Title: START-CKD: Strategies Using Darbepoetin alfa to Avoid Transfusions in Chronic Kidney Disease

Amgen Protocol Number (Darbepoetin alfa) 20110226

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I have read the attached protocol entitled START-CKD: Strategies Using Darbepoetin alfa to Avoid Transfusions in Chronic Kidney Disease, dated **16 December 2013** 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.

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 subinvestigators (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 Investigator

Date (DD Month YYYY)

The START-CKD study is designed to describe the benefits and potential risks of a new treatment strategy using a fixed dose of darbepoetin alfa in subjects with chronic kidney disease and not on dialysis (ND-CKD). Subjects will be randomly allocated to treatment with a fixed dose of darbepoetin alfa or to treatment with darbepoetin alfa using a hemoglobin (Hb)-based titration strategy, which has been the conventional dosing strategy. This study aims to estimate the incidence of red blood cell (RBC) transfusions (administered as deemed clinically necessary) in each group and the difference in incidence of RBC transfusions between the 2 groups. In addition, multiple aspects, such as cumulative darbepoetin alfa dose, total number of units of transfusions, Hb concentration, Hb-related parameters (eg, Hb variability, excursions, rate of change), and adverse (eg, cardiovascular) events, will also be considered in order to determine a preferred dosing regimen.

Protocol Synopsis

Title: START-CKD: Strategies Using Darbepoetin alfa to Avoid Transfusions in Chronic Kidney Disease

Study Phase: 3

Indication: Management of anemia in chronic kidney disease patients not on dialysis.

Primary Objective: To evaluate the incidence of RBC transfusions in ND-CKD subjects using either a Hb-based titration algorithm or a weight-based dose that will not be titrated (fixed dose), and to evaluate the difference in the incidence of RBC transfusions between the 2 groups.

Secondary Objective(s)

To summarize the following for each dosing strategy:

- Transfusion burden
- Time to first RBC transfusion
- Achieved Hb concentration
- Cumulative dose of darbepoetin alfa

To describe the difference in each of the above between the two dosing strategies.

Safety Objective: To describe the safety profile of darbepoetin alfa, including adverse events and the occurrence of adjudicated clinical events of interest.

Exploratory Objective(s)

To describe with each dosing strategy:

- Dose and Hb-related parameters
- Initial Hb response and resulting dose and achieved Hb
- Duration of hospitalization
- Allosensitization over time

Hypotheses: The incidence of RBC transfusions in each treatment group (Hb-based titration group and fixed dose group) and their difference will be estimated, and no formal hypothesis will be tested. The width of the 95% confidence interval (CI) of the transfusion incidence rate is expected to be < 10% (ie, ± 5% around the point estimate) in each group and the width of the 95% CI of the difference in transfusion incidence rates is expected to be < 14% (ie, ± 7% around the point estimate). The efficacy and safety of each treatment group will be described, as these aspects will assist in the determination of a preferred dosing regimen.

Primary Endpoint: Receipt of 1 or more RBC transfusion

Secondary Endpoint(s)

- Total number of units of RBC transfused
- Time to first RBC transfusion
- Average achieved Hb concentration while receiving investigational product
- Cumulative dose of darbepoetin alfa

Safety Endpoint(s)

- Time to major clinical events:
  - Composite of all-cause mortality and the occurrence of major cardiovascular events (stroke, myocardial infarction, and decompensated heart failure)
  - Composite of all-cause mortality, stroke or myocardial infarction, ie, major adverse cardiovascular events (MACE)
  - All-cause mortality
  - Cardiovascular mortality
  - Stroke
  - Myocardial infarction
  - Decompensated heart failure
  - Thromboembolic events
  - Vascular access thrombosis
- Adverse events
- Blood pressure and pulse
- Anti-erythropoietic protein antibodies

Exploratory Endpoint(s)

- Darbepoetin alfa dose received at each study visit
- Hb concentration at each study visit
- Hb concentration change from baseline at each study visit
- Time to first Hb concentration ≥ 10.0 g/dL
- Proportion of Hb measurements ≥ 10.0 g/dL
- Hb rate of change in a 4 week interval at each study visit
- Hb variability, defined as the intrasubject standard deviation over a 6 month rolling window
- Initial Hb response, defined as the change of Hb concentration from baseline at week 5
- Darbepoetin alfa dose over time by initial Hb response
- Hb over time by initial Hb response
- Number of days hospitalized
- Anti-human leukocyte antigen (HLA) antibodies

Study Design: This is a phase 3, multicenter, randomized, double-blind, parallel group study. Anemic, ND-CKD subjects, without recent ESA use, will be randomized to 1 of 2 dosing strategies. In the Hb-based titration group, darbepoetin alfa doses will be titrated to maintain Hb ≥ 10.0 g/dL. In the other group, subjects will receive a fixed dose of darbepoetin alfa. All subjects will receive investigational product (IP) as a subcutaneous injection every 4 weeks (Q4W). Treatment group, darbepoetin alfa doses, and protocol specified Hb concentrations will be blinded to the investigator, subjects and study team. Subjects will be followed for approximately 2 years from the date of randomization.

Sample Size: A total of approximately 750 subjects (approximately 375 per treatment group) will be randomized.

Summary of Subject Eligibility Criteria

Anemic ND-CKD subjects:

- Age 18 or older
- Two Hb concentrations < 10.0 g/dL at least 2 weeks apart
- **Not currently receiving dialysis with an estimated** glomerular filtration rate of < 45.0 mL/min/1.73m^2 **during screening**
- Iron replete, defined as a transferrin saturation (TSAT) ≥ 20% and a ferritin ≥ 100 ng/mL
- Clinically stable by the investigator

Who have not:

- Received erythropoiesis stimulating agents (ESAs) within **4** weeks of screening
- Received an RBC transfusion within **8** weeks of screening
- Received intravenous iron or had changes to oral iron therapy within 4 weeks of screening

For a full list of eligibility criteria, please refer to Section 4.

Amgen Investigational Product Dosage and Administration

Investigational product (darbepoetin alfa or placebo) will be administered subcutaneously every 4 weeks. Darbepoetin alfa will be supplied as a clear, colorless, sterile protein solution in single use prefilled syringes (PFS) at concentrations of 10, 20, 30, 40, 50, 60, 80, 100, 150, 200 and 300 μg. Placebo will be provided in similar PFS as a clear, colorless, sterile solution.

The protocol specified doses (PSD) for use in this study are 10, 20, 30, 40, 50, 60, 80, 100, 120, 150, 200, 250, and 300 μg.

Every 4 weeks a protocol specified Hb will be measured using an **modified** Hb point of care (POC) device and the results will be blinded. The codes provided by the **modified** Hb POC device and the mean systolic blood pressure (SBP) will be entered into the interactive voice response/interactive web response (IVR/IWR) system at each dosing visit. The mean SBP obtained from additional blood pressure monitoring visits will also be entered into the IVR/IWR system.

In both dosing groups, the dose of investigational product will be withheld if the subject's mean SBP is ≥ 160 mmHg for three consecutive visits (including blood pressure monitoring visits). Investigational product will be restarted at the dosing visit when the mean SBP is ≤ 140 mmHg.

Subjects randomized to the Hb-based titration group will receive an initial dose of darbepoetin alfa of 0.45 μg/kg, based on the subject's screening weight, rounded down to the next lower PFS strength. Subsequently, the dose of darbepoetin alfa will be titrated based on the Hb concentration at the current visit and rate of rise (ROR) as outlined in the table below. The Hb ROR will be determined by the protocol specified Hb concentrations obtained from the previous dose to the current dose. An IVR/IWR system will be used to determine and assign each dose. Subjects may be assigned 2 injections to ensure they receive the dose assigned for that visit.

Dosing Algorithm for Hb-based Titration Group

Hb (g/dL)	Hb ROR (g/dL/4W)		
	≤ 1.0	> 1.0 and ≤ 2.0	> 2.0
<10.0	↑ to next higher PSD[a]	Maintain	↓ to next lower PSD[b]
10.0-10.5	Maintain	↓ to next lower PSD[b]	↓ to next lower PSD[b]
>10.5 -11.0	↓ to next lower PSD[b]	↓ to next lower PSD[b]	Placebo[c]
>11.0	Placebo[c]	Placebo[c]	Placebo[c]

[a] Subjects receiving 300 μg who require a dose increase will continue to receive 300 μg
[b] Subjects receiving 10 μg who require a dose reduction will receive placebo
[c] Restart darbepoetin alfa when Hb < 10.0 g/dL, at next lower PSD

Subjects randomized to the fixed dose group will receive a fixed dose of darbepoetin alfa throughout the study of 0.45 μg/kg, based on the subject's screening weight, rounded down to the next lower PFS strength. The same dose of darbepoetin alfa will then be administered Q4W for the duration of the study, with 1 exception: if the Hb is > 12.0 g/dL, the darbepoetin alfa dose will be withheld and placebo will be administered until the Hb falls below 10.0 g/dL, at which time the darbepoetin alfa dose will be restarted. In order to maintain the blind when a subject in the Hb-based titration group is assigned 2 injections of investigational product, subjects in the fixed dose group will be assigned at random to receive 2 injections of investigational product.

Throughout the study, investigators should provide adequate supportive care. It is recommended that iron be administered to ensure TSAT levels of ≥ 20% and serum ferritin ≥ 100 ng/mL and blood pressure be monitored and managed as appropriate, such as to target a SBP < 130 mmHg and a diastolic blood pressure (DBP) < 80 mmHg. Subjects should not receive any other ESAs while receiving investigational product during the study.

Procedures

Informed consent will be obtained prior to the execution of any study procedures. Subject visits and assessments will occur from the time of screening through the end of study. At the conclusion of the screening period, eligible subjects will be randomized in a 1:1 ratio to 1 of 2 dosing strategies:

- Hb-based titration group: Darbepoetin alfa titrated to maintain Hb≥ 10.0 g/dL
- Fixed dose group: Weight-based dose of darbepoetin alfa that will not be titrated

Randomization will be stratified by RBC transfusion received within 12 months prior to randomization (yes/no) and site practice setting (nephrology/non-nephrology).

Assessments during the study visits may include:

- Recording of transfusions, adverse events, concomitant medications, hospitalizations and collection of study endpoint data for adjudication
- Physical assessments (eg, blood pressure)
- Collection of laboratory samples for evaluation of blood chemistry, hematology and iron status
- Collection of blood samples for biomarkers

Subjects ending investigational product prior to week 97 will be asked to complete scheduled visits and study procedures. At a minimum, subjects must be followed for the collection of RBC transfusions and endpoint data for adjudication.

RBC transfusions should be performed as deemed necessary by the treating physician and criteria are not stipulated by this study protocol. Information regarding the context surrounding RBC transfusions will be collected throughout the study including units of RBCs transfused, the transfusion setting (eg, dialysis center, intensive care unit, emergency department) and clinical

events (eg, bleeding, surgery). This information will be reviewed by an independent Clinical Endpoint Committee (CEC).

Events of death, myocardial infarction, stroke, decompensated heart failure and thromboembolism, including vascular access thrombosis, will also be collected from randomization through the end of the study and adjudicated in a blinded fashion by the independent CEC.

Adverse events (AEs) will be collected from the time of randomization through 4 weeks following the last dose of investigational product. Serious adverse events will be collected from the date of consent. Any serious adverse events with a fatal outcome (regardless of possible relationship to investigational product) occurring through the end of the subject's participation on the study are to be reported to Amgen.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and Appendix A.

Statistical Considerations

Subjects who receive at least 1 dose of investigational product will be included in the primary analysis. The evaluation period will begin at the date of randomization and subjects will be censored at the last administration of investigational product plus 3 months or end of study, whichever is earlier (on-treatment approach).

For the primary endpoint, the proportion of subjects in each treatment group receiving at least 1 RBC transfusion during the evaluation period will be presented with 2-sided 95% CIs. The difference in proportions between treatment groups and the relative risk ratio will be described with 2-sided 95% CIs. Confidence intervals will be derived using normal approximation. The primary analysis will be repeated by subgroups of interest.

As a sensitivity analysis, the primary analysis will be repeated using all randomized subjects with the evaluation period beginning at the date of randomization and subjects will be censored at the end of study (on-study approach).

Sensitivity analyses will also be performed to assess the impact of potential differential follow-up on the primary endpoint. Exposure-adjusted subject incidence of receiving at least 1 RBC transfusion will be calculated with 95% CI using Chi-square approximation to the Poisson distribution for both on-treatment and on-study approaches.

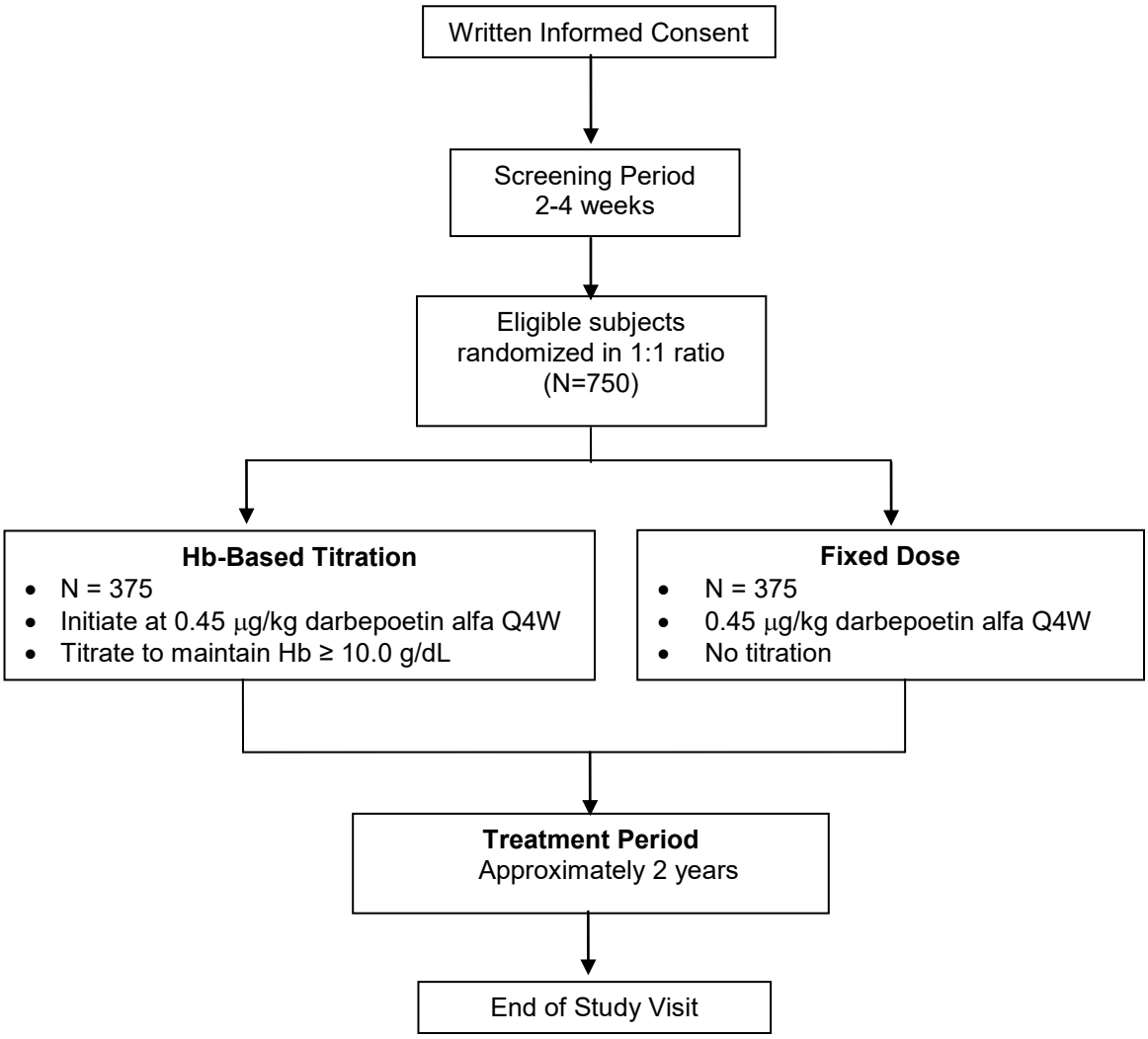
For the analyses of the secondary endpoints: total number of units of RBC transfused per subject will be summarized for each treatment group. Time to first RBC transfusion using both on-treatment and on-study approaches will be described for each treatment group. Average achieved Hb concentration while receiving investigational product will be analyzed as average Hb using the area under the curve (AUC) method. Cumulative doses of darbepoetin alfa adjusted for investigational product exposure time will also be described.

Safety endpoints will include the descriptive summary of the time to adjudicated event endpoint by treatment group, using Kaplan-Meier curves, Kaplan-Meier percentiles, the number of subjects censored, and the number of subjects with events. Subject incidence of adverse events will be tabulated by system organ class, high level group term, and preferred term by treatment group. Adverse events of interest will be tabulated by treatment group. Subgroup analyses will be presented for all adverse events.

An independent Data Monitoring Committee (DMC) will review unblinded study data on a regular basis throughout the duration of the study. The DMC may recommend modifying or stopping the study, or suspending enrollment. This recommendation can be based on any safety concerns, lack of efficacy/futility, or preponderance of early evidence of efficacy. The DMC will conduct an interim analysis, which will occur when approximately 33% of subjects have completed 12 months of planned study follow-up.

For a full description of statistical analysis methods, please refer to Section 10.

Study Design and Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
AUC	Area Under the Curve
CBC	Complete Blood Count
CEC	Clinical Endpoint Committee
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRP	C-Reactive Protein
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
Electronic Source Data (eSource)	Source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
Electronic Trial Operations (ETO) System	An electronic system that is used to facilitate the operations of a clinical trial through the collection of study related data. Most common applications of an ETO system within a clinical trial are: subject randomization and product management. Term synonymous with the industry term IVR or IVRS. Note: An individual can interface with an ETO system by using either an IVR or IWR interface. See definitions of IVR and IWR below.
End of Study for individual subject (EOS)	Defined as the last day that protocol specified procedures are conducted for an individual subject
End of Study (primary completion)	Defined as the date when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint
Enrollment	Defined as the date the subject is randomly assigned to a treatment group or "randomized"
EPO	Erythropoietin
ESA	Erythropoiesis Stimulating Agent
ET	Early Termination
GCP	Good Clinical Practice
GI	Gastrointestinal
Hb	Hemoglobin
HBV	Hepatitis B Virus

Abbreviation or Term	Definition/Explanation
HCT	Hematocrit
HCV	Hepatitis C Virus
HemoCue	**Modified** hemoglobin point of care device
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HTLV	Human T-Lymphotropic Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Interactive Voice Response (IVR)	Telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
Interactive Web Response (IWR)	Web based technology that is linked to a central computer in real time as an interface to collect and process information.
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
KDOQI	The National Kidney Foundation Kidney Disease Outcomes Quality Initiative
MACE	Major Adverse Cardiovascular Events
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MPV	Mean Platelet Volume
ND-CKD	Chronic Kidney Disease Not on Dialysis
PFS	Prefilled Syringe
PIN	Personal Identification Number
POC	Point of Care
PSD	Protocol Specified Dose
PTCA	Percutaneous Transluminal Coronary Angioplasty
Q4W	Every 4 Weeks
Randomization	Defined as the date the IVR/IWR system is contacted to randomize a subject to a treatment group. Randomization occurs only after the subject has successfully met all screening eligibility criteria.

Abbreviation or Term	Definition/Explanation
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
rHuEPO	recombinant Human Erythropoietin
ROR	Rate of Rise
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
Source Data	Information from an original record or certified a copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject ID, Randomization ID, and Stratification Value.
Study week	7 calendar days
TACO	Transfusion Associated Cardiac Overload
Target visit date	The calculated date for study visits based on the date of randomization
TIA	Transient Ischemic Attack
TIBC	Total Iron Binding Capacity
TRALI	Transfusion-Related Acute Lung Injury
TREAT	Trial to Reduce Cardiovascular Events with Aranesp® Therapy
TSAT	Transferrin Saturation
WBC	White Blood Cell

Table of Contents

Page

List of Tables

List of Appendices

1. OBJECTIVES

1.1 Primary

To evaluate the incidence of red blood cell (RBC) transfusions in chronic kidney disease subjects not on dialysis (ND-CKD) using either a hemoglobin (Hb)-based titration algorithm or a weight-based dose that will not be titrated (fixed dose), and to evaluate the difference in the incidence of RBC transfusions between the 2 groups.

1.2 Secondary

To summarize the following for each dosing strategy:

- Transfusion burden
- Time to first RBC transfusion
- Achieved Hb concentration
- Cumulative dose of darbepoetin alfa

To describe the difference in each of the above between the two dosing strategies.

1.3 Safety

To describe the safety profile of darbepoetin alfa, including adverse events and the occurrence of adjudicated clinical events of interest.

1.4 Exploratory

To describe with each dosing strategy:

- Dose and Hb-related parameters
- Initial Hb response and resulting dose and achieved Hb
- Duration of hospitalization
- Allosensitization over time

2. BACKGROUND AND RATIONALE

2.1 Disease

Anemia is a common and debilitating complication of chronic kidney disease (CKD). It results primarily from decreased production of erythropoietin by the kidney (Eschbach and Adamson, 1985) and becomes increasingly prevalent and severe as kidney function declines (Moranne et al, 2009; Astor et al, 2002; Kazmi et al, 2001). This renal anemia itself may be severe enough to require RBC transfusions or may contribute to the need for a RBC transfusion in patients who experience a clinical event which worsens the anemia (eg, bleeding, infection, or inflammation).

Avoidance of RBC transfusions is desirable due to the association of transfusions with a number of risks as well as because of blood inventory constraints

(Goodnough and Shander, 2007). Some risks, including transfusion-related acute lung injury (TRALI), transfusion associated cardiac overload (TACO), hemolytic reactions, and bacterial sepsis, have been associated with transfusion-related death (Leo and Pedal, 2010; Eder and Chambers, 2007). Transmission of blood-borne viral pathogens such as human immunodeficiency virus (HIV), human T-lymphotropic virus (HTLV), hepatitis B (HBV) or hepatitis C (HCV) is a lesser risk of RBC transfusions due to contemporary screening practices, but the risk has not been completely eliminated. Concerns remain regarding transmission of pathogens such as West Nile virus for which blood products are not routinely screened (Busch et al, 2003). The possibility for RBC transfusions to transmit Creutzfeldt-Jakob disease is also a concern (Busch et al, 2003). Chronic transfusions can also lead to iron overload and its complications (Despotis et al, 2007; Goldman and Vanherweghem, 1987).

CKD patients are at higher risk for specific complications of transfusions. These include volume overload and hyperkalemia (Despotis et al, 2007; Simon and Bove, 1971). In addition, transfusions may lead to allosensitization (Murphey and Forsthuber, 2008). Allosensitization can increase the time a patient spends on the kidney transplant wait-list or even preclude transplant eligibility (Susal et al, 2009), and has also been associated with shorter graft survival (Seetharam et al, 2010; Opelz, 2005) and accelerated atherosclerosis (Hill et al, 2011).

2.2 Darbepoetin alfa Background

Erythropoiesis stimulating agents (ESAs) bind to the erythropoietin receptor and stimulate erythropoiesis by the same mechanism as endogenous erythropoietin (EPO). They have been shown to effectively elevate and maintain Hb concentrations in patients with renal anemia and reduce transfusion requirements.

Darbepoetin alfa is an ESA produced in Chinese hamster ovary cells as a secreted glycoprotein by recombinant DNA technology. It is a 165 amino acid protein that contains 5 N-linked oligosaccharide chains, rather than the 3 contained in human EPO. The additional carbohydrate chains increase the molecular weight and carbohydrate content of the glycoprotein, which gives darbepoetin alfa an approximately 3-fold longer serum half-life and mean residence time than recombinant human erythropoietin (rHuEPO) in animal models and subjects with CKD, allowing extended administration dosing intervals (Macdougall, 2000; Egrie et al, 1993). Details of the chemistry, preclinical pharmacology, pharmacokinetics, toxicology, and clinical experience with darbepoetin alfa are contained in the Investigator's Brochure.

Darbepoetin alfa is licensed and approved in the United States, Europe, Canada, Australia and a number of other countries for the treatment of anemia in patients with CKD, including patients on dialysis and patients not on dialysis, and for the treatment of anemia in patients with non-myeloid malignancies when anemia is due to concomitantly administered chemotherapy.

2.3 Rationale

Since their approval, ESAs have been in wide use in CKD patients both on dialysis and not on dialysis to raise Hb concentrations and reduce the need for RBC transfusions. Because observational studies had shown an association between anemia and increased cardiovascular (CV) morbidity and mortality in ND-CKD patients (Collins, 2003; McClellan et al, 2002; Sarnak et al, 2002; Al Ahmad et al, 2001; Mann, 1999; Levin et al, 1999), clinical trials were conducted in this population to evaluate potential CV benefits of ESAs. Contrary to the hypothesis, 2 large clinical trials did not demonstrate a CV benefit when anemia was treated. The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study evaluated outcomes in subjects with moderate anemia treated with epoetin alfa to Hb concentrations of 13.5 g/dL vs 11.3 g/dL (Singh et al, 2006). The CHOIR study identified an increased risk for death and serious CV events in the higher Hb target arm (hazard ratio 1.34; 95% confidence interval [CI] 1.03 to 1.74), the imbalance being mostly for death and hospitalization for heart failure. The Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) evaluated ND-CKD subjects with moderate anemia and type 2 diabetes who were randomized to receive either treatment with darbepoetin alfa to a target Hb concentration of 13 g/dL or placebo with rescue darbepoetin alfa therapy if Hb concentration fell < 9 g/dL (Pfeffer et al, 2009). The TREAT study did not demonstrate a benefit on the primary composite CV endpoint of all cause mortality or CV event (hazard ratio 1.05; 95% CI 0.94 to 1.17), however, an increased risk of stroke was observed when compared to the placebo group (hazard ratio 1.92; 95% CI 1.38 to 2.68). The mechanism for the increased risk observed when targeting high Hb concentrations has not been determined. It has been suggested that exposure to high doses, high cumulative dose of ESA, Hb excursions, and rapid Hb rises might contribute to these risks. Thus, there is a desire to define a dosing regimen that can retain the transfusion benefits of ESA treatment while minimizing potential contributing factors listed above.

Although in CKD patients ESAs have historically been titrated to achieve a predefined Hb concentration, this may not be the only possible dosing strategy. In particular, a

dosing strategy using a fixed dose could mitigate some of the potential contributing factors of increased risk while effectively avoiding RBC transfusions. A fixed dose strategy will avoid exposure to high doses entirely and could decrease the cumulative dose exposure. Additionally, by not increasing doses, the occurrence of Hb excursions and rapid Hb rises may be minimized. A fixed dose may also reduce Hb cycling, which may be associated with frequent dose changes, which has been associated with worse outcomes in some observational studies of dialysis patients (Gilbertson et al, 2008; Weinhandl et al, 2011). A consistent, fixed dosing strategy, without titration, may also simplify therapy for patients and providers, which may potentially improve compliance and minimize dosing errors.

The ability of treatment with a fixed dose to effectively reduce the need for transfusions is unknown. One prospective single arm study designed to use primarily 1 fixed dose of epoetin alfa has suggested that such a strategy can reduce RBC transfusions in anemic ND-CKD patients (Provenzano et al, 2004). During the short 16-week study, 3.7% of patients were transfused compared to 11.1% of patients within 6 months prior to enrollment. However, this study enabled the "fixed dose" to be increased or decreased, and less than half the patients were maintained on the original 10,000 unit per week fixed dose of epoetin alfa throughout the study.

This START-CKD study is designed to describe the benefits and potential risks of a new treatment strategy using a fixed dose of darbepoetin alfa. Anemic ND-CKD subjects, without recent ESA use, will be randomly allocated to treatment with a fixed dose of darbepoetin alfa or to treatment with darbepoetin alfa using a Hb-based titration strategy, which has been the conventional dosing strategy. This study will estimate the subject incidence of RBC transfusions (administered as deemed clinically necessary) in each group and the difference in incidence of RBC transfusions between the 2 groups. However, determining a preferred dosing regimen will also be based on multiple considerations, such as cumulative darbepoetin alfa dose, total number of units of transfusions, Hb concentration, Hb-related parameters (eg, Hb variability, excursions, rate of change), and adverse (eg, CV) events. Given these considerations, an estimation approach was chosen for this study.

The dosing algorithm that will be used in the Hb-based titration group is intended to maintain Hb concentration ≥ 10.0 g/dL, with a starting dose of 0.45 μg/kg, to be administered every 4 weeks (Q4W). Model-based simulations were used to select a fixed dose that would achieve approximately the same population mean

Hb concentration at the end of the study. The simulations, conducted in a similar fashion as previously published (Doshi et al, 2010), predicted that a darbepoetin alfa dose of 0.45 μg/kg/Q4W should be used.

The starting dose is the same for both of the dosing algorithms. Thus it will be possible to analyze the dose received and achieved Hb concentrations by subgroups of initial Hb response using the same definition of Hb response for both treatment groups.

2.4 Clinical Hypotheses

The incidence of RBC transfusions in each treatment group (Hb-based titration group and fixed dose group) and their difference will be estimated, and no formal hypothesis will be tested. The width of the 95% CI of the transfusion incidence rate is expected to be < 10% (ie, ± 5% around the point estimate) in each group and the width of the 95% CI of the difference in transfusion incidence rates is expected to be < 14% (ie, ± 7% around the point estimate). The efficacy and safety of each treatment group will be described, as these aspects will assist in the determination of a preferred dosing regimen.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 3, multicenter, randomized, double-blind, parallel group study. Anemic, ND-CKD subjects, without recent ESA use, will be randomized to 1 of 2 dosing strategies. In the Hb-based titration group, darbepoetin alfa doses will be titrated to maintain Hb ≥ 10.0 g/dL. In the other group, subjects will receive a fixed dose of darbepoetin alfa. All subjects will receive investigational product (IP) as a subcutaneous injection Q4W. Treatment group, darbepoetin alfa doses, and protocol specified Hb concentrations will be blinded to the investigator, subjects and study team. The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.

3.2 Number of Centers

The study will be conducted in approximately 350 sites in North America. 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”.

Approximately 750 subjects in total will be enrolled into this study, with approximately 375 per treatment group. Refer to Section 10.2 for additional information regarding the calculation of the sample size.

3.4 Estimated Study Duration

3.4.1 Study Duration for Participants

The total duration on-study for an individual subject is approximately 2 years, which includes the following:

- 2- to 4-week screening period
- 100-week on-study period including
  - 96-week treatment period
  - 4-week follow-up period, after final dose of investigational product for collection of RBC transfusions and safety information (eg, adverse events)

3.4.2 End of Study

The end of study is defined as the date on which the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint.

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 (eg, sex, age, race), date and outcome of the screening process (eg, enrolled into the study, reason for ineligibility, or refused to participate). This log may be completed and updated via an Electronic Trial Operations (ETO) System (eg, interactive voice response system).

Before **any** study specific procedure, the appropriate written informed consent must be obtained (see Section 11.1). For purposes of eligibility, screening is defined as the first screening procedure following signing of the informed consent.

4.1 Inclusion Criteria

4.1.1 Age 18 or older

4.1.2 Clinical history of advanced CKD not on dialysis with at least 1 historic estimated glomerular filtration rate (eGFR) < 45.0 mL/min/1.73m^2 at least 12 weeks prior to screening

4.1.3 **Not currently receiving dialysis with an** eGFR < 45.0 mL/min/1.73m^2, per the central laboratory during screening

4.1.4 Chronic anemia due to renal failure

4.1.5 Two Hb concentrations < 10.0 g/dL, at least 2 weeks apart during screening using the **modified** Hb point of care (POC) device

4.1.6 Iron replete, defined as a transferrin saturation (TSAT) ≥ 20% and a ferritin ≥ 100 ng/mL, per the central laboratory during screening

4.1.7 Vitamin B12 and folate replete, defined as a vitamin B12 level > 180 pg/mL and a folate concentration > 7 nmol/L, per the central laboratory during screening

4.1.8 Clinically stable in the opinion of the investigator

4.1.9 Subject has provided written informed consent

4.2 Exclusion Criteria

General

4.2.1 Systemic hematologic disease (eg, sickle cell anemia, myelodysplastic syndrome, hematologic malignancy)

4.2.2 Current or prior malignancy within 5 years of screening, with the exception of non-melanoma skin cancers and cervical intraepithelial neoplasia

4.2.3 Treatment for any malignancy (eg, radiation, chemotherapy, hormone therapy, or biologics) within 5 years of screening, with the exception of locally excised non-melanoma skin cancer or cervical intraepithelial neoplasia

4.2.4 Female subject not willing to use highly effective methods of birth control during treatment and for 4 weeks after the end of treatment

4.2.5 Subject is pregnant or breast feeding, or might become pregnant during the study or within 4 weeks after the end of treatment

4.2.6 Currently receiving **intravenous** antibiotics for treatment of an active infection

4.2.7 Known HIV positive

4.2.8 Currently receiving systemic immunosuppressive therapy with the exception of prednis(ol)one ≤ 10 mg per day (or the steroid equivalent)

4.2.9 History of any organ transplant

4.2.10 Currently enrolled in another interventional study (eg, studies which require medical device use or drug therapy or with protocol required procedures), or less than 4 weeks since ending another interventional study(s) or receiving investigational agent(s)

4.2.11 Known neutralizing anti-erythropoietic protein antibodies

4.2.12 Known sensitivity to any of the products to be administered during dosing

4.2.13 Previously enrolled in this study

4.2.14 Not expected to be available for protocol required study visits or procedures to the best of the subject and investigator's knowledge

4.2.15 Subject has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent and/or comply with all required study procedures

Within 24 weeks of screening

4.2.16 Occurrence of any of the following:

- Stroke
- Myocardial Infarction (MI)

Within **8** weeks of screening

4.2.17 Receipt of any of the following:

- RBC transfusion

4.2.18 Occurrence of any of the following:

- Seizure
- Clinically relevant active bleeding (eg, gastrointestinal [GI] bleed)
- Any hospitalization

Within 4 weeks of screening

4.2.19 Receipt of any intravenous (IV) iron therapy

4.2.20 Changes in oral iron therapy

4.2.21 **Receipt of ESA therapy**

During screening

4.2.22 Diagnosis or treatment of malignancy, with the exception of non-melanoma skin cancers and cervical intraepithelial neoplasia

4.2.23 Receipt of any of the following:

- ESA therapy
- RBC transfusions
- IV iron therapy

4.2.24 Changes in oral iron therapy

4.2.25 Occurrence of any of the following:

- Stroke
- MI
- Seizure
- Clinically relevant active bleeding (eg, GI bleed)
- Any hospitalization
- Any outpatient surgery

4.2.26 Uncontrolled hypertension, defined in this study, as

- a mean systolic blood pressure (SBP) > 140 mmHg at both screening visits, or
- a mean SBP ≥ 160 mmHg at any screening visit, or
- a mean diastolic blood pressure (DBP) ≥ 90 mmHg, at any screening visit

Expected or scheduled

4.2.27 Change in oral iron therapy or receipt of IV iron therapy within 4 weeks after randomization

4.2.28 Receipt of a RBC transfusion within 8 weeks after randomization

4.2.29 Any organ transplant within 24 weeks after randomization

4.2.30 Initiation of dialysis within 24 weeks after randomization

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 (see Section 11.2*)*. All subjects must sign and personally date the consent form before commencement of study specific procedures. Subjects are considered enrolled when they have been randomized to treatment.

All subjects who enter into the screening period for the study will receive a unique subject identification number before any study procedures are performed. The investigator or designee should contact the Interactive Voice Response/Interactive Web Response System (IVR/IWR) to register subjects that sign the consent form and to obtain the unique subject identification number. 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 study; it must not be changed at the time of rescreening, enrollment, or randomization. PPD [redacted]

5.1 Screening

The screening period begins when the subject signs and dates the informed consent and concludes when the subject is randomized or screen failed. The screening period is a

minimum of 14 days and must not exceed 28 days. Eligibility criteria will be evaluated throughout the screening period.

Screening procedures are described in Section 7.1.1. Upon either completion of the final screening procedure or determination of ineligibility, the investigator or designee must contact the IVR/IWR system.

If subjects are confirmed as eligible, the IVR/IWR system will continue to the randomization call and assign the investigational product. Subjects must have their first dose of investigational product administered on this date. At the completion of the call, a confirmation fax and/or e-mail will be sent to the site to verify that the correct information has been entered and to confirm the randomization.

If subjects are not eligible for the study due to:

- the screening Hb concentration only, the IVR/IWR system will notify the investigator or designee that the subject is not eligible and record the date of the screen failure
- reasons other than the screening Hb concentration, the investigator or designee will enter the date and reason for screen failure

Subjects who fail screening may be rescreened as described in Section 7.1.2 beginning **14** days after the date of the last screening procedure.

5.2 Randomization

Randomization by the IVR/IWR system will be done in a 1:1 ratio to 1 of the 2 treatment groups (Hb-based titration group or fixed dose group) based on the following stratification factors at the time of study entry:

- Receipt of any RBC transfusion within the 12 months prior to randomization (yes/no)
- Site practice setting (nephrology/non-nephrology), pre-specified by the specialty of the principal investigator at the time of site initiation

Randomization will be based on a schedule generated before the start of the study by an Amgen representative not involved in the conduct of the study.

5.3 Site Personnel Access to Individual Treatment Assignments

The identity of the treatment group assigned to the subject, the protocol specified Hb measurements, and the dose of investigational product assigned will be maintained by the IVR/IWR system. The investigator will be provided with a unique personal identification number (PIN) to access the IVR/IWR system in the event that they need to unblind the subject treatment assignment.

The subject, site personnel, and Amgen study personnel and designees will be blinded to the 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. 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 is required to do so within 1 working day after the event and must document the unblinding in the subject's electronic case report form (eCRF).

6. TREATMENT PROCEDURES

6.1 Classification of Products and Medical Devices

The Amgen Investigational Products used in this study include: Darbepoetin alfa and placebo in a prefilled syringe (PFS).

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, and administration of darbepoetin alfa and placebo.

The medical devices that are provided by Amgen for use in this study include: A modified HemoCue Hb 201+ system hemoglobin analyzer and an auto inflate Blood Pressure Monitor.

6.2 Darbepoetin alfa

Darbepoetin alfa will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Darbepoetin alfa will be presented as a clear, colorless, sterile protein solution in single use PFS in the following strengths: 10, 20, 30, 40, 50, 60, 80, 100, 150, 200, and 300 μg.

6.3 Placebo

Placebo will be provided as a clear, colorless, sterile solution in PFS identical to those containing the active drug.

6.4 Dosage, Administration, and Schedule

Subjects' Hb will be measured Q4W using an **modified** Hb POC device provided by Amgen. The device will provide coded values that will be entered into IVR/IWR system at each scheduled dosing visit. The IVR/IWR system will determine and assign the appropriate dose and individual box(es) of investigational product (darbepoetin alfa or placebo) for that specific visit based on the Hb concentration and the dosing algorithms

in Section 6.4.1 below. Each box of investigational product will contain only 1 PFS that is to be administered at the study visit for which it has been assigned.

The protocol specified doses (PSD) for use in this study are 10, 20, 30, 40, 50, 60, 80, 100, 120, 150, 200, 250, and 300 μg. Subjects who require either a 120 or 250 μg dose will require the administration of 2 injections. When this occurs, in order to maintain the blind, a subject in the fixed dose arm will be assigned at random to receive 2 injections of investigational product by the IVR/IWR system. When this is required, the IVR/IWR will assign 2 boxes of investigational product for administration during the study visit. Investigational product will be administered subcutaneously (SC) by appropriately trained medical personnel Q4W for the duration of the treatment period. The starting dose of investigational product will be 0.45 μg/kg for both groups, using the subject's body weight at screening Visit 1. The dose obtained from this calculation will be rounded down to the next lower PFS strength.

6.4.1 Dosage Adjustments

All dose adjustments will be managed using the IVR/IWR system. In order to maintain the blind, subjects will receive a placebo injection in place of darbepoetin alfa therapy when the dose of study drug is to be withheld per the dosing algorithm, for reasons other than elevated SBP.

The maximum dose of darbepoetin alfa administered at any time during the study will be 300 μg.

The dose of investigational product may be adjusted based on Hb parameters and SBP values.

6.4.1.1 Dosage Adjustments Based on Systolic Blood Pressure Values

If the subject's mean SBP is ≥ 160 mmHg for **two** consecutive visits (including blood pressure monitoring visits), the dose of investigational product will be withheld.

If the subject's dose is withheld for ≤ 2 consecutive dosing visits, the investigational product will be restarted at the subject's previous dose at the dosing visit when the mean SBP is ≤ 140 mmHg.

If the subject's dose is withheld for > 2 consecutive dosing visits, the investigational product will be restarted on the initial study dose at the dosing visit when the mean SBP is ≤ 140 mmHg.

6.4.1.2 Dosage Adjustments Based on Hb Parameters

6.4.1.2.1 Hb-based Titration Group

Subjects randomized to the Hb-based titration group will have their dose of investigational product titrated based on the Hb concentration on the date of the visit, the corresponding Hb rate of rise (ROR), and the previously assigned dose, as outlined in Table 1 below. The Hb ROR will be determined by the protocol specified Hb concentrations obtained from the previous dose to the current dose.

Table 1. Dosing Algorithm for Hb-based Titration Group

	Hb ROR (g/dL/4W)		
Hb (g/dL)	≤ 1.0	> 1.0 and ≤ 2.0	> 2.0
<10.0	↑ to next higher PSD[a]	Maintain	↓ to next lower PSD[b]
10.0-10.5	Maintain	↓ to next lower PSD[b]	↓ to next lower PSD[b]
>10.5 -11.0	↓ to next lower PSD[b]	↓ to next lower PSD[b]	Placebo[c]
>11.0	Placebo[c]	Placebo[c]	Placebo[c]

[a] Subjects receiving 300 μg who require a dose increase will continue to receive 300 μg
[b] Subjects receiving 10 μg who require a dose reduction will receive placebo
[c] Restart darbepoetin alfa when Hb < 10.0 g/dL, at next lower PSD

When darbepoetin alfa therapy is withheld per the dosing algorithm, placebo will be administered. Once the Hb falls to < 10.0 g/dL, darbepoetin alfa therapy will be resumed at the next lower PSD.

6.4.1.2.2 Fixed Dose Group

Subjects randomized to the fixed dose group will receive the same dose as the one assigned at the time of randomization for the duration of the treatment period with 1 exception: if the Hb is > 12.0 g/dL, darbepoetin alfa therapy will be withheld and placebo administered. Once the Hb falls to < 10.0 g/dL, darbepoetin alfa therapy will resume at the same dose.

6.4.1.3 Missed Doses

If a subject in either group misses a scheduled dose of investigational product (defined as Q4W ± 5 days), this dose will not be administered off schedule. The missed dose and reason should be entered into the eCRF. For the next dosing visit, the subject should return to their original visit schedule.

If a subject misses > 2 consecutive dosing visits, they will be restarted at their initial study dose at the next dosing visit.

6.5 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 6.8.

It is recommended that all subjects be iron replete during the study. Supplemental iron therapy should be administered as needed and as tolerated. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that TSAT be maintained ≥ 20% and ferritin ≥ 100 ng/mL.

Blood pressure should be monitored and managed as appropriate. The KDOQI guidelines recommend to target a SBP < 130 mmHg and a DBP < 80 mmHg.

6.6 Medical Devices

The following medical devices will be used in this study and provided by Amgen:

- Modified HemoCue Hb 201+ system hemoglobin analyzer
- **Auto inflate blood pressure monitor**

Medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not usually provided or reimbursed by Amgen. The investigator will be responsible for obtaining supplies of these devices.

6.6.1 Modified HemoCue Hb 201+ System Hemoglobin Analyzer

The HemoCue Hb 201+ system hemoglobin analyzer is a Hb POC device manufactured by HemoCue AB. The device has been modified by HemoCue for the purpose of this trial to provide study specific coded hemoglobin values. The modified HemoCue **will be** provided by Amgen for use in this study to determine protocol specified hemoglobin values **while maintaining the blind**.

Additional details for the **modified** HemoCue Hb POC device may be found in the study specific user manual that accompanies the device.

6.6.2 Other Medical Devices Provided

Amgen will also provide **an auto** inflate blood pressure monitor to be used throughout the trial for protocol specified blood pressure measurements. The blood pressure will be measured as described in Section 7.2.4.

Additional details for the automated blood pressure monitor may be found in the user manual that accompanies the device.

6.7 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

Any product complaint(s) associated with an investigational product or device supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.8 Excluded Treatments During Study Period

Subjects are prohibited from participating in other interventional studies (eg, studies which require medical device use or drug therapy or with protocol required procedures) while participating in this study.

Subjects should not receive commercial ESAs while receiving investigational product during the study.

7. STUDY PROCEDURES

Screening assessments and study procedures are outlined in this section and in Appendix A. The informed consent must be obtained prior to performing any screening or study procedures.

All on-study visits and dosing should be scheduled from Study Day 1. It is important to perform study procedures and obtain samples at the time points outlined in the protocol. When it is not possible to perform the study visit at the specified time point, the visit may be performed within the acceptable visit window as defined in Section 7.1. If a study visit is missed, subsequent study visits should resume on the original visit schedule. Missed assessments at prior visits should not be duplicated at subsequent visits.

With the exception of the screening and rescreen visits, all study procedures for a visit must be completed on the same day.

It is the responsibility of the investigator to ensure all procedures are performed according to the protocol.

7.1 General Study Procedures

Any blood or serum sample collected according to the Schedule of Assessments (Appendix A) may be analyzed for any of the tests outlined in the protocol and for any tests necessary to ensure subject safety. This includes testing to ensure analytical

methods produce reliable and valid data throughout the course of the study. This may also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

If informed consent is provided by the subject, Amgen may do additional testing on remaining samples (ie, residual and back-up) as well as those collected for biomarker development as described in Section 7.4. These samples may be used to investigate and better understand CKD, the dose response and/or prediction of response to darbepoetin alfa, characterize antibody response, and characterize aspects of the molecule (eg, metabolites). Results from this analysis will be documented and maintained, but may not be reported as part of this study.

The procedures performed at each study visit are outlined below and in Appendix A.

Details regarding each type of procedure are provided in Section 7.2.

7.1.1 Screening Evaluations

Informed consent must be obtained before completing any other screening procedures. After signing the informed consent form, subjects will be screened in order to assess eligibility for study participation. The screening window is up to 28 days; subjects must complete 2 visits at least 14 days apart during this period. If a subject has not met all eligibility criteria during or by the end of the 28-day window, the subject will be registered as a screen failure. Subjects who screen fail may be eligible to rescreen per Section 7.1.2.

The following procedures will be completed for all subjects during the first screening visit:

- Informed consent
- Blood pressure and pulse
- Weight
- eGFR, serum creatinine
- Hb, using the **modified** Hb POC device
- Serum pregnancy test for all women (except for women who are surgically sterile or are at least 1 year postmenopausal)
- TSAT, ferritin, iron, total iron binding capacity (TIBC)
- Serum vitamin B12 and folate

Serious adverse events will be collected from the time the informed consent is signed.

The second screening visit will take place at least 14 days but no more than 28 days after the first screening visit. The following procedures will be performed during the second screening visit:

- Blood pressure and pulse
- Serious adverse event assessment
- Hb, using the **modified** Hb POC device

7.1.2 Rescreening Evaluations

Subjects who do not meet eligibility criteria during the initial screening attempt will be permitted to rescreen **4 times**, for a total of **5** screening attempts. Rescreen subjects must first be registered as screen failed in the IVR/IWR system and subsequently registered as a rescreen subject. Once the subject is registered as rescreened, a new 28-day screening window will begin. All screening procedures will need to be repeated.

7.1.3 Study Day 1 Evaluations

The Day 1 visit will be the same day as screening Visit 2. After completion of the screening period, when the subject has met all eligibility criteria, sites will need to complete the randomization call in the IVR/IWR system prior to beginning the Day 1 evaluations. All subsequent doses and study visits will be scheduled based on the Day 1 date.

The following procedures will be completed on Day 1:

- Medical and surgical history, including history of transfusions
- Physical exam, including height and weight
- Electrocardiogram
- Concomitant medications (as specified in Section 7.2.9)
- eGFR, serum creatinine
- Complete blood count (CBC; results will remain blinded)
- TSAT, ferritin, iron, TIBC
- Troponin-T
- Serum albumin, high sensitivity C-reactive protein (CRP)
- Reticulocytes (results will remain blinded)
- Blood samples for biomarkers
- Spot urine albumin and creatinine
- Anti-erythropoietic protein antibodies
- Anti-human leukocyte antigen (HLA) antibodies
- Investigational product administered

Once the subject is enrolled, collection of the following will begin:

- RBC transfusions, as well as transfusions of other blood-derived products
- Endpoint data for adjudication
- Hospitalizations, including observational stays, and emergency department visits
- Adverse events

7.1.4 Treatment Period Evaluations

7.1.4.1 Routine Study Visits

Routine study visits will occur Q4W, as noted in the Schedule of Assessments (Appendix A), during the treatment period beginning at week 5 through the week 97 visit. On-study visits may be completed within ± 5 days of the target visit date. The following procedures and data collection will be completed:

- At Week 5
  - CBC (results will remain blinded)
  - TSAT, ferritin, iron, TIBC
- At Week 5 and every 4 weeks thereafter
  - Blood pressure and pulse
  - Concomitant medications (as specified in Section 7.2.9)
  - RBC transfusions, as well as transfusions of other blood-derived products
  - Endpoint data for adjudication
  - Hospitalizations, including observational stays, and emergency department visits
  - Adverse event and serious adverse event assessment
  - Hb, using the **modified** Hb POC device
  - Investigational product administration
- Every 12 weeks
  - CBC (results will remain blinded)
  - TSAT, ferritin, iron, TIBC
  - Anti-HLA antibodies
- Every 24 weeks
  - eGFR, serum creatinine
  - Blood samples for biomarkers

7.1.4.2 Additional Visits for Blood Pressure Monitoring

For any subject with a mean SBP ≥ 160 mmHg measured during a routine study visit, an additional blood pressure monitoring visit is required 2 weeks later. This visit may be completed within ± 5 days of the scheduled visit date.

For subjects with mean SBP < 160 mmHg an additional study visit for blood pressure monitoring may also be scheduled 2 weeks after a routine study visit at the discretion of the investigator. This visit may be completed within ± 5 days of the scheduled visit date.

The procedures and data collected at blood pressure monitoring visits will include:

- Blood pressure and pulse
- Concomitant antihypertensive medications
- Adverse event and serious adverse event assessment

The SBP obtained during these visits will be entered into the IVR/IWR system.

7.1.5 Evaluations After End of Investigational Product

Subjects ending investigational product prior to week 97 will be asked to continue to complete scheduled visits and study procedures outlined in Section 7.1.4 for the remainder of the treatment period. At a minimum, subjects must be followed for the collection of RBC transfusions and endpoint data for adjudication. **Refer to Section 8.1 for additional information.** In addition, serum for anti-erythropoietic protein antibody testing will be collected at the scheduled visit that occurs closest to the receipt of the last dose of investigational product. Adverse events and serious adverse events will be collected as described in Section 9.

7.1.6 Early Termination

Subjects who choose not to continue in the study prior to week 97 will be asked to complete an early termination visit and should have all End of Study (EOS) evaluations performed as outlined in Section 7.1.7 below.

7.1.7 End of Study Evaluations

Subjects will complete an EOS visit at week 101 within ± 5 days of the target visit date or at early termination. The following procedures apply to the EOS visit:

- Physical examination
- Blood pressure and pulse
- Weight
- Concomitant medications (as specified in Section 7.2.9)
- RBC transfusions, as well as transfusions of other blood-derived products

- Endpoint data for adjudication
- Hospitalizations, including observational stays, and emergency department visits
- Adverse event and serious adverse event assessment
- eGFR, serum creatinine
- Hb, using the **modified** Hb POC device
- Blood samples for biomarkers
- Anti-erythropoietic protein antibodies
- Anti-HLA antibodies

7.2 Description of General Study Procedures

7.2.1 Informed Consent

All subjects must sign and personally date the IRB approved informed consent before any study specific procedures are performed. See Section 11.1 for further details.

7.2.2 Medical and Surgical History

The subject's complete medical and surgical history will be obtained on Day 1 and recorded in the eCRF.

7.2.3 Physical Examination

A physical exam will be performed on Day 1. Breast, genital, and rectal examinations are not required for any study visit unless specific evaluation is warranted. Weight and height should be measured with the subject wearing light clothing and with shoes removed.

The physical examination, including weight, at EOS visit will consist of a follow-up examination to monitor for any changes from the Day 1 physical examination. Any clinically significant changes in physical examination per the investigator's opinion should be recorded on the adverse event eCRF.

7.2.4 Blood Pressure and Pulse

Blood pressure and pulse will be obtained using an automated blood pressure machine provided by Amgen for purposes of this study.

Blood pressure measurements should follow the recommended technique from the American Heart Association (Pickering et al, 2005). The blood pressure should be taken with the subject's arm supported at heart level using the appropriate sized cuff with the subject seated comfortably in a chair with their back supported and both feet on the ground. Subjects should be resting quietly for at least 5 minutes before taking blood pressure measurements. At the first screening visit, blood pressure will be taken in each

arm in triplicate at least 1 minute apart, except when there is a contraindication, such as a dialysis vascular access. The arm with the higher mean blood pressure measurements will be recorded and then used at each of the visits for the duration of the study unless there is a contraindication, such as a dialysis vascular access. Three successive measurements will be taken in the noted arm at least 1 minute apart during subsequent visits.

If the mean SBP is > 140 mmHg or the mean DBP is > 90 mmHg at any study visit, additional information regarding the management of hypertension (eg, modification of antihypertensive medications) will be collected in the eCRF.

7.2.5 Hemoglobin

All Hb measurements specified by the protocol for determination of eligibility, dosing, and as instructed by Amgen, will be blinded and obtained using an **modified** Hb POC device provided by Amgen. All measurements should occur on the day of the study visit prior to the administration of investigational product. The blood sample to be used for the Hb measurement will be obtained by venipuncture. The utilization of blood obtained by a finger stick for Hb evaluations is not permitted.

If a subject's Hb is < 8.0 g/dL or > 13.0 g/dL, the investigator will be notified by the IVR/IWR system so that he/she may follow-up as clinically indicated.

In addition, CBCs will be collected as specified in the Schedule of Assessments (Appendix A). The results of the CBC will remain blinded.

7.2.6 RBC Transfusions

RBC transfusions should be performed as deemed necessary by the treating physician and criteria are not stipulated by this study protocol. All RBC transfusions received while the subject is on-study will be recorded on the RBC transfusion eCRF. Information regarding the context surrounding transfusions will be collected at each study visit including units of RBCs transfused, the transfusion setting (eg, dialysis center, intensive care unit, emergency department), and clinical events (eg, bleeding, surgery). This information will be reviewed by an independent Clinical Endpoint Committee (CEC).

7.2.7 Hospitalizations and Emergency Department Visits

All hospitalizations, including observational stays, and emergency department visits that occur while the subject is on-study will be recorded on the eCRF, including the primary reason for the visit/stay.

7.2.8 Adverse Events

The incidence of adverse events will be collected for each subject at all study visits. A serious adverse event that occurs in a subject after signing the informed consent but prior to randomization will be recorded on the screening serious adverse event eCRF. All adverse events that occur after randomization through 4 weeks after the last dose of investigational product will be recorded on the adverse event eCRF and on the serious adverse event eCRF if they are serious. See Section 9 for additional information.

7.2.9 Concomitant Medications

Concomitant medications will be collected beginning on Day 1 and recorded on the eCRF for this study as described below.

The usage of concomitant medications will be collected every 4 weeks for the duration of the study.

The administration of antihypertensive medications, including the name of the medication, dose, route, frequency, and dates of administration will be collected at every study visit, including any additional visits for blood pressure management.

The administration of iron, including the name of the medication, dose, route and dates of administration, will be collected.

The use of commercial ESAs in subjects who are no longer receiving investigational product is permitted in this study. Administration of commercial ESAs while receiving investigational product will be documented as a protocol deviation. For subjects who receive commercial ESAs, the name of the medication, dose, route and dates of administration will be collected.

7.2.10 Electrocardiogram (ECG)

A standard 12-lead ECG will be obtained after the subject has been supine for at least 5 minutes and prior to blood samples being drawn. The investigator or designated physician will review and sign the ECG. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, the original ECG tracing may be made available to Amgen.

7.2.11 Endpoint Collection for Adjudication

Data for the specified endpoints will be collected for adjudication as outlined in the endpoint manual that will be provided to the study sites. Data will be transferred to a CEC for analysis per Amgen instructions. The original potential endpoint data package will be retained with the subject's source documents.

Clinical events to be collected for adjudication include:

- All-cause mortality
- Stroke, TIA, MI, decompensated heart failure, thromboembolism, and vascular access thrombosis
- The clinical context surrounding RBC transfusions

7.2.12 Laboratory Assessments

All screening and on-study laboratory samples, with the exception of Hb samples utilizing the **modified** Hb POC device, will be processed and sent to the central laboratory. The central laboratory will be responsible for all screening and on-study hematology, serum chemistry, iron, serum pregnancy, spot urine albumin and creatinine, and other laboratory tests required. Amgen or designee will be responsible for anti-erythropoietic protein antibody and anti-HLA antibody assessments, and the central laboratory will ship the samples to Amgen or a specialty laboratory for assay testing.

The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all blood and urine samples. All blood samples will be obtained by venipuncture before investigational product administration. The date and time of blood and urine collection will be recorded in the source documents at the site.

Table 2 below outlines the specific analytes for serum chemistry, iron and other testing to be conducted on blood and urine samples.

Table 2. Analyte Listing

Chemistry	Urine	Hematology	Other
Creatinine	Spot albumin	White blood cell count (WBC)	Serum pregnancy test
Albumin	Spot creatinine	RBC	eGFR
		Hb	High sensitivity CRP
Iron		Hematocrit (HCT)	Folate
TSAT		Platelets	Vitamin B12
Ferritin		Mean corpuscular hemoglobin (MCH)	Troponin-T
		Mean corpuscular hemoglobin	Anti-erythropoietic
Iron		concentration (MCHC)	protein antibodies
TIBC		Mean corpuscular volume (MCV)	Anti-HLA antibodies
		Red cell distribution width (RDW)	
		Mean platelet volume (MPV)	
		Reticulocytes	

7.3 Antibody Testing Procedures

7.3.1 Anti-Erythropoietic Antibodies

Blood samples will be collected from all subjects for the measurement of anti-erythropoietic protein antibodies. Samples testing positive for binding antibodies

will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-erythropoietic protein antibodies during the study.

Subjects who test positive for neutralizing antibodies at the final scheduled study visit will be asked to return for additional follow-up testing. This testing should occur approximately every 12 weeks starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks). More frequent testing (eg, Q4W) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing will not be required where it is established that the subject did not receive darbepoetin alfa.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-erythropoietic protein antibody response may also be asked to return for additional follow-up testing.

7.3.2 Anti-HLA Antibodies

Samples for assessment of allosensitization will be collected. Allosensitization is the development of an immune response against foreign antigens, and in particular foreign HLA. The detection of anti-HLA antibodies (allosensitization) has changed dramatically over the last few years, becoming much more sensitive and more specific (Murphey and Forsthuber, 2008). Given the rapid innovation in the determination of allosensitization, samples collected for anti-HLA antibodies during the course of the trial will be stored until the completion of the study. Anti-HLA antibodies will then be measured using the state-of-the-art and accepted methods at that time.

7.4 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Amgen may attempt to develop blood tests designed to identify subjects most likely to respond positively or negatively to darbepoetin alfa. These samples may also be used to investigate and better understand CKD and characterize aspects of darbepoetin alfa. Biomarker development may be pursued by use of advanced biochemical analyses, such as proteomic methods. If informed consent is provided by the subject, blood samples will be collected for biomarker development on Day 1 and

every 24 weeks thereafter for the duration of the study. Refer to the laboratory manual for detailed collection and handling procedures for all biomarker development samples.

Sample Storage and Destruction

These biomarker development samples and any other components from the cells may be stored for up to 20 years from the end of the study to research scientific questions related to nephrology and/or darbepoetin alfa. The subject retains the right to request that the sample material be destroyed at any time by contacting the principal investigator. The sponsor will be the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the principal investigator or at the end of the storage period or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). Following the request from the subject, the principal investigator will provide the sponsor with the required study and subject numbers so that any remaining serum samples and any other components from the cells can be located and destroyed. If a commercial product is developed from this research project, the sponsor will own the commercial product. The subject will have no commercial rights to such product and will have no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

Subjects have the right to withdraw 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.

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product at any time during the course of the study. If this occurs, the investigator is to discuss with the subject the appropriate procedures for discontinuation from investigational product and must discuss with the subject the options for continuation of the schedule of assessments and collection of data, including endpoints and adverse events. These subjects, as well as those who have stopped receiving investigational product for other reasons (eg, initiation of dialysis), are encouraged to continue the schedule of study visits. If the subject is unable or unwilling to continue the schedule of visits:

- At a minimum, subjects should be followed for the occurrence of RBC transfusions and collection of endpoint data for adjudication

- The investigator must document the change in schedule of assessments and the level of follow-up the subject is permitting: in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, and/or from review of the medical records

Withdrawal of 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; subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator will discuss with the subject appropriate procedures for withdrawal from the study.

Should a subject (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable eCRFs.

Reasons for removal from protocol-required investigational product or procedural assessments include:

- subject request to end investigational product administration
- pregnancy in a female subject (report on Pregnancy Notification Worksheet; see Appendix D)
- safety concern (eg, due to an adverse event)
- initiation of dialysis or receipt of a kidney transplant
- lack of efficacy (eg, need for a commercial ESA regularly)

Reasons for removal of a subject from the study include:

- withdrawal of consent from the study
- death
- lost to follow-up
- administrative decision by Amgen

8.2 Replacement of Subjects

Subjects who withdraw from this study or are removed will not be replaced.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event 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.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates the pre-existing medical condition (eg, diabetes, migraine headaches, 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 and involves an intervention while on-study, such as elective cosmetic surgery or a medical procedure, is not considered an adverse event.

An adverse device effect is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device(s), or adverse events resulting from use error or from intentional misuse of the device(s).

9.1.2 Reporting Procedures for Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after randomization through 4 weeks after the last dose of investigational product are reported using the applicable eCRF (eg, Adverse Event Summary eCRF).

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution,
- Severity [and/or toxicity per protocol],
- Assessment of relatedness to darbepoetin alfa, and
- Action taken

The adverse event toxicity grading scale used will be the Amgen adverse event standard grading score**.** The toxicity grading scale used in this study is described in Appendix B.

The investigator must assess whether the adverse event is possibly related to darbepoetin alfa. 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 darbepoetin alfa?

The investigator must assess whether the adverse event is possibly related to **a** device. 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 **a** device?

The investigator must assess whether the serious adverse event is possibly related to any study-mandated screening procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may be related to screening procedures?"

The investigator must assess whether the adverse event is possibly related to any study-mandated activity or procedure. 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 a study activity/procedure?"

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

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, or subject's parent/legal guardian, may also voluntarily withdraw from treatment due to an adverse event. If the subject requests to withdraw consent for further participation in the study, the subject should be encouraged to undergo, at a minimum, an end-of-study assessment.

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 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
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

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 the informed consent through 4 weeks after the last dose of investigational product are recorded in the subject's medical record and are submitted to Amgen. Any serious adverse events with a fatal outcome (regardless of possible relationship to investigational product) occurring through the end of the subject's participation on the study are to be reported to Amgen. This would include subjects who have been removed from investigational product and continued on-study.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

The serious adverse event must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable eCRF. 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 an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix C for a sample of the Serious Adverse Event Worksheet/eSAE Contingency Report Form. When the first notification of a Serious Adverse Event is reported to Amgen via the eSAE Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. 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 a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

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. Information provided about the serious adverse event must be consistent with that recorded on the applicable eCRF (eg, Adverse Event Summary eCRF).

If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be submitted to Amgen.

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 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.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

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 4 weeks after end of treatment, the pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix D). The Pregnancy Surveillance Program will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while the female subject is taking protocol-required therapies and for 4 weeks after end of treatment, the lactation case should be reported to Amgen's

global Lactation Surveillance Program (LSP) within 24 hours of the investigator's knowledge of the lactation case. Report a lactation case on the Lactation Notification Worksheet (Appendix E).

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Subsets, and Covariates

10.1.1 Study Endpoints

Primary endpoint

- Receipt of 1 or more RBC transfusion

Secondary endpoints

- Total number of units of RBC transfused
- Time to first RBC transfusion
- Average achieved Hb concentration while receiving investigational product
- Cumulative dose of darbepoetin alfa

Safety endpoints

- Time to major clinical events:
  - Composite of all-cause mortality and the occurrence of major cardiovascular events (stroke, myocardial infarction, and decompensated heart failure)
  - Composite of all-cause mortality, stroke or myocardial infarction, ie, major adverse cardiovascular events (MACE)
  - All-cause mortality
  - Cardiovascular mortality
  - Stroke
  - Myocardial infarction
  - Decompensated heart failure
  - Thromboembolic events
  - Vascular access thrombosis
- Adverse events
- Blood pressure and pulse
- Anti-erythropoietic protein antibodies

Exploratory endpoints

- Darbepoetin alfa dose received at each study visit
- Hb concentration at each study visit
- Hb concentration change from baseline at each study visit
- Time to first Hb concentration ≥ 10.0 g/dL
- Proportion of Hb measurements ≥ 10.0 g/dL

- Hb rate of change in a 4 week interval at each study visit
- Hb variability, defined as the intrasubject standard deviation over a 6 month rolling window
- Initial Hb response, defined as the change of Hb concentration from baseline at week 5
- Darbepoetin alfa dose over time by initial Hb response
- Hb over time by initial Hb response
- Number of days hospitalized
- Anti-HLA antibodies

10.1.2 Full Analysis Set

The full analysis set will include all randomized subjects who receive at least 1 dose of investigational product. Subjects will be analyzed according to their randomized treatment assignment.

10.1.3 Subgroups and Covariates

Subgroups and covariates to be considered include the stratification factors used at randomization, and the following baseline factors: age, sex, race, baseline Hb concentration and baseline eGFR. Subgroups are defined as

- Age: < 65, ≥ 65 and < 75, ≥ 75 years
- Gender: Female, Male
- Race: White, Black, Other
- Baseline Hb concentrations: <9.0, 9.0 – < 9.5, 9.5 – < 10.0 g/dL
- Baseline eGFR: < 30.0, ≥ 30.0 mL/min/1.73m^2

Additional analyses may be performed if other prognostic factors emerge in this study or in this population.

10.2 Sample Size Considerations

The objective of the study is to provide estimations with acceptable precision. Thus, the sample size is chosen to ensure that the width of the 95% confidence interval (CI) for the proportion of subjects who receive at least 1 RBC transfusion in each treatment group will be ≤ 10% (ie, ± 5% around the point estimate), assuming the proportion to be 25%. The choice of the precision of the estimated transfusion rate is based on clinical relevance and experience. The estimated proportion of 25% of subjects receiving at least 1 RBC transfusion is based on post hoc analyses in both treatment groups of TREAT of subjects who met the eligibility criteria for this study (Amgen data on file) and transfusion rates observed in other studies (Provenzano et al, 2004; Lawler et al, 2010).

To ensure the 95% CI with a width of ≤ 10%, 300 subjects per group will be needed to enroll into the study. In order to ensure this precision can be maintained for sensitivity analyses, 20% drop out is accounted for, and enrollment of 375 subjects per treatment group is planned. This total sample size of 750 subjects will also ensure that the width of the 95% CI of the difference in transfusion incidence rates will be ≤ 14% (ie, ± 7% around the point estimate), assuming the proportion of subjects receiving at least 1 RBC transfusion during the study in both treatment groups is 25%. All confidence intervals are derived using normal approximation.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Individual subject treatment assignments will be maintained by the IVR/IWR system. Only the Data Monitoring Committee (DMC) and the supporting independent biostatistics group will have access to unblinded data. Members of the Amgen study team will not have access to unblinded data until the study is unblinded for the final analysis.

The external, independent biostatistics group will provide unblinded results, including aggregate and subject level data, to the DMC for regular data reviews. The role of the DMC is discussed in Section 10.4. Any unplanned unblinding occurring during the study period will be documented and reported in the final clinical study report.

Amgen staff from the Clinical Supply Chain Management and Biological Sample Management departments will not be blinded to the treatment assignments in this study.

10.4 Interim Analysis and Early Stopping Guidelines

Prior to the completion of the recruitment period, the sponsor may conduct a reassessment of the study assumptions (eg, transfusion rate) based on blinded aggregated data and revise the sample size in order to ensure that the desired precision of transfusion rate estimates can be achieved.

An independent, external DMC will review unblinded study data throughout the duration of the study and may request additional data. If warranted, the DMC can recommend modifying or stopping the study, or suspending enrollment. This recommendation can be based on any safety concerns, lack of efficacy/futility, or preponderance of early evidence of efficacy. The DMC will convene approximately once every 3-6 months. The DMC will oversee an interim analysis to assess the totality of the data , which will occur when approximately 33% of subjects have completed 12 months of planned study follow-up.

10.5 Planned Methods of Analysis

10.5.1 General Approach/Considerations

Descriptive statistics will be presented for all endpoints by treatment group. For continuous variables, these include number of observations, mean, standard error (SE) and/or standard deviation (SD), median, 25th percentile (Q1), 75th percentile (Q3), minimum and maximum. For categorical variables, the frequency and percentage are presented. For time to event endpoints: Kaplan-Meier curves, Kaplan-Meier percentiles, the number of subjects censored, and the number of subjects with events will be summarized. Confidence intervals will be constructed as 2-sided at the 95% level. Summaries of laboratory data, Hb and dose related parameters, and vital signs will be completed using the full analysis set, limited to measurements obtained while the subject is receiving the investigational product.

10.5.2 Analysis of Key Study Endpoints

10.5.2.1 Efficacy Endpoints

The primary analysis of the primary endpoint will be conducted using the full analysis set. The evaluation period will begin from the date of randomization and subjects will be censored at the last dose of investigational product plus 3 months or end of study, whichever is earlier (on-treatment approach). For the primary endpoint, the proportion of subjects in each treatment group receiving at least 1 RBC transfusion during the evaluation period will be presented with 2-sided 95% CIs. The difference in proportions between treatment groups and the relative risk ratio will be described with 2-sided 95% CIs. Confidence intervals will be derived using normal approximation.

The primary analysis will be repeated by subgroups of stratification factors used at randomization, and also by subgroups of age, gender, race, baseline Hb concentrations and baseline eGFR.

Sensitivity analyses of the primary endpoint will be repeated using all randomized subjects with the evaluation period beginning at the date of randomization and subjects will be censored at the end of study (on-study approach).

Sensitivity analyses will be performed to assess the impact of potential differential follow up on the primary endpoint. Exposure-adjusted subject incidence of receiving at least 1 RBC transfusion will be calculated with 95% CI using Chi-square approximation to the Poisson distribution for both on-treatment and on-study approaches. Other sensitivity analyses, such as completer analyses for investigational product and study, may be performed as appropriate.

The reason for investigational product discontinuation will be reviewed to evaluate its relationship and potential impact on the primary endpoint. Additional transfusion related information collected will be summarized descriptively by treatment group using both on treatment approach and on study approach. These include the transfusion setting and clinical context surrounding transfusions. These summaries will be of transfusion event incidence instead of subject incidence.

10.5.2.2 Secondary Endpoints

Total number of units of RBC transfused per subject will be described for each treatment group, and will be analyzed using a negative binomial regression model which will include the stratification factors used at randomization. As a sensitivity analysis, exposure adjusted event incidence of total number of units RBC transfused will be presented with 95% CI using Chi-square approximation to the Poisson distribution. These analyses will be performed using both on-treatment and on-study approaches.

Time to first RBC transfusion using both on-treatment and on-study approaches will be analyzed by each treatment group with Kaplan-Meier curves, Kaplan-Meier percentiles, the number of subjects censored, and the number of subjects transfused. A supportive analysis will be performed using Cox proportional hazards model (Cox, 1972) stratified by the stratification factors used at randomization to evaluate the difference between the treatment groups. The hazard ratio and its corresponding 95% CI will be estimated.

Average achieved Hb concentration while receiving investigational product will be described as average Hb using the area under the curve (AUC) method. The median of the difference in achieved Hb concentration (Hodges–Lehmann estimate) between treatment groups will be calculated and 2-sided 95% confidence limits will be derived by using a nonparametric Wilcoxon rank-sum statistic (Holander and Wolfe, 1973).

Cumulative doses of darbepoetin alfa adjusted for investigation product exposure time will also be summarized, and the median of the difference (Hodges–Lehmann estimate) between treatment groups will be calculated and 2-sided 95% confidence limits will be derived by using a nonparametric Wilcoxon rank-sum statistic.

10.5.2.3 Safety Endpoints

Time to adjudicated event endpoints, such as composite endpoints of mortality and CV morbidity, all-cause mortality, and fatal and non-fatal CV events, will be summarized by each treatment group with Kaplan-Meier curves, Kaplan-Meier percentiles, the number of subjects censored, and the number of subjects with events.

Adverse events will be coded using the most current version of MedDRA. Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class, high level group term, and preferred term by randomized treatment group. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or from study, and significant treatment-emergent adverse events, will also be provided. Adverse events of interest will be tabulated by each randomized treatment group. Subgroup analyses (by age group, race, and gender) will be presented for all adverse events.

Vital signs at each study visit will be summarized descriptively by treatment group. Average blood pressure on treatment will be described as average value using the AUC method, and medication changes secondary to elevated blood pressure will be summarized descriptively in each treatment group.

The incidence and percentage of subjects who develop anti-erythropoietic protein antibodies (binding and if positive, neutralizing) at any time will be tabulated by treatment group.

10.5.2.4 Exploratory Endpoints

All exploratory endpoints, except otherwise mentioned in this section, will be described by each treatment group. In addition to Hb concentration and change from baseline at each study visit, the subgroups of Hb concentrations, will also be presented.

Number of days hospitalized will be summarized by treatment group using the on-treatment approach.

Achieved Hb concentration and cumulative dose over time will be summarized by the initial Hb responsiveness and treatment group.

Anti-HLA antibodies over time will be tabulated by each treatment group.

10.5.3 Additional Analyses

The number and percentage of subjects screened, randomized, and received at least 1 dose of investigational product will be presented. The study disposition and investigational product disposition will be tabulated by the reason for ending study and ending investigational product respectively for each treatment group.

Demographic, medical history and baseline characteristics will be described by treatment group. Use of selected concomitant medications at baseline and on-study, such as iron therapies and other erythropoietic agents, will be summarized by treatment

group. The analyses of laboratory parameters will include summary statistics at the scheduled visit by treatment group.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial generic informed consent form (ICF) is provided for 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 Amgen 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 after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any investigational products are administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and 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. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator should document such in the subject's medical record. 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 informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject.

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.

11.2 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 ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

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 /renewal throughout the duration of the study. Copies of the investigator's reports and the IEC/IRB continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

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

- On the eCRFs or other documents submitted to Amgen, subjects should be identified by a subject identification number only, with a complete and accurate date of birth on the demographics eCRF.
- For Serious Adverse Events reported to Amgen subjects should be identified by their initials, date of birth, and a subject identification number.
- 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/International Conference on Harmonisation (ICH) Good Clinical Practice (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, including personal information, without violating the confidentiality of the subject.

11.4 Investigator Signatory Obligations

Each clinical study report should be signed by the investigator or, in the case of multicenter 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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the investigator must be obtained. 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.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in 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 Amgen investigational product by an 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 Amgen investigational product, and by what mechanism, after termination of the trial and before it is available commercially.

12.2 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 eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF 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.

In this study, the ETO System captures the following data points and these are considered source data: hemoglobin.

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

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

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 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, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen monitor is responsible for verifying the eCRFs 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 eCRFs.

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 eCRFs, 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 Global Compliance Auditing function (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:

- All source documentation supporting entries into the eCRFs must be maintained and readily available.
- Updates to eCRFs 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 will be created in the 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 eCRF, the data queries, and the site notifications, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit—week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

12.4 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.

12.5 Publication Policy

To coordinate dissemination of data from this study, a publication committee consisting of members of the executive committee and appropriate Amgen staff will be formed, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for executive committee members 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 **International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals,** 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**; (4) and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved**. Authors should meet conditions 1, 2, **3,** and **4**.
- When a large, multicenter 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.

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14. APPENDICES

Appendix A. Schedule of Assessments

Treatments and Procedures	Screening		Visit Frequency						
	Visit 1	Visit 2 (g)	Day 1	Week 5	Q4W	Q2W (i)	Q12W	Q24W	EOS/ET Week 101
General and Safety Assessments									
Informed consent (a)	X								
Medical/surgical history , including history of transfusions			X						
Physical exam and height (b)			X						X
Electrocardiogram			X						
Blood pressure, pulse	X	X		X	X	X			X
Weight	X		X						X
Concomitant medications including iron, and commercial ESAs			X	X	X				X
Concomitant medications – antihypertensive medications			X	X	X	X			X
RBC transfusions and transfusions of other blood-derived products (c)			Record continuously						
Endpoint data collection for adjudication (c)			Record continuously						
Hospitalizations, including observational stays, and emergency department visits (c)			Record continuously						
Adverse events/serious adverse events (d, e)	Record continuously								
Laboratory Assessments (f)									
eGFR, serum creatinine (h)	X		X					X	X
Complete blood count (CBC)			X	X			X		
Hb, using **modified** Hb point of care device	X	X		X	X				X
TSAT, ferritin, iron, TIBC	X		X	X			X		
Vitamin B12, folate	X								
Serum pregnancy test (all women of child bearing potential)	X								
Blood samples for biomarkers			X					X	X
Anti-HLA antibodies			X				X		X
Spot urine albumin and creatinine			X						
Troponin-T, serum albumin, high sensitivity CRP			X						
Reticulocytes			X						
Anti-erythropoietic protein antibodies			X						X
Dosing									
Investigational product administration			X	X	X				

a) To occur before any study procedure
b) Rectal and gynecological not required
c) Record continuously throughout duration of study
d) Serious adverse events collected from date of consent through 4 weeks after final dose of IP (see Section 9.2.2 for) additional details
Adverse events, collected from Day 1 through 4 weeks after final dose of IP
f) Samples should be drawn before investigational product administration
g) Eligible subjects must have Visit 2 and Day 1 completed on the same date
h) eGFR and serum creatinine will not be performed on subjects who require renal replacement therapy
i) Required if SBP ≥ 160 mmHg during routine study visit, at investigator discretion if SBP < 160 mmHg

Appendix B. Additional Safety Assessment Information

Adverse Event Toxicity Grading Scale

Grade	Amgen Standard Adverse Event Toxicity Grading Scale
1	MILD: Aware of sign or symptom, but easily tolerated
2	MODERATE: Discomfort enough to cause interference with usual activity
3	SEVERE: Incapacitating with inability to work or do usual activity
4	LIFE-THREATENING: Refers to an event in which the patient was, in the view of the investigator, at risk of death at the time of the event. (This category is not to be used for an event that hypothetically might have caused death if it were more severe.)
5	FATAL

Appendix C. Sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event (eSAE) Contingency Report Form

AMGEN Study # 20110226 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*

US: +888 814 8653

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?		**Relationship** Is there a reasonable possibility that the event may have been caused by an Amgen device?			**Outcome of Event** Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
					No✓	Yes✓	No✓	Yes✓	If yes, what device?		

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.*		

FORM-056006 *Version 3.0 Effective Date 04-FEB-2013*

Page 1 of 3

AMGEN Study # 20110226 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: _____	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
☐ (✓) Blinded ☐ (✓) Open Label						

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:

Date Day Month Year	Test											
	Unit											

AMGEN Study # 20110226 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. 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: 20110226

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 E. Lactation Notification Worksheet

Print Form

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20110226

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

Amendment 3

Protocol Title: START-CKD: Strategies Using Darbepoetin alfa to Avoid Transfusions in Chronic Kidney Disease

Amgen Protocol Number (Darbepoetin alfa) 20110226

Amendment Date: 16 December 2013

Rationale:

The purpose of this amendment is to address challenges with enrollment into the trial and potentially reduce the screen failure rate.

The following eligibility criteria have been modified to have a positive impact on enrollment without a significant impact on the population being studied:

- Removal of lower limit for eGFR required for inclusion
- Modification of time required between events and screening including :
    - Receipt of a red blood cell transfusion
    - Occurrence of:
        - Seizure
        - Clinically relevant active bleeding
        - Hospitalization
        - Receipt of erythropoiesis stimulating agents

Minor administrative changes and clarifications have also been incorporated.

Additions are noted in **bold** text.

Description of Changes:

Section: Global

Replace date of protocol:

25 June 2013

With:

16 December 2013

Section: Global

Replace:

Investigational Hb point of care (POC) device

With:

Modified Hb point of care (POC) device

Page 1, Title Page

Add:

Amendment 3

Page 5, Synopsis

Replace:

- Estimated glomerular filtration rate of ≥ 15 to < 45 ml/min/1.73m^2

With:

- **Not currently receiving dialysis with an estimated** glomerular filtration rate of < 45.0 mL/min/1.73m^2 **during screening**

Page 5, Synopsis

Replace:

- Received erythropoiesis stimulating agents (ESAs) within 12 weeks of screening
- Received an RBC transfusion within 12 weeks of screening

With:

- Received erythropoiesis stimulating agents (ESAs) within **4** weeks of screening
- Received an RBC transfusion within **8** weeks of screening

Page 6, Synopsis

Add:

Subjects ending investigational product prior to week 97 will be asked to complete scheduled visits and study procedures. At a minimum, subjects must be followed for the collection of RBC transfusions and endpoint data for adjudication.

Page 21, Section 4.1, Inclusion Criteria

Replace:

4.1.3 eGFR ≥ 15.0 and < 45.0 mL/min/1.73m^2, per the central laboratory during screening

With:

4.1.3 **Not currently receiving dialysis with an** eGFR < 45.0 mL/min/1.73m^2, per the central laboratory during screening

Page 22, Section 4.2, Exclusion Criteria

Replace:

4.2.6 Currently receiving systemic antibiotics for treatment of an active infection

With:

4.2.6 Currently receiving **intravenous** antibiotics for treatment of an active infection

Page 23, Section 4.2, Exclusion Criteria

Replace:

Within 12 weeks of screening

4.2.17 Receipt of any of the following:

- RBC Transfusion
- ESA Therapy

With:

Within **8** weeks of screening

4.2.17 Receipt of any of the following:

- RBC Transfusion

Page 23, Section 4.2, Exclusion Criteria

Replace:

Within 4 weeks of screening

4.2.19 Receipt of any intravenous (IV) iron therapy

4.2.20 Changes in oral iron therapy

4.2.21 Any outpatient surgery

With:

Within 4 weeks of screening

4.2.19 Receipt of any intravenous (IV) iron therapy

4.2.20 Changes in oral iron therapy

4.2.21 Receipt of ESA therapy

Page 24, Section 5.1, Screening

Replace:

Subjects who fail screening may be rescreened as described in Section 7.1.2 beginning 28 days after the date of the last screening procedure.

With:

Subjects who fail screening may be rescreened as described in Section 7.1.2 beginning **14** days after the last screening procedure.

Page 26, Section 6.1, Classification of Products and Medical Devices

Replace:

The medical devices that are provided by Amgen for use in this study include: A modified HemoCue Hb 201+ system hemoglobin analyzer (investigational) and an Omron HEM 705 CP Auto Inflate Blood Pressure Monitor (commercially available).

With:

The medical devices that are provided by Amgen for use in this study include: A modified HemoCue Hb 201+ system hemoglobin analyzer and an **a**uto inflate Blood Pressure Monitor.

Page 27, Section 6.4.1.1, Dosage Adjustments Based on Systolic Blood Pressure Values

Replace:

If the subject's mean SBP is ≥ 160 mmHg for three consecutive visits (including blood pressure monitoring visits), the dose of investigational product will be withheld.

With:

If the subject's mean SBP is ≥ 160 mmHg for **two** consecutive visits (including blood pressure monitoring visits), the dose of investigational product will be withheld.

Page 29, Section 6.6, Medical Devices

Replace:

6.6 Investigational Medical Devices

The following investigational medical devices will be used in this study and provided by Amgen:

- Modified HemoCue Hb 201+ system hemoglobin analyzer

With:

6.6 Medical Devices

The following medical devices will be used in this study and provided by Amgen:

- Modified HemoCue Hb 201+ system hemoglobin analyzer
- Auto inflate blood pressure monitor

Page 29, Section 6.6.1, Modified HemoCue Hb 201+ System Hemoglobin Analyzer

Replace:

The modified HemoCue is an investigational device provided by Amgen for use in this study to determine protocol specified hemoglobin values.

With:

The modified HemoCue **will be** provided by Amgen for use in this study to determine protocol specified hemoglobin values **while maintaining the blind**.

Page 29, Other Medical Devices Provided

Replace:

6.7 Other Medical Devices Provided

Amgen will also provide the Omron HEM 705 CP Auto inflate blood pressure monitor to be used throughout the trial for protocol specified blood pressure measurements. The blood pressure will be measured as described in section 7.2.4.

With:

6.6.2 Other Medical Devices Provided

Amgen will also provide **an auto** inflate blood pressure monitor to be used throughout the trial for protocol specified blood pressure measurements. The blood pressure will be measured as described in section 7.2.4.

Additional details for the automated blood pressure monitor may be found in the user manual that accompanies the device.

Page 30, Section 6.7.1, Omron HEM 705 CP Auto Inflate Blood Pressure Monitor

Remove:

6.7.1 Omron HEM 705 CP Auto Inflate Blood Pressure Monitor

The Omron HEM 705 CP auto inflate blood pressure monitor is an automated blood pressure device manufactured by Omron Healthcare, Inc. and provided by Amgen for use in this trial. A printer is also provided to document the blood pressure readings. The printed blood pressure results should be placed with the subject's source documents.

Additional details for the Omron automated blood pressure monitor may be found in the user manual that accompanies the device.

Page 32, Section 7.1.2, Rescreening Evaluations

Replace:

Subjects who do not meet eligibility criteria during the initial screening attempt will be permitted to rescreen twice, for a total of 3 screening attempts.

With:

Subjects who do not meet eligibility criteria during the initial screening attempt will be permitted to rescreen **4 times**, for a total of **5** screening attempts.

Page 34, Section 7.1.5, Evaluations After End of Investigational Product

Replace:

At a minimum, subjects must be followed for the collection of RBC transfusions and endpoint data for adjudication. In addition, serum for anti-erythropoietic protein antibody testing will be collected at the scheduled visit that occurs closest to the receipt of the last dose of investigational product.

With:

At a minimum, subjects must be followed for the collection of RBC transfusions and endpoint data for adjudication. **Refer to Section 8.1 for additional information.** In addition, serum for anti-erythropoietic protein antibody testing will be collected at the scheduled visit that occurs closest to the receipt of the last dose of investigational product.

Page 41, Section 9.1.1, Definition of Adverse Events

Replace:

An adverse device effect is any adverse event related to the use of an investigational medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the investigational device(s), or adverse events resulting from use error or from intentional misuse of the investigational device(s)

With:

An adverse device effect is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device(s), or adverse events resulting from use error or from intentional misuse of the device(s)

Page 42, Section 9.1.2, Reporting Procedures for Adverse Events

Replace:

The investigator must assess whether the adverse event is possibly related to the investigational device. 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 investigational device?

With:

The investigator must assess whether the adverse event is possibly related to **a** device. 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 **a** device?

Page 56, Section 12.5, Publication Policy

Replace:

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) which states:

With:

Authorship of any publications resulting from this study will be determined on the basis of the **International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals** which states:

Page 56, Section 12.5, Publication Policy

Replace:

- 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.

With:

- 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**; (4) and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved**. Authors should meet conditions 1, 2, **3,** and **4**.

Page 58, Section 13, References

Replace:

International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2006. http://www.icmje.org/

With:

International Committee of Medical Journal Editors, **Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. 2013.** http://www.ismje.org/

Amendment 2

Protocol Title: START-CKD: Strategies Using Darbepoetin alfa to Avoid Transfusions in Chronic Kidney Disease

Amgen Protocol Number (Darbepoetin alfa) 20110226

Amendment Date: 25 June 2013

Rationale:

The purpose of this amendment is to further limit the potential for subjects with elevated blood pressure to be exposed to investigational product in the START-CKD study. Therefore, the exclusion criteria for uncontrolled hypertension has been modified.

Additions are noted in **bold** text.

Amendment 1

Protocol Title: START-CKD: Strategies Using Darbepoetin alfa to Avoid Transfusions in Chronic Kidney Disease

Amgen Protocol Number (Darbepoetin alfa) 20110226

Amendment Date: 03 April 2013

Rationale:

The key purpose of this amendment is to provide additional measures to improve blood pressure control in subjects enrolled in the START-CKD study who are receiving investigational product.

The following changes have been made throughout the protocol:

- The protocol eligibility criteria have been modified and subjects with a mean systolic blood pressure > 140 mmHg or a mean diastolic blood pressure > 90 mmHg at both screening visits will be excluded
- Additional visits have been added for subjects with elevated blood pressures. These blood pressure monitoring visits will be required for subjects with a mean systolic blood pressure ≥ 160mmHg and may be conducted at the investigators discretion for those whose mean systolic blood pressure is < 160 mmHg
- The dosing algorithm has been modified such that investigational product will be withheld if a subject's mean systolic blood pressure is ≥ 160 mmHg for 3 consecutive visits (including blood pressure monitoring visits) and restarted only when the mean systolic blood pressure is ≤ 140 mmHg
- Additional information regarding antihypertensive medication use will be collected at each study visit
- Additional information regarding the investigational hemoglobin point of care device for the collection of study specific hemoglobin concentrations and the automated blood pressure monitor for the collection of blood pressure measurements has been provided. Both of these devices are provided by Amgen for use in this trial and the results obtained are incorporated into the dosing algorithm.

Additional clarifications and administrative changes have also been made.

Additions are noted in **bold** text.