change that requires treatment or adjustment in current therapy would be considered an adverse event. Where applicable, clinical sequelae, and not the laboratory abnormality, should be considered an adverse event.

9.1.2 Reporting Procedures for Adverse Events

All adverse events occurring after randomization through 30 days after last dose of IP as recorded in the subject's medical record, will be reported to Amgen via the Adverse Event Summary CRF. TVEs, and adverse events associated with RBC transfusions administered during the treatment period, that occur through the EOTP or 30 days after the last dose of IP, whichever occurs later, also will be documented in the CRF. VTEs are captured on a specific CRF page.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- Event description (with detail appropriate to the event)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to IP
- Assessment of relatedness to transfusion
- Assessment of relatedness to chemotherapy
- Action taken

The adverse event severity grading scale used will be the CTCAE. The severity grading scale used in this study is described in Appendix B.

The investigator must assess whether the adverse event is possibly related to the IP. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the IP?"

The investigator must assess whether the adverse event is possibly related to transfusion. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by RBC transfusion?"

The investigator must assess whether the adverse event is possibly related to chemotherapy. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by chemotherapy?"

Medically significant adverse events considered related to the IP by the investigator will be followed until resolved or considered stable.

The investigator's clinical judgment will be used to determine whether a subject should be removed from treatment or from the study due to an adverse event. A subject may also voluntarily withdraw from treatment due to an adverse event. If the subject is withdrawn, the subject should be strongly encouraged to undergo at a minimum an end-of-treatment assessment. The subject should be followed until symptoms cease or the condition becomes stable.

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Event

A serious adverse event (SAE) is an adverse event that meets at least one of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect, and/or
- other significant medical hazard

The investigator is responsible for ensuring, for all subjects who have signed an informed consent, that all serious adverse events occurring from signing of informed consent (inclusive of the screening phase) through 30 days after last dose of IP are recorded in the subject's medical record. This includes serious adverse events

observed by the investigator or reported by the subject. These records are the source documents from which data are extracted and reported to Amgen per the reporting procedures (Section 9.2.2).

An adverse event meets the serious criterion of "requires hospitalization", if the event necessitates an admission that includes a minimum of an overnight stay in a health care facility.

If an investigator considers an event to be clinically important, but it does not meet any other serious criteria, the event could be reported under the criterion of "other significant medical hazard". Examples of such events include allergic bronchospasm, convulsions, and blood dyscrasias, which result in an emergency room visit, outpatient surgery, or other urgent intervention.

If the following interventions are performed as standard of care and not associated with a new health issue or worsening of a pre-existing health issue, the health issue for which the intervention is performed will not be considered an adverse event, nor a serious adverse event.

- Insertion of a central line as an outpatient or associated with hospitalization
- Blood transfusion(s)
- Hospitalization for the purpose of chemotherapy administration

If there is a health complication as a result of the intervention, the complication would be reported as an adverse event; if the complication meets at least 1 serious criterion, the complication would be also reported as a serious adverse event.

9.2.2 Reporting Procedures for Serious Adverse Events

The Investigator is responsible for ensuring that all serious adverse events observed by the Investigator or reported by the subject that occur after signing of informed consent through 30 days after last dose of IP as recorded in the subject's medical record **and are submitted to Amgen.** Serious TVEs, and SAEs associated with RBC transfusions administered during the treatment period, that occur through the EOTP or 30 days after the last dose of IP, whichever occurs later, also will be reported to Amgen. During long-term follow-up period, SAEs will not be reported to Amgen, **except for** SAEs occurring after 30 days post last dose of IP AND thought to be possibly related to IP. **These events are to be submitted to Amgen.**

The serious adverse event must be submitted to Amgen within 24 hours following the Investigator's knowledge of the event via the applicable CRF. If the electronic

data capture (EDC) system is unavailable to the site staff to report the Serious Adverse Event, the information is to be reported to Amgen via a Serious Adverse Event (SAE) Contingency Reporting Form within 24 hours of the Investigator's knowledge of the event. See Appendix C for a sample of the Serious Adverse Event Contingency Reporting Form. If the first notification of a Serious Adverse Event is reported to Amgen via the Serious Adverse Event Contingency Reporting Form, the data must be entered into the EDC system when the system is again available.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The Investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record; autopsy reports should be provided for deaths, if available. **Information provided about the serious adverse event must be consistent with that recorded on the applicable CRF (eg, Adverse Event Summary CRF).** If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be **submitted to Amgen**.

The investigator should notify the appropriate IRB, ethics committee, or head of the medical institution, when applicable, of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

To comply with **worldwide** reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen **before submission to regulatory authorities**. **Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.**

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and **IRBs/IECs** in compliance with all **reporting requirements according to local regulations and good clinical practice**.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-specified product and for 1 month after end of

IP, the pregnancy should be reported to Amgen's global Pregnancy Surveillance Program using the Pregnancy Notification Worksheet (Appendix F).

If a lactation case occurs in a female subject, while the subject is taking protocol-specified product and for 1 month after the end of IP, the lactation case should be reported to Amgen's global Lactation Surveillance Program within 7 business days of the site receiving notification using the Lactation Notification Worksheet (Appendix G).

10. STATISTICAL CONSIDERATIONS

10.1 Study Design

This is a double-blind, randomized, placebo-controlled, phase 3 non-inferiority study in CIA subjects receiving multi-cycle chemotherapy for the treatment of stage IV NSCLC cancer. Randomization will occur in a 2 to 1 ratio (darbepoetin alfa to placebo) and will be stratified by geographic region, histology (squamous versus other), and screening hemoglobin (< 10.0 g/dL versus ≥ 10.0 g/dL). Subjects will receive IP Q3W during the treatment period. IP will be discontinued within 3 weeks after the last dose 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. The EOTP visit will occur at the next Q3W visit after disease progression has been determined. Subjects will then enter long-term follow-up and will be followed for survival until death, or until approximately 2700 deaths have occurred.

The primary objective of the study is to demonstrate that subjects treated with darbepoetin alfa to a hemoglobin ceiling of 12 g/dL is non-inferior to subjects on placebo with respect to survival. Key secondary objectives include demonstrating that subjects treated with darbepoetin alfa to a hemoglobin ceiling of 12 g/dL is non-inferior to subjects on placebo with respect to PFS and demonstrating that darbepoetin alfa is superior to placebo with respect to transfusions.

10.2 Study Endpoints, Subsets, and Covariates

10.2.1 Study Endpoints

Primary Endpoint

- Overall survival

Secondary Endpoint

- Progression-free survival
- Incidence of at least 1 RBC transfusion or hemoglobin ≤ 8.0 g/dL from week 5 (day 29) to EOETP

Other Safety Endpoints

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

Other Efficacy Endpoints

- CCI [redacted]
- CCI [redacted]

10.2.2 Primary Analysis Set

The primary analysis set will include all randomized and consented subjects who receive at least 1 dose of IP. Subjects will be analyzed according to their randomized treatment assignment. Sensitivity analyses will be based on all randomized and consented subjects and a prospectively defined per-protocol analysis set.

10.2.3 Covariates

The analysis of the primary and secondary endpoints will be stratified by the stratification factors at randomization. Additional analyses may include the following baseline factors as covariates: age, sex, planned on study treatment for NSCLC (eg, chemotherapy with or without any anti-EGFR or anti-angiogenic agents), time from start of chemotherapy to anemia, stage, pre-chemotherapy weight loss, race, smoking status, past medical history (eg, VTEs, ATEs, diabetes), pre-chemotherapy hemoglobin, and baseline serum erythropoietin level. Pre-specified analyses of additional covariates may be performed if other prognostic factors emerge in this population during the time it takes to complete this study.

10.3 Sample Size Considerations

A total of 2700 deaths will 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 will 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.

This estimation assumes survival time is exponentially distributed which allows for a conversion from a hazard ratio to medians. A median survival of 12.3 months (Sandler et al, 2006) was assumed as the median survival in the placebo arm in order to derive the difference in medians that correspond to a hazard ratio of 1.15.

10.4 Access to Individual Subject Treatment Assignments

A subject's treatment assignment should only be unblinded when this knowledge is essential for the further management of the subject. Unblinding for any other reason will be considered a protocol violation.

The principal investigator is strongly encouraged to contact Amgen or its designee before unblinding any subject's treatment assignment, and must do so within 1 working day after the event.

For the review of unblinded safety data by the Data Monitoring Committee (DMC), an independent biostatistics group will be responsible for analyzing the unblinded data. The study personnel will remain blinded to the individual subject treatment assignments.

10.5 Interim Analysis and Early Stopping Guidelines

An independent Data Monitoring Committee (DMC) will assess safety on a regular basis throughout the duration of the study. The DMC will convene approximately once every 6 months for the first 2 years and once a year thereafter during the course of the trial. In addition, the DMC will oversee 5 formal interim analyses to assess harm (ie, inferiority of darbepoetin alfa), 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 trial. Prior to the completion of the recruitment period, the sponsor will re-assess the study assumptions (eg, recruitment rate and mortality rate) on a blinded basis, and may revise the sample size in order to ensure that the study completes.

10.6 Planned Methods of Analysis

10.6.1 General Approach/Considerations

The primary analysis will be triggered by the date when the 2700th death is reported in the clinical trial database. Once this death is reported, 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. The timing of the interim analyses is described in Section 10.6.2.

Continuous variables will be summarized by the mean, standard deviation, median, and range. 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 censored, and the number of subjects with events. Point estimates will be accompanied by 2-sided 95% confidence intervals. Overall survival and PFS will be assessed using a 1-sided significance level of 0.025; all other statistical hypothesis testing will use a 2-sided significance level of 0.05 unless otherwise specified.

For stratified analyses, the value for the stratification factors will be taken from IVR/IWR System rather than the case report form; a cross-tabulation of the values recorded in the IVR/IWR System and CRF will be generated to assess the potential impact 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 then 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.

10.6.2 Analysis of Key Study Endpoints

10.6.2.1 Analysis of Primary Endpoint

The analysis of OS will use a Cox proportional hazards model, stratified by the randomization factors, with treatment group as the only covariate (a sensitivity analysis will include additional covariates described in Section 10.2.3 to assess the robustness of the primary approach). 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 is less than 1.15 using a 1-sided significance level of 0.025.

10.6.2.2 Analysis of Secondary Endpoints

The same method used to analyze OS will be used to analyze PFS. Progression-free survival 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 using investigator-assessed scans) or death from any cause; subjects without either event will be censored at the last disease assessment date. Non-inferiority will be declared if the upper confidence limit for the hazard ratio is less than 1.15 using a 1-sided significance level of 0.025. This analysis will be performed on all subjects in the primary analysis set who have not had disease progression prior to randomization.

If non-inferiority is declared for both OS and PFS, then the effectiveness of darbepoetin alfa in reducing the incidence of RBC transfusions or a hemoglobin ≤ 8.0 g/dL will be formally tested. To assess treatment group differences, a 2-sided Cochran-Mantel-Haenszel test at a significance level of 0.05 will be used which will adjust for the stratification factors at randomization. The incidence will be assessed from day 29 to the EOETP. This analysis will be performed on all subjects in the primary analysis set whose EOETP is ≥ day 29.

10.6.2.3 Analysis of Other Safety Endpoints

CCI [redacted]

CCI [redacted]

10.6.2.4 Analysis of Other Efficacy Endpoints

CCI [redacted]

10.6.3 Additional Analyses

The number and percentage of subjects screened, randomized, and received at least one dose of IP will be presented. The number and percentage of subjects who withdrew prematurely will be tabulated by the reason for withdrawal.

The following demographic characteristics and baseline variables will be summarized by treatment group:

- Age, sex, and race
- Weight, body mass index, ECOG performance status, stage of disease, histology, and pre-chemotherapy weight loss
- Extent of pre-treatment chemotherapy and time from start of chemotherapy to anemia
- Smoking status and past medical history including hypertension, prior VTEs, prior ATEs, and diabetes
- Hemoglobin value, platelet count, WBC, ferritin level, and serum erythropoietin level

The total number of doses of darbepoetin alfa, the cumulative dose of darbepoetin alfa administered, and the average total weekly dose will be summarized by treatment group using mean, standard deviation, median, and range. In addition, the number and proportion of subjects with dose adjustments in each treatment group will be tabulated.

Use of selected concomitant medications, including chemotherapy, other erythropoietic agents, anti-hypertensives, anti-anginals and anticoagulants will be grouped according

to medication class. The number and proportion of subjects receiving each medication will be summarized by medication class for each treatment group.

11. INVESTIGATIONAL PRODUCT

11.1 Darbepoetin alfa

Darbepoetin alfa will be manufactured and packaged by Amgen and distributed according to Amgen's clinical trial drug procedures. Darbepoetin alfa will be provided in single dose vials of human serum albumin free (HSA-free) polysorbate solution. Four vial concentrations will be available: 500 μg, 300 μg, 200 μg, and 100 μg, each containing a 1.0 ml withdrawable volume of solution (ie, 500, 300, 200 and 100 μg per ml). Placebo will be provided in similar single dose vials as a clear, colorless, sterile, protein-free solution containing a 1.0 ml withdrawable volume. Vials will be packed and shipped in boxes. Each box of investigational product will have a unique number and will contain one vial. The box number with the corresponding vial strength and identity of investigational product will be available to IVR/IWR system.

The box number of investigational product administered is to be recorded on each subject's Drug Administration case report form for each dose. This must be done in such a manner that a subject's treatment assignment will not be unblinded during the trial.

The vials of investigational product must be stored in a secured location and refrigerated at a temperature of 2°C to 8°C and protected from light.

Initial shipments of drug and ongoing re-supply will be conducted through the IVR/IWR system. For more detail refer to the IVR/IWR system manual and study guide.

Investigational product details including labeling, storage, preparation, etc are provided in the Pharmacy Guide Appendix E.

11.2 Access to Treatment Assignments

In this study, the identity of IP assigned to subject numbers or to individual boxes of IP will be contained in IVR/IWR system. Authorized site staff will be provided with a unique Personal Identification Number (PIN) to access IVR/IWR system to obtain unblinding information. This PIN is unique to the individual and must not be shared.

Since all subjects will be given investigational product, a subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation.

The principal investigator is strongly encouraged to contact the Amgen study manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event and must document the unblinding in the subject's case report form.

12. REGULATORY OBLIGATIONS

12.1 Informed Consent

An initial generic informed consent form is provided to the investigator to prepare the informed consent document to be used at his or her site. Updates to the template will be communicated by letter from the clinical study manager to the investigator. The written informed consent document should be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any IP is administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study. The investigator is also responsible for asking the subject if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator shall inform the subject's primary care physician of the subject's participation in the clinical study.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician should be documented in the subject's medical records, and the ICF should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily an investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

12.2 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of IP.

The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IEC/IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator will be responsible for obtaining annual IEC/IRB approval and IRBs renewal throughout the duration of the study. Copies of the investigator's reports and the IEC/IRB's continuance of approval must be sent to Amgen.

12.3 Pre-study Documentation Requirements

The investigator is responsible for forwarding the following documents to Amgen or designee for review before study initiation can occur:

- Signed and dated protocol signature page (Investigator's Agreement)
- Copy of approved informed consent form and subject information sheet, if applicable
- Copy of the IEC/IRB approval of the protocol, consent form, and subject information sheet
- Up-to-date curricula vitae of principal investigator and all co/sub-investigators
- IEC/IRB composition and/or written statement that IEC/IRB is in compliance with regulations
- Laboratory normal ranges and documentation of laboratory certification (or equivalent)
- Current subject/investigator indemnity insurance
- Signed study contract
- Completed FDA form 1572 (or equivalent). Central and local laboratories for the study must be listed on the form.
- Other country-specific forms, as defined in the country-specific requirements such as completed Financial Disclosure statements for the principal investigator, all sub-investigators, and their spouses (legal partners) and dependent children

12.4 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- On the case report forms or other documents submitted to Amgen, subjects should be identified by a subject identification number only.
- On Serious Adverse Event forms submitted to Amgen, subjects should be identified by their initials and a subject identification number only.
- Documents that are not for submission to Amgen (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

12.5 Investigator Signatory Obligations

Each clinical study report should be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will either be:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

13. ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 Protocol Amendments and Study Termination

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of Amgen. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IEC/IRB must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IEC/IRB to Amgen.

Both Amgen and the investigator reserve the right to terminate the study according to the study contract. The investigator should notify the IEC/IRB in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with investigational product by extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply the investigational product, and by what mechanism, after termination of the trial and before it is available commercially.

13.2 Study Documentation and Archive

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on case report forms will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Case report form entries may be considered source data if the case report form is the site of the original recording (ie, there is no other written or electronic record of data).

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed case report forms, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation (see Section 12.3), and all correspondence to and from the IEC/IRB and Amgen
- If kept, proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

No study document should be destroyed without prior written agreement between Amgen and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify Amgen in writing of the new responsible person and/or the new location.

13.3 Study Monitoring and Data Collection

The Amgen representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, case report forms and other pertinent data) provided that subject confidentiality is respected.

The Amgen monitor is responsible for verifying the case report forms at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the case report forms.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Clinical Quality Assurance Department (or designees). Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- Updates to electronic case report forms (eCRF) will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review will be performed on subject data received at Amgen. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be created in the electronic data capture (EDC) system database for site resolution and closed by Amgen reviewer.
- The principal investigator signs only the Investigator Verification Form for this electronic data capture study. This signature will indicate that the principal investigator inspected or reviewed the data on the case report form, the data queries, and the site notifications, and agrees with the content.
- Amgen's clinical data management department will correct the database for the following eCRF issues without notification to site staff:
  - deletion of obvious duplicate data (eg, same results sent twice with the same date but different clinical planned events—week 4 and early termination)
  - clarifying "other, specify" if data are provided (eg, race, physical examination)

- addition of a leading zero to date and/or time entries if necessary
- deletion of leading and/or trailing spaces to adverse event or concomitant medication terms to facilitate uploading of coded files
- where query responses confirm worsening of a baseline/previous condition but the data field was not updated accordingly by the site, CDM will update AE terms/entries with “worsening”

13.4 Language

Case report forms must be completed in English. Generic names for concomitant medications may be entered in the local language.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. Consult the country-specific requirements for language requirements.

13.5 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several principal investigators and appropriate Amgen staff. The committee is expected to solicit input and assistance from other investigators and Amgen staff as appropriate. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship—the criteria described below should be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2005), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multi-center group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The Clinical

Study Agreement among the institution, principal investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

13.6 Compensation

Subject will be treated and/or compensated for any study-related illness/injury pursuant to the information provided in the Compensation for Injury section of the Informed Consent. Subjects may be compensated for other inconveniences not associated with study-related injuries (eg, travel costs, child care costs).

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15. APPENDICES

Appendix A. Schedule of Assessments

	Screening [a]	Treatment Period [n]			EOTP Visit	LTFU [m]
Study Week	**-3**	**Day 1 /** Wk 1	Q3W (± 6 days) (eg, Wk 4, 7, 10, 13, 16, 19, 22, 25, 28...)	Last dose of IP	Next Q3W visit after disease progression	Every 3 months (± 2 weeks)
Informed consent, medical history, and **complete** physical exam	X					
Vital signs**; other** [b]	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	
Adverse events [c], concomitant meds and RBC transfusions	→	→	→	→	→	
Tumor evaluation and assessment of disease progression					→	
Investigational product administration [d]		X	X	X		
Lab testing						
Central lab clinical chemistries [e]	X	X	X	X	X °	
Central lab CBC [f]	X	X	X	X	X °	
Local lab hemoglobin [g]	X	X	X	X	X °	
Central lab serum folate and vitamin B_{12}	X					
Central lab iron studies [h]	X	**X**	X	X		
Tumor samples [i]	X					
Darbepoetin alfa antibody [j]		X			X	
Endogenous erythropoietin level		X				
Central lab pregnancy test [k]	X					
Imaging studies						
CT scan, MRI, or PET-CT [l]	X		Every 9 weeks until disease progression (eg, Wk 10, 19, 28...)			
LTFU						
Collect information on survival, ESA usage, anti-cancer therapy, radiotherapy, anti-cancer surgery						X

a. The screening period, which starts when the subject signs and dates the ICF and ends when the subject is randomized or screen failed, must not exceed 21 days. The local laboratory hemoglobin sample to confirm the eligibility hemoglobin value ≤ 11.0 g/dL must be obtained within 7 days prior to randomization. If the pre-chemotherapy baseline scan was performed more than 28 days prior to randomization, an additional scan must be performed and reviewed by the investigator to confirm that the patient has not progressed before randomization.

b. Vital signs include temperature and resting BP (systolic and diastolic). Weight, presence of new / replaced central or mid-line venous catheters, and radiotherapy information will be collected during screening and during the treatment period. Anti-cancer therapy and anti-cancer surgery information will be collected during the treatment period.

c. All SAEs that occur after the subject signed the ICF through 30 days post last dose of IP will be collected. All AEs will be collected after randomization until 30 days post last dose of IP. Signs and symptoms of clinically relevant TVEs will be assessed at each visit during the treatment period. If present, appropriate labs, diagnostic, and imaging will be performed. All TVEs, and adverse events associated with RBC transfusions occurring during the treatment period, will be documented in the CRF through the EOTP or until 30 days after the last dose of IP, whichever occurs later.

d. IP will be administered SC Q3W during the treatment period. IP will be discontinued within 3 weeks after the last dose of chemotherapy, or upon the determination of disease progression, whichever occurs first. Subjects who discontinued IP but have not had disease progression will continue Q3W visits and Q9W imaging studies until progression has been determined. Subjects who are unable to continue Q3W visits and Q9W imaging studies until disease progression should complete EOTP procedures at their next Q3W visit and will be asked to enter the LTFU period.

e. Central lab clinical chemistries includes creatinine, bilirubin, ALT, AST. CRP will be performed **at Day 1** only.

f. Central lab CBC includes WBC with differential, hemoglobin, hematocrit, platelet count.

g. The hemoglobin sample to confirm eligibility must be obtained within 7 days prior to randomization. During the treatment period, the hemoglobin sample for dosing decisions / adjustments may be obtained on the day of IP dosing or up to 1 day prior to the day of IP dosing.

h. Central lab iron studies consist of serum iron, ferritin, TIBC, and Tsat%. **Only** soluble transferrin receptor will be performed **at Day 1**. Iron, ferritin, Tsat%, **and TIBC** will be performed Q3W.

i. If available, paraffin embedded tumor block or unstained slides from previous biopsy, along with the matching pathology report will be collected during screening

j. Serum antibody samples must be collected pre-dose.

k. Central lab pregnancy testing performed for all female subjects of reproductive potential.

l. Subjects must have had a baseline scan (CT, MRI, or PET-CT) of the chest to assess disease burden before starting on first line chemotherapy for NSCLC and the images must be reviewed by the investigator prior to randomization. Images to assess disease status will be obtained Q9W (or sooner if clinically indicated) from Week 1 until disease progression using the same type of scan as at baseline. Bone scans, MRI, CT, PET, PET/CT, or X-ray will be performed when signs or symptoms suggestive of bone metastasis are present, and positive bone scans or PET scans must be confirmed by another imaging method (ie, X-ray, CT or MRI). Once disease progression has been determined, imaging studies are no longer required.

m. Subjects will be followed in LTFU for survival until death, or until approximately 2700 deaths have occurred on the study (End of Study).

n. The treatment period starts when the subject is randomized and ends at the next Q3W visit after disease progression has been determined (EOTP). Note that EOTP is based on disease progression, not IP dosing. All study visits during the treatment period may occur over a 2 consecutive day period. Study procedures (eg, ECOG, laboratory sample draws) may be performed up to 1 day prior to IP dosing.

o. Central lab clinical chemistries, central lab CBC and local lab hemoglobin tests are not performed if the EOTP visit occurs following the Q3W visit after the last dose of IP.

Appendix B. Adverse Event Severity Scoring System

The Common Terminology Criteria for Adverse Events (CTCAE) is available at the following link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix C. Serious Adverse Event Contingency Reporting Form

AMGEN Study # 20070782 darbepoetin alfa	Electronic Serious Adverse Event (eSAE) Contingency Reporting Form For Restricted Use

Complete either Section A or Section B and follow the instructions provided:

Section A

☐ **EDC system (eg, Rave) is active for this study but is not accessible to allow reporting within 24 hours of the Investigator's knowledge of the event. I am submitting (check/complete all that apply):**

- ☐ An event that applies to a specialty CRF page titled _____ (eg, clinical fracture)
- ☐ Screening event (as defined by the protocol) | **OR** | ☐ On-study event (as defined by the protocol)

– *Complete ONLY Sections 1, 2 and 3 (page 1)*
– *Sign and date the signature section following Section 3*
– *Fax completed page of the form to the number noted in the header above Section 1*

Section B

☐ **Access to the EDC system (eg, Rave) has either not begun or has ended for this study. I am submitting (check all that apply):**

- ☐ Screening event (as defined by the protocol)
  - ☐ This is a new event report
  - ☐ This is follow-up information for a previously reported event

OR

- ☐ Event after access to the EDC system (eg, Rave) has ended (*provide subject's End of Study date in Section 2*)
  - ☐ This is a new event report
  - ☐ This is follow-up information for a previously reported event

– *Complete ALL sections of the form (all 3 pages)*
– *Sign and date the signature section at the end of the form*
– *Fax completed form (all 3 pages) to the number noted in the header above Section 1*

<<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth Day Month Year	Sex ☐F ☐M	Race	If applicable, provide End of Study date

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day _____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day____ Month____ Year_____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the event may have been caused by IP? No ✓ Yes ✓	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required/prolonged hospitalization; **04** Persistent or significant disability/incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

If you temporarily cannot access the EDC system (eg, Rave), sign below and submit ONLY this page to the number noted in the header above Section 1.

Signature of Investigator or Designee -	Title	Date

I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.

AMGEN Study # 20070782 darbepoetin alfa	Electronic Serious Adverse Event (eSAE) Contingency Reporting Form For Restricted Use

If **access to the EDC system (eg, Rave) has either not begun or has ended for this study, *complete the remainder of this form.***

Site Number	Subject ID Number

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes, If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP administered prior to this event? ☐No ☐Yes, If yes, please complete all of Section 5

IMP: _____ ☐ (✓) Blinded ☐ (✓) Open Label	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld

6. RELEVANT CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Relevant Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	 Yes✓	Continuing No✓	 Yes✓	Dose	Route	Freq.	Treatment Med No✓	 Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Test / Unit / Date (Day Month Year)											

AMGEN Study # 20070782 darbepoetin alfa	Electronic Serious Adverse Event (eSAE) Contingency Reporting Form For Restricted Use

Site Number	Subject ID Number

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee -	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.		

Appendix D. ECOG Performance Status Scale

ECOG PERFORMANCE STATUS	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, (eg, light house work, office work)
2	Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair

Appendix E. Pharmacy Guide

Darbepoetin alfa

Packaging and Formulation

Human serum albumin-free (HSA-free) polysorbate darbepoetin alfa will be manufactured and packaged by Amgen Inc and distributed using Amgen clinical IP distribution procedures. Darbepoetin alfa will be presented as a clear, colorless, preservative-free, sterile protein solution in vials containing 500, 300, 200 or 100 μg of darbepoetin alfa per ml. The vials supplied will contain 1.0 ml of study drug and are for single-dose use only. Placebo will be provided in similar vials as a clear, colorless, sterile protein-free solution. Each box of IP will contain a single vial.

The identity of investigational product assigned to subject numbers or to individual boxes of IP will be maintained by the IVR/IWR system. Authorized Amgen (for safety reporting) and site staff will be provided with a unique Personal Identification Number (PIN) to access the IVR/IWR system to obtain unblinding information. This PIN is unique to the individual and must not be shared.

A subject's treatment assignment should only be unblinded by the site when knowledge of the treatment is essential for the further management of the subject, or is needed for safety reporting to regulatory authorities. Unblinding at the study site for any other reason will be considered a protocol deviation.

The principal investigator is strongly encouraged to contact the Amgen study manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the even and must document the unblinding in the subject's CRF.

Labeling

Information provided on the labels will comply with ICH GCP and local regulatory requirements.

Storage

The supplied darbepoetin alfa and placebo must be stored in a secured location and refrigerated at a temperature of 2 to 8° C, protected from light. The stability of darbepoetin alfa and placebo have been demonstrated for at least 24 months when stored at a temperature between 2°C and 8°C, and further stability testing is ongoing. Vials may be allowed to warm to room temperature immediately before use, but should not be left unrefrigerated for more than 30 minutes before use. If vials are left out for more than 30 minutes, the study monitor should be contacted and the darbepoetin alfa

should not be administered to any subjects until further notice. Exposure to temperatures above or below this range should be avoided, as should vigorous shaking, as this may denature the protein.

Investigational product must not be used if the contents freeze in transit or in storage, or if any particulate matter or discoloration is observed.

Records of actual storage conditions during the period of the study must be maintained (eg, records of the date and time, and the initials of persons checking, and the "working day" temperatures of the refrigerator used for storage of trial supplies, continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording).

Preparation

Doses are to be administered SC with an appropriate syringe and hypodermic needle. Each vial is designed to be used only once, with the rest of the content kept until reconciled by Amgen or its designee. The site is to assess the IVR/IWR system prior to each dosing visit to determine the box number and volume of investigational product to administer to a subject.

Supply and Return of Drug

At study initiation and as needed thereafter, investigation product (darbepoetin alfa and placebo) will be shipped to a responsible person (eg, a pharmacist) at the investigator's institution, who will check the amount and condition of the drug and enter these data on the Investigational Product Accountability Record and via the electronic Proof of Receipt during the medication arrival call into IVR/IWR system. Initial supply and subsequent re-supply of darbepoetin alfa will be managed by the IVR/IWR system. Medication assignment calls must be made to the IVR/IWR system in a timely manner to ensure proper inventory control. At the end of the study, or as directed, all IP supplies, including used vials will be returned to Amgen's designated vendor for destruction.

Investigational Product Accountability

An Investigational Product Accountability Record for the investigational products mandated by the protocol must be kept current and should contain:

- the dates and quantities of investigational product received from Amgen
- fill lot numbers or box numbers for product received
- subject's identification number
- date and quantity of investigational product dispensed

- the initials of the dispenser
- date and quantity of drug returned to the investigator/pharmacy, if appropriate

The Return of Investigational Product for Destruction Form must be completed and included in the shipment of used and unused IP to Amgen or designee. At the end of the study, the Final Investigational Product Reconciliation Statement must be completed and provided to Amgen. These inventories must be made available for inspection by an authorized Amgen representative or designee and regulatory agency inspectors. The investigator is responsible for the accountability of all used and unused clinical study supplies.

Appendix F. Pregnancy Notification Worksheet

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20070782

Study Design: ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm ▾ / dd ▾ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm ▾ /dd ▾ /yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ▾ /dd ▾ /yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm ▾ / dd ▾ / yyyy____ ☐ Unknown

Estimated date of delivery mm ▾ / dd ▾ / yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm ▾ / dd ▾ / yyyy____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm ▾ / dd ▾ / yyyy____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page **1** of **1**

Appendix G. Lactation Notification Worksheet

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20070782

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2. Page 1 of 1

Appendix H. RECIST 1.1 With Modifications

These guidelines describe a standard approach to solid tumor measurement and definitions for objective assessment of change in tumor size and are based on guidelines developed and published by Eisenhauer et al (2009).

Methods

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have a slice thickness greater than 5 mm, the minimum size for a measurable lesion should be the greater of either at least 10 mm or twice the slice thickness. MRI is acceptable to assess disease extent if used throughout the study.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion throughout the trial.
- Ultrasound (US) cannot be used to measure objective tumor response or progression. For this protocol, a response of complete response, partial response or stable disease will be determined as assessed by cross-sectional imaging techniques (CT or MRI). FDG-PET will not contribute to the assessment of response. It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression. For the determination of progressive disease (PD), FDG-PET could be used to identify new lesions as follows:

    1) Negative PET at baseline, with a positive PET at follow-up is a sign of PD based on a new lesion
    2) No PET at baseline and a positive PET at follow-up: If the positive PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal PET can). If the positive PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

  If a combined PET-CT scan is performed at the discretion of the investigator the CT portion of that exam should not be substituted for the dedicated CT exams required by this protocol for RECIST measurements unless the site can document that the CT performed as part of the PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

  Cytology and histology can be used to differentiate between partial response and complete response in rare cases (eg, after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and PD.

Definitions of "Measurable" and "Non-Measurable"

All measurements should be taken and recorded in metric notation, using a ruler or calipers. Measurements should be recorded unidimensionally. At baseline, tumor lesions/pathologic lymph nodes are categorized as measurable or non-measurable according to the following definitions:

- Measurable: Measurable lesions are defined at baseline as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) ≥ 10 mm by CT scan (CT scan slice thickness no greater than 5 mm). When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be the greater of either at least 10 mm or twice the slice thickness. Malignant lymph nodes: To be considered pathologically enlarged and measurable a lymph node must be ≥ 15 mm in short axis when assessed by CT scan.
- Non-measurable: All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 or < 15 mm short axis) and other truly non-measurable lesions are considered non-measurable and characterized as non target lesions. Other examples of non-measurable lesions include some bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, and lymphangitic involvement of skin or lung, abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and measure ≥ 10 mm by calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Lesions which cannot be accurately measured with calipers should be recorded as non-measurable.

Special considerations:

Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions: Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patients these are preferred for selection as target lesions.

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Baseline (ie, Pre-chemotherapy) Identification of "Target" and "Non-Target" Lesions

Up to 5 target lesions (a maximum of 2 per organ) will be chosen to measure over the course of therapy. Target lesions should be selected on the basis of their size

and their suitability for accurate repeated measurements by imaging techniques or clinically.

A sum of the diameter (longest for non-nodal lesions, short axis for nodal lesions) for *all target lesions* will be calculated and reported as the *baseline sum diameters.* The baseline sum diameters will be used as reference by which to characterize the objective tumor response.

- All other lesions (or sites of disease) including any measurable lesions or pathological lymph nodes that were not chosen as target lesions, should be identified as non-target lesions. Non-target lesions should be recorded and assessed qualitatively over the course of therapy. These non-measurable, non target lesions should be followed as 'present,' 'absent,' or in rare cases, 'unequivocal progression.'

- Bone lesions: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. If there are signs or symptoms suggestive of bone metastasis, a bone scan, MRI, CT, PET, PET/CT, or X-ray will be performed. For subjects with a positive bone scan or PET scan, the bone metastasis must be confirmed with another method of imaging (ie, X-ray, CT or MRI).

Response Criteria

The subject's tumor response will be assessed based on the response of the target lesions, the response of the non-target lesions, and the presence or absence of new lesions.

Evaluation of Target Lesions

* Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
* Partial Response (PR):	At least a 30% decrease in the sum of the diameters* of the target lesions, taking as reference the baseline sum diameters.
* Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum of all target lesions recorded since the treatment started. The sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.
Not Applicable (NA):	No target lesions were identified at baseline.
Inevaluable (NE):	Scans were not performed, were incomplete, or were inevaluable due to poor scan quality at this time point to evaluate target lesions.

*Diameters used:

For nodal disease: shortest axis
For non-nodal disease: sum of longest diameters

Once on study, the convention will be used that if a lesion being measured decreases to the point that it is faintly seen and/or too small to measure a value of 5 mm will be assigned. If the lesion subsequently increases in size to greater than or equal to 5 mm in one dimension, its true size will be recorded. Nodal disease should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the 'sum' of target lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis)
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s)
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
Not Applicable (NA):	No non-target lesions identified at baseline
Inevaluable (NE):	Scans were not performed, were incomplete or were inevaluable due to poor scan quality at this time point to evaluate non-target lesions.

When the patient also has measurable disease, to achieve an unequivocal progression there must be an overall level of substantial worsening in non-target disease such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. When the patient has only non-measurable disease, the increase of non-measurable disease should be comparable in magnitude to the increase required to declare PD for measurable disease (eg, equivalent to a 20% increase in sum of diameters of all measurable lesions).

Evaluation of Best Overall Response

The overall response status is calculated at each time point for subjects as follows:

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
PR	NA	No	PR
CR	NA	No	CR
SD	NA	No	SD
NE	NA	No	NE

Time Point Response in Subjects with Non-target Disease Only

Non-target Lesions (response)	New Lesions (Yes or No)	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
NE	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Non-CR/non-PD is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Special Notes on Response Assessment

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at the time should be classified as "symptomatic deterioriation." In this case "progressive disease" cannot be assigned at the time as the overall objective tumor response. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, the residual lesion may be further investigated (fine needle aspirate/biopsy) at investigator discretion to confirm the complete response status.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for complete response or partial response (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

Superseding Amendment 3

Protocol Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Long-term 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

Amgen Protocol Number Darbepoetin alfa 20070782

Superseding Amendment Date: 13 November 2012

Rationale:

This superseding amendment is necessary to comply with recent European Medicines Agency (EMA) guidance that revised the Serious Adverse Event (SAE) reporting requirements from 1 business day to 24 hours. Additionally, in order to address findings from a recent Medicines and Healthcare products Regulatory Agency (MHRA) inspection, language describing the assessment of expectedness for expedited reporting of safety events was also updated. Amgen will continue to utilize Core Safety Information in Appendix A of the Investigator's Brochure (IB) to assess expectedness for applicable expedited reporting of safety events.

A correction was made to the testing frequency for the TIBC iron performed by the central laboratory to remove the Q9W reference. Additionally, a minor revision was made to move the collection and analyses for C-reactive protein (CRP) and soluble transferrin receptor from Screening to Day 1, since these laboratory tests are not used for eligibility. Other updates to Key Sponsor Contacts, updated sample forms (Appendices C, F, and G), and corrections to typographical errors were also completed.

Specific Changes for this Superseding Amendment are outlined below:

Section: Header

Replace:

Date: 25 May 2010

With:

Date: **13 November 2012**

Section: Cover page; Key Sponsor Contact

Replace:

Key Sponsor Contact:

PPD
Global Study Manager, Amgen Ltd.
PPD
PPD

PPD
Regional Study Manager, Amgen Inc.
One Amgen Center Drive.
Thousand Oaks, CA 91320, USA
PPD

PPD
Regional Study Manager, Amgen Ltd.
PPD
PPD

With:

Key Sponsor Contact:

PPD
Global Study Manager, Amgen Inc.
One Amgen Center Dr.
Thousand Oaks, CA 91320, USA
PPD

PPD
Regional Study Manager, Amgen Ltd.
PPD
PPD

Section: Cover page, date

Add:

Superseding Amendment 3 **13 November 2012**

Section: Investigator Agreement
Paragraph 1

Replace:

I have read the attached protocol entitled, "A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Long-term 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", dated 25 May 2010, and agree to abide by all provisions set forth therein

With:

I have read the attached protocol entitled, "A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Long-term 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", dated **13 November 2012**, and agree to abide by all provisions set forth therein.

Section: 5.1 Screening
Paragraph 2, line 7

Delete:

Screen failed subjects may be re-screened at the investigator's discretion (the subject will maintain the same subject ID number provided at the initial screening).

Section: 6.1 Investigational Product Dosage, Administration, and Schedule
Paragraph 3

Replace:

Investigational product should be stored, prepared and administered according to the instructions in the Pharmacy Guide (Appendix D).

With:

Investigational product should be stored, prepared and administered according to the instructions in the Pharmacy Guide (**Appendix E**).

Section: 7.1.6 Imaging Studies
Paragraph 2, line 4

Replace:

Tumor assessments will be performed according to the modified RECIST 1.1 criteria (Appendix F) and must be conducted according to protocol specified techniques.

With:

Tumor assessments will be performed according to the modified RECIST 1.1 criteria (**Appendix H**) and must be conducted according to protocol specified techniques.

Section: 7.1.11 Survival Status
Line 4

Add:

Site staff can access publicly available records to determine survival status where permitted by law.

Section: 7.1.12 Central Laboratory Assessments
Analyte Table

Replace:

Chemistry	**CBC**	**Folate and Vitamin B12**	**Iron Studies**	**Other Labs**
Total bilirubin	Hemoglobin	Serum folate	Iron	Darbepoetin alfa antibody
Direct bilirubin	Hematocrit	Vitamin B_{12}	Ferritin	Serum pregnancy
Alkaline	RBC		TIBC	Endogenous EPO
Phosphatase	MCV		Tsat	CRP (screening only)
ALT(SGPT)	MCH		Soluble transferrin receptor (screening only)	Reticulocyte count
AST (SGOT)	MCHC			
GGT	RBC morphology			
LDH	WBC			
BUN	Neutrophils			
Creatinine	Lymphocytes			
Glucose	Monocytes			
Uric Acid	Eosinophils			
Sodium	Basophils			
Potassium	Platelets			
Chloride				
Bicarbonate				
Calcium				
Phosphorus				
Total protein				
Albumin				

With:

Chemistry	**CBC**	**Folate and Vitamin B12**	**Iron Studies**	**Other Labs**
Total bilirubin	Hemoglobin	Serum folate	Iron	Darbepoetin alfa antibody
Direct bilirubin	Hematocrit	Vitamin B_{12}	Ferritin	Serum pregnancy
Alkaline	RBC		TIBC	Endogenous EPO
Phosphatase	MCV		Tsat	**CRP**
ALT(SGPT)	MCH		**Soluble transferrin receptor**	Reticulocyte count
AST (SGOT)	MCHC			
GGT	RBC morphology			
LDH	WBC			
BUN	Neutrophils			
Creatinine	Lymphocytes			
Glucose	Monocytes			
Uric Acid	Eosinophils			
Sodium	Basophils			
Potassium	Platelets			
Chloride				
Bicarbonate				
Calcium				
Phosphorus				
Total protein				
Albumin				

Section: 7.2 Screening
Bullet 11

Replace:

- Central laboratory tests: serum chemistries, CBC with differential (including hemoglobin), reticulocyte count, serum folate, vitamin B_{12}, CRP, and iron studies

With:

- Central laboratory tests: serum chemistries, CBC with differential (including hemoglobin), reticulocyte count, serum folate, vitamin B_{12}, and iron studies

Section: 7.4 Study Day 1/Week1
Bullet 9

Replace:

- Central laboratory tests: clinical chemistries and CBC with differential (including hemoglobin for statistical analyses)

With:

- Central laboratory tests: clinical chemistries and CBC with differential (including hemoglobin for statistical analyses)**, CRP, and soluble transferrin receptor**

Section: 7.5 Treatment Period (Q3W Visits)
Bullet 7

Replace:

Central laboratory tests: clinical chemistries and CBC with differential (including hemoglobin for statistical analyses), Tsat, ferritin, iron, and TIBC (Q9W). Central laboratory tests will continue until the next Q3W study visit that occurs after the last dose of IP

With:

Central laboratory tests: clinical chemistries and CBC with differential (including hemoglobin for statistical analyses), Tsat, ferritin, iron, and TIBC. Central laboratory tests will continue until the next Q3W study visit that occurs after the last dose of IP

Section: 8.1 Removal of Subjects
Paragraph 4, bullet 4

Replace:

- pregnancy (report on Pregnancy Notification Worksheet, see Appendix E)

With:

- pregnancy (report on Pregnancy Notification Worksheet, see **Appendix F**)

Section: 9.2.2 Reporting Procedures for Serious Adverse Events
Paragraph 1

Replace:

All SAEs occurring after signing of informed consent through 30 days after last dose of IP as recorded in the subject's medical record will be reported to Amgen via a Serious Adverse Event Report (SAER) form. Serious TVEs, and SAEs associated with RBC transfusions administered during the treatment period, that occur through the EOTP or 30 days after the last dose of IP, whichever occurs later, also will be reported to Amgen via a SAER form. These events must be faxed to Amgen within 1 working day of discovery or notification of the event. During long-term follow-up period, SAEs will not be reported to Amgen.

With:

The Investigator is responsible for ensuring that all serious adverse events observed by the Investigator or reported by the subject that occur after signing of informed consent through 30 days after last dose of IP as recorded in the subject's medical record **and are submitted to Amgen.** Serious TVEs, and SAEs associated with RBC transfusions administered during the treatment period, that occur through the EOTP or 30 days after the last dose of IP, whichever occurs later, also will be reported to Amgen. During long-term follow-up period, SAEs will not be reported to Amgen, **except for** SAEs occurring after 30 days post last dose of IP AND thought to be possibly related to IP. **These events are to be submitted to Amgen.**

Section: 9.2.2 Reporting Procedures for Serious Adverse Events
New Paragraph 2

Add:

The serious adverse event must be submitted to Amgen within 24 hours following the Investigator's knowledge of the event via the applicable CRF. If the electronic data capture (EDC) system is unavailable to the site staff to report the Serious Adverse Event, the information is to be reported to Amgen via a Serious Adverse Event (SAE) Contingency Reporting Form within 24 hours of the Investigator's knowledge of the event. See Appendix C for a sample of the Serious Adverse Event Contingency Reporting Form. If the first notification of a Serious Adverse Event is reported to Amgen via the Serious Adverse Event Contingency Reporting Form, the data must be entered into the EDC system when the system is again available.

Section: 9.2.2 Reporting Procedures for Serious Adverse Events
Paragraph 3

Replace:

All amendments or additions to any serious adverse event data must be recorded on a SAER form and faxed to Amgen. The investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records or CRFs. Relevant medical records should be faxed to Amgen as soon as they become available; autopsy reports should be provided for deaths if available. Information provided on the SAER form must be consistent with that recorded for the same event on the Adverse Event Summary CRF. SAEs for screen-failed subjects will not be collected on the CRF and only collected on the SAER form submitted to Amgen. If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be reported via a SAER form.

With:

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The Investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record; autopsy reports should be provided for deaths, if available. **Information provided about the serious adverse event must be consistent with that recorded on the applicable CRF (eg, Adverse Event Summary CRF).** If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be **submitted to Amgen**.

Section: 9.2.2 Reporting Procedures for Serious Adverse Events

Paragraph 5

Replace:

To comply with local or regional serious adverse event reporting regulations, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded before submission to regulatory authorities by Amgen. Investigators will receive notification of related serious adverse event reports sent to regulatory authorities in accordance with local requirements. Determination of

expectedness for Amgen products will be based on the contents of Appendix A and B in the Investigator's Brochure for pre-approval investigational products and the regional prescribing information for products being studied for an approved use.

With:

To comply with **worldwide** reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen **before submission to regulatory authorities**. **Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.**

Section: 9.2.2 Reporting Procedures for Serious Adverse Events
Paragraph 6

Replace:

Amgen will report serious adverse events (SAEs) and/or suspected unexpected serious adverse reactions (SUSARs) as required to regulatory authorities, investigators/ institutions and ethics committees in compliance with all applicable regulatory requirements and ICH GCP guidelines.

With:

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and **IRBs/IECs** in compliance with all **reporting requirements according to local regulations and good clinical practice**.

Section: 9.2.2 Reporting Procedures for Serious Adverse Events
Paragraph 6

Delete:

Serious adverse events occurring after 30 days post last dose of IP AND thought to be possibly related to IP will be recorded on an SAER form and faxed to Amgen within 1 working day of discovery or notification of the event.

Section: Insert New Section 9.3 Pregnancy and Lactation Reporting

Add:

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-specified product and for 1 month after end of IP, the pregnancy should be reported to Amgen's global Pregnancy Surveillance Program using the Pregnancy Notification Worksheet (Appendix F).

If a lactation case occurs in a female subject, while the subject is taking protocol-specified product and for 1 month after the end of IP, the lactation case should be reported to Amgen's global Lactation Surveillance Program within 7 business days of the site receiving notification using the Lactation Notification Worksheet (Appendix G).

Section: Appendix A
Footnote e

Replace:

[e] Central lab clinical chemistries includes creatinine, bilirubin, ALT, AST. CRP will be performed during screening only.

With:

[e] Central lab clinical chemistries includes creatinine, bilirubin, ALT, AST. CRP will be performed **at Day 1** only.

Section: Appendix A
Line: Central lab iron studies[h]
Column: Day 1 / Wk 1

Add:

X

Section: Appendix A
Footnote h

Replace:

[h] Central lab iron studies consist of serum iron, ferritin, TIBC, and Tsat%. Soluble transferrin receptor will be performed during screening only. Iron, ferritin, and Tsat% will be performed Q3W and TIBC Q9W on study.

With:

[h] Central lab iron studies consist of serum iron, ferritin, TIBC, and Tsat%. **Only** soluble transferrin receptor will be performed **at Day 1**. Iron, ferritin, Tsat%, **and TIBC** will be performed Q3W.

Section: Appendix C. Serious Adverse Event Contingency Reporting Form
Section caption updated

Replace:

Appendix C. ECOG Performance Status Scale

With:

Appendix C. **Serious Adverse Event Contingency Reporting Form**

Section: Appendix C. Serious Adverse Event Contingency Reporting Form

Insert new sample reporting form

Section: Appendix D. ECOG Performance Status Scale
Section caption updated

Replace:

Appendix D. Pharmacy Guide

With:

Appendix D. **ECOG Performance Status Scale**

Section: Appendix E. Pharmacy Guide
Section caption updated

Replace:

Appendix E. Pregnancy Notification Worksheet

With:

Appendix E. **Pharmacy Guide**

Section: Appendix F. Pregnancy Notification Worksheet
Section caption updated

Replace:

Appendix F. RECIST 1.1 With Modifications

With:

Appendix F. **Pregnancy Notification Worksheet**

Section: Appendix F. Pregnancy Notification Worksheet

Updated worksheet

Section: Appendix G. Lactation Notification Worksheet

New Section and sample worksheet

Add:

Appendix G. Lactation Notification Worksheet

Section: Appendix H. RECIST 1.1 With Modifications

New Section

Add:

Appendix H. RECIST 1.1 With Modifications