STATISTICAL ANALYSIS PLAN

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

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Table of Abbreviations

Abbreviation / Acronym	Definition
AE	Adverse Event
AUC	Area Under the Curve
BMI	Body Mass Index
BP	Blood Pressure
CDM	Clinical Data Management
CEC	Clinical Endpoint Committee
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMPREF	Concomitant Medication Preferred Term
CPEVENT	Clinical Planned Event
CRP	C-reactive Protein
CSR	Clinical Study Report
CTCAE	NCI Common Terminology Treatment Collaboration
DMC	Data Monitoring Committee
DMP	Data Management Plan
DQR	Data Quality Review
DTP	Data Transfer Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOI	Event of Special Interest
EOIP	End of Investigational Product
EOS	End of Study
ESA	Erythropoiesis Stimulating Agent
FAS	Full Analysis Set
GFR	Glomerular Filtration Rate
Hb	Haemoglobin
HLA	Human Leukocyte Antigen
IBG	Independent Biostatistics Group
IP	Investigational Product
IPD	Important Protocol Deviation
MACE	Major Adverse Cardiovascular Events
MedDRA	The Medical Dictionary for Regulatory Activities
ND-CKD	Chronic Kidney Disease Subjects Not on Dialysis
PRCA	Pure Red Cell Aplasia
Q1	25^{th} percentile
Q3	75^{th} percentile
Q4W	Once Every Four Weeks
RBC	Red Blood Cell
ROC	Rate Of Change
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
Scr	Serum Creatinine
SD	Standard Deviation
SE	Standard Error
TREAT	Trial to Reduce Cardiovascular Events with Aranesp® Therapy
TSAT	Transferrin Saturation
WBC	White Blood Cell

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for darbepoetin alfa study 20110226 dated 09 Marxch 2012. The scope of this plan includes the interim analysis and the final analysis that are planned and will be executed by the Biostatistics department or designee.

2. OBJECTIVES

2.1 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.

2.2 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.

2.3 Safety

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

2.4 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

3. STUDY OVERVIEW

3.1 Study Design

This is a phase 3, multicenter, randomized, double-blind, parallel group study. Anemic, ND-CKD subjects, without recent Erythropoiesis Stimulating Agent (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, with dose reduction if Hb exceeds 10.5 g/dL or Hb rate of rise exceeds 1.0 g/dL/4W. In the other group, subjects will receive a fixed dose of darbepoetin alfa. All subjects will receive investigational product (IP) as a subcutaneous injection once every 4 week (Q4W). Randomization will be stratified by RBC transfusion received within 12 months prior to randomization (yes/no) and site practice setting (nephrology/non-nephrology). Treatment group, darbepoetin alfa doses, and protocol specified Hb concentrations will be blinded to the investigator, subjects and study team.

3.2 Sample Size

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 Trial to Reduce Cardiovascular Events with Aranesp® Therapy (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.

4. STUDY ENDPOINTS

4.1 Primary endpoint

The primary endpoint is the receipt of 1 or more RBC transfusion

4.2 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

4.3 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

4.4 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-human leukocyte antigen (HLA) antibodies

5. HYPOTHESES AND/OR ESTIMATION

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.

6. DEFINITIONS

6.1 Study Time Points

Informed Consent Date

The inform consent date for each subject is the date the subject signs the original informed consent for this study.

Enrolled

Individuals are considered enrolled if they have been assigned a randomization number and have a non-missing randomization date. Enrolled individuals are referred to as "subjects".

Randomization (Enrollment) Date

The randomization date for each subject is the date the investigator (or designee) confirms in the IVRS that the subject has met all eligibility criteria and is randomized.

Study Day 1

Per protocol, all subjects must receive the first dose of investigational product on the date of randomization. Therefore, for each subject, Study Day 1 will be defined as the day of randomization.

Study Day

For each subject and for a given study visit date, study day is defined as the number of days since Study Day 1:

Study day = (study visit date – Study Day 1 date) + 1

If the date of interest is prior to the Study Day 1:

Study day = (study visit date – Study Day 1 date).

Date of Last Dose of Investigational Product Received

For each subject, the date of last dose of investigational product received is defined as the date of last administration of the investigational product during the study.

End of Investigational Product (EOIP) Date

For each subject, the end of investigational product date is defined as the date recorded on the End of Investigational Product Electronic Case Report Form (eCRF).

End of Study (EOS) Date

For each subject, the end of study date is the date recorded on the End of Study eCRF.

Study End Date

The study end date is the last end of study date of all randomized subjects.

Study Month

One study month is defined as 4 weeks (28 days)

Last Known Date

Defined as the last available complete date in the clinical database for a subject, eg, date a scheduled measurement is taken or an investigational product is administered, concomitant date, adverse event date, end of study date, reported endpoint onset date, etc.

6.2 Demographics and Baseline Related Definitions

Age

Age will be calculated as the subject's (floor) integer age in years at the randomization date.

Screening Weight

Weight measured at the first screening visit, which the starting dose is calculated upon.

Baseline Hb Value

The baseline Hb value is defined as the mean of the 2 most recent non-missing Hb concentrations measured through the Hemocue device prior to or on the randomization date. If for any reason only 1 value is available, then that value will be used as baseline.

Baseline Values (other than Hb)

The baseline value is the last non-missing value measured prior to or on the randomization date.

Baseline Body Mass Index

The baseline body mass index (BMI) is calculated as [baseline weight (kg) / baseline height $(m)^2$].

Change from Baseline

The arithmetic difference between a post-baseline value and baseline value for a given time point:

Change from baseline = (post-baseline value – baseline value)

Percent Change from Baseline

The percent change from baseline for a given variable at a given time point is defined as:

100 x [(value at given time point – baseline value) / baseline value]

Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate (eGFR, mL/min/1.73m^2) will be calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al, 2009):

$$eGFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, age is the age at the time the measurement is taken, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Stratification Factors

- RBC transfusion received within 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

Baseline Subgroups

- 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
- Diabetes at baseline: Yes, No

6.3 Other Study Related Definitions

Analytical Window Assignments

Analytical windows will be used to summarize protocol specified parameters according to the protocol schedule. This algorithm is provided in Appendix A.

Analytical Window Assignments

Analytical windows will be used to summarize protocol specified parameters according to the protocol schedule.

Exposure to Investigational Product

For each subject who received at least one dose of IP, the number of days of IP exposure Period is calculated as [(Date of Last Dose of Investigational Product Received – first dose date + 1) + 28 days]. The exposure to IP in study month = exposure to IP / 28 days.

Study Exposure

For each randomized subject, study exposure is defined as time from the randomization date to the end of study date.

Evaluation Periods for Different Analysis Approaches

The evaluation period of the on-treatment approach begins 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.

The evaluation period of the on-study approach begins at the date of randomization and subjects will be censored at the end of study date.

Treatment Emergent Adverse Events

Treatment emergent adverse events are adverse events occurring on or after the first dose of IP.

Adverse Events of Special Interest

Adverse events falling into categories of special interest (EOI) will be reported according to the special interest category. The categories of interest for the study are:

- Hypertension
- Ischemic Heart Disease
- Cardiac Failure
- Cerebrovascular Disorders
- Dialysis Vascular Access Thrombosis
- Embolic and Thrombotic Events (including arterial thromboembolic events, venous thromboembolic events and vessel type unspecified and mixed arterial and venous)
- Convulsions
- Antibody-Mediated Pure Red Cell Aplasia (PRCA)
- Hypersensitivity
- Lack of Efficacy-Effect
- Malignancies

The definition of each EOI may be modified and a new EOI may be added based on findings from ongoing pharmacovigilance. Updates of the search strategy due to MedDRA upgrades or other reasons may not trigger a SAP amendment. However, the most recent EOIs per Amgen EOI search strategy will be used at the time of the analysis and these search terms will be included in an appendix of the study report.

Adverse Event Subject Incidence

Defined as the number and percentage of subjects with a reported event(s). For subjects with multiple reports of the same event during the study, the subject will be counted only once. If a pre-existing condition worsens on or after the first dose of investigational product administered, the event will be counted as if it occurred on the day it worsened. For adverse event tabulations involving relationship to investigational product, the subject is counted in the tabulations if at least 1 occurrence of the event is

related. For adverse event tabulations involving severity, the highest severity of the particular adverse event will be used for each subject.

Hemoglobin

For all Hb-related endpoints, the Hb measured using the point of care device will be used. For Hb measured by the central laboratory, they will only be summarized descriptively by treatment group at each scheduled visit.

Achieved Hb Concentration while Receiving Investigational Product

For each subject, the achieved Hb concentration while receiving IP will be derived using the area under the curve (AUC) method with all Hb measured during the period starting from Week 13 (Study Day 85) to the last dose date will be included in the calculation. The 12 week interval is indicated in the USPI as escalation period.

Post-baseline Hb Concentration Subgroup

Post-baseline Hb concentration subgroup is defined as < 8.0, ≥ 8.0 and < 9.0, ≥ 9.0 and < 9.5, ≥ 9.5 and < 10.0, ≥ 10.0 and ≤ 10.5, > 10.5 and ≤ 11.0, > 11.0 and ≤ 12.0, > 12.0 and ≤ 13.0, > 13.0 g/dL

Hb Rate of Change (ROC)

Only Hb measured on and after Study Day 1 and while the subject is receiving the investigational product will be included in the calculation.

ROC (g/dL per 4 weeks) is calculated using the following equation:

ROC (g/dL/4weeks) = [(Hb at visit X – Hb at Visit Y) / (Date of Visit X – Date of Visit Y)] * 28, where X and Y are consecutive post-baseline visits.

Time to Reach Hb ≥ 10.0 g/dL

Time from the Study Day 1 to the date the Hb measurement reached ≥ 10.0 g/dL for the first time. Subjects who never reach Hb ≥ 10.0 g/dL will be censored on the last date of IP.

Proportion of Hb measurements ≥ 10.0 g/dL

Proportion of Hb measurements ≥ 10.0 g/dL = the number of Hb measurements ≥ 10.0 g/dL / Total number of Hb measurements. Only Hb measured on or after Study Day 1 and while the subject is receiving the investigational product will be included in the calculation.

Hb variability

At any study visit, the Hb variability is the intra-subject Hb standard deviation over the prior 6 months. The Hb variability will be calculated at each scheduled visit from Week 25.

Initial Hb Response

Initial Hb response is defined as the change of Hb concentration from baseline at Week 5.

Initial Hb Response Subgroup

Initial Hb response subgroups are defined as the initial Hb response quartiles based on the initial Hb response analysis set subjects (Section 7.3) from both treatment groups.

Dose

The dose referred in this analysis plan is the darbepoetin alfa dose from the IP administration. The dose from a placebo injection equals zero darbepoetin alfa dose.

Weight-based Dose at Specific Study Visit

The weight-based dose at any time point = Dose in µg at specific study visit / subject's screening weight in kg.

Cumulative Dose at Specific Study Visit

The cumulative dose at specific study visit = sum of all darbepoetin alfa doses received from Study Day 1 through the specific study visit.

Average Cumulative Dose per 4 Week at Specific Study Visit

Average cumulative dose per 4 week at specific study visit is defined as the 4-week equivalent cumulative dose received at specific study visit.

Average Cumulative Weight-adjusted Dose per 4 Week at Specific Study Visit

Average cumulative weight-adjusted dose per 4 week at specific study visit = average cumulative dose per 4 week at specific study visit / the screening weight in kg.

Transfusion Subgroups

Subjects will be categorized into transfusion subgroups based on the number of transfusion events: No transfusion event, one transfusion event, more than 1 transfusion event.

Transfusion subgroup (on-treatment approach) will be defined using the number of transfusion events where the start date of the transfusion event falls within the evaluation period of the on-treatment approach.

Transfusion subgroup (on-study approach) will be defined using the number of transfusion events where the start date of the transfusion event falls within the evaluation period of the on-study approach.

Time to Event Derivation

For time to event such as time to first transfusion, or time to first major clinical event (eg, major adverse cardiovascular events (MACE), all-cause mortality), time to event is derived from the randomization date to the date of specific event. Subjects that do not experience the event will be censored. For time to event analysis using the on-treatment approach, the censoring date is the last dose date + 3 months (84 days) or the end of study date, whichever is earlier. For time to event analysis using the on-study approach, the censoring date is the end of study date.

Context surrounding RBC Transfusion

Clinical context surrounding RBC transfusion will be collected for each RBC transfusion event, and will be reviewed by an independent Clinical Endpoint Committee (CEC). The clinical context includes the primary reason for the transfusion event, the transfusion setting (eg, dialysis center, intensive care unit, emergency department), Hb at the time of the first transfusion of the transfusion event, clinical events (eg, bleeding, surgery), symptoms and vital signs of concerns.

Total number of units of RBC transfused

The total number of units of RBC transfused using the on-treatment approach is the sum of RBC units transfused between the randomization date and the earlier date of the last dose date + 3 months (84 days) and the end of study date. The total number of units of RBC transfused using the on-study approach is the sum of RBC units transfused between the randomization date and the end of study date.

Number of Days Hospitalized

This is the total number of days of hospitalization between the randomization date and earlier of the date of last IP + 3 months (84 days) and the end of study date for the on-treatment approach; between the randomization date and the end of study date for the on-study approach. Duration of each hospitalization stay is calculated as day of discharge - day of admission + 1. Hospitalizations with identical admission and discharge days will be counted as a hospitalization with duration of 1 day.

Area under the Curve (AUC) Calculation

The AUC is calculated by adding the areas under the graph between each pair of consecutive observations. For measurements y_1 and y_2 at times t_1 and t_2, the AUC between these 2 times is the product of the time difference and the average of the 2 measurements $(t_2-t_1)*(y_1+y_2)/2$ (Matthews et al, 1990). This is referred to as the trapezoidal method. For n+1 measurements y_i at times t_i (i = 0,…n),

$$\text{AUC} = \frac{1}{2}\sum_{i=0}^{n-1}(t_{i+1} - t_i)(y_i + y_{i+1})$$

Average AUC is AUC divided by the time (day).

7. ANALYSIS SUBSETS

7.1 Full Analysis Set

The full analysis set will include all randomized subjects who receive at least 1 dose of investigational product. Subjects will be grouped according to their randomized treatment assignment. The full analysis set will be used in the primary analysis and safety analysis.

7.2 Completer Analysis Set

The completer analysis set will include all randomized subjects who receive at least 1 dose of investigational product and either complete the investigational product administration, or end investigational product due to death. Subjects will be analyzed according to their randomized treatment assignment.

7.3 Initial Hb Response Analysis Set

The initial Hb response analysis set will include all randomized subjects who receive at least 1 dose of investigational product, excluding those who ended investigational product prior to Week 5 or those who do not have Hb measurement at Week 5. Subjects will be analyzed according to their randomized treatment assignment. Subjects

will be excluded if: they do not receive the first dose at Day 1, they receive RBC transfusion during the period from randomization to prior to Week 5, they end investigational product prior to Week 5, or they do not have a Hb measurement at Week 5.

8. 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 external independent Data Monitoring Committee (DMC) will be established to review the unblinded study data throughout the duration of the study and the DMC may request additional data. If warranted, the DMC can recommend modifying or stopping the study, or suspending enrollment. This recommendation may 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 to 6 months. The DMC will oversee an interim analysis to assess whether the study objective is likely to be achieved based on the totality of the data. This interim analysis will occur when approximately 33% of subjects have completed 12 months of planned study follow-up

Analyses for the DMC will be provided by an external Independent Biostatistics Group (IBG). The IBG and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and IBG will not have any direct contact with study center personnel or subjects. The DMC will communicate major safety concerns and recommendations regarding study modification or termination based on the safety and efficacy parameters to Amgen in accordance with the DMC charter.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be stored in the Amgen official document management system at the conclusion of the study. Further details are provided in the DMC charter.

9. DATA SCREENING AND ACCEPTANCE

9.1 General Principles

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

9.2 Data Handling and Electronic Transfer of Data

Amgen's Clinical Data Management (CDM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

All data collected in the eCRF will be extracted from RAVE. Important protocol deviations will be transferred from eClinical. Unblinded subject and box ID randomization lists will be provided by Amgen's randomization group upon unblinding of the study. See Data Transfer Plan (DTP) and Data Management Plan (DMP) for details.

9.3 Handling of Missing and Incomplete Data

9.3.1 Patterns of Missing Data

Subjects may be missing specific data points for various reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or nonevaluability of a data point at a particular point in time. In the Data Quality Review (DQR) process, queries will be made to the sites to distinguish true missing values from other unknown values (eg, due to measurement or sample processing error). All attempts will be made to capture missing or partial data for this trial prior to the database lock.

The frequency and pattern of missing data such as reasons for investigational product not given, and missing response to the question regarding at each study visit while receiving investigational product will be assessed through descriptive summaries over time.

9.3.2 Handling of Missing Data

For all time-to-event outcomes, there will be no imputation of data, except incomplete dates. Missing values will not be imputed and no imputation will be done for the AUC calculation. Missing safety endpoints will not be imputed.

9.3.3 Handling of Incomplete Dates

Adverse events with a valid answer to the question "Did event start before first dose of investigational product?" on eCRF can be well defined based on the answer regardless of dates being completely or partially missing. Adverse events for which the start date is entirely missing will be counted as occurring on the date of first investigational product

administered. Adverse events with a partially missing start date that is conclusively prior to the date of first investigational product administered will be considered pre-treatment adverse events and excluded from safety analyses. All other partially missing adverse event dates will be handled as described below, with the reference date being the date of first investigational product administered:

- If the adverse event year is available and the day and month are missing, the day and month will be set to the 1st of January of the onset year.
- If the year and month are available and the day is missing, the day will be set to the 1st of the onset month.
- If the day and month are available and the year is missing, the year will be set to the year of the reference date.
- If the year and day are available and the month is missing, the month will be set to January of the onset year
- If the resulting date is prior to the reference date, the date will be reset to the reference date.
- If the imputed adverse event end date is prior to the imputed adverse event start date, the imputed end date will be reset to the imputed start date.

Concomitant medication with completely or partially missing dates will be queried. If after the query is resolved, the date is still incomplete with year only or year and month only, the concomitant medication start date will be imputed using the algorithm above, with the reference date being the randomization date.

All missing and partially missing onset dates of time-to-event outcomes will be queried. If after the query is resolved, the event onset date is still incomplete, this date will be imputed using the algorithm above with the reference date being the randomization date. Partial/missing death date and missing fatal AE end date will be imputed to be the last known date on study, or the imputed date as defined above, whichever is later.

Medical history partial/missing dates will be imputed using the algorithm above, with the reference date being one day prior to the randomization date.

Hospitalization and transfusion partial/missing dates will be imputed using the above algorithm as well with the reference date being randomization date.

No other date imputation will be done.

9.4 Detection of Bias

This study has been designed to minimize potential bias by the use of stratified randomization of subjects into treatment groups and the use of blinding. Other factors that may bias the results of the study include:

- Important protocol deviations
- Inadvertent blind breaking before database lock and formal unblinding
- Investigational product dosing compliance
- The timing of, and reasons for, early withdrawal from treatment and from study

The occurrence of these factors will be assessed. Important protocol deviations will be listed and/or tabulated in the clinical study report (CSR). If necessary, the occurrence of other factors will be tabulated.

Any breaking of the blind for individual subjects prior to formal unblinding of the study will be documented in the CSR. The impact of such unblinding on the results observed will be assessed. Data such as the timing and reason for unblinding from subjects whose treatment assignments are unblinded prior to formal unblinding will be examined.

The timing of and reasons for early withdrawal from treatment and from study will be tabulated.

Additional sensitivity analyses may be included to assess the impact of the biases on the primary endpoint. If any sensitivity analyses are required to evaluate potential biases in the study's conclusions, then the sources of the potential biases and results of the sensitivity analyses will be documented in the CSR.

9.5 Outliers

Various methods, including univariate summaries, histograms, scatter plots, box plots, and line graphs, may be used to identify outliers in key safety and efficacy variables. Extreme data points will be identified during the blinded review of the data prior to database lock. Such data points will be reviewed with clinical data management to ensure accuracy. The primary analyses will include outliers in the data. Sensitivity analyses may be performed if extreme outliers for a variable are observed.

9.6 Distributional Characteristics

Statistical assumptions for the primary endpoint method of analysis will be assessed. If the assumptions for the primary analysis are not met, then nonparametric methods will be utilized. The use of alternative methods will be fully justified in the CSR.

9.7 Validation of Statistical Analyses

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

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

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software, for example the SAS System and S-plus.

10. STATISTICAL METHODS OF ANALYSIS

10.1 General Principles

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, 25^{th} percentile (Q1), 75^{th} 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.

For variables that are summarized over time, the actual visit for a subject may not exactly coincide with their targeted scheduling. The visit windows defined in Appendix A will be used to assign evaluations to a most appropriate nominal visit for analysis and summarization.

10.2 Subject Accountability

The number of subjects screened, randomized, receiving IP, completing the IP and completing the study will be summarized by randomized treatment group. The date of first subject enrolled, the date of early study termination (if applicable), the date the last subject was enrolled, and date of the last subject completed follow-up will be described in a summary table.

Reasons for study discontinuation and IP discontinuation will be tabulated separately by randomized treatment group. In addition, a figure of the cumulative distribution will depict subject IP discontinuation over time by randomized treatment group, with the reasons for ending IP noted.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's first visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes and descriptions will be used during the course of the study. The final IPD list is used to produce the Summary of IPDs table (see Section 12.1) and the List of Subjects with IPDs (see Section 12.2).

10.4 Demographic and Baseline Characteristics

All baseline tables will be summarized by randomized treatment group. Baseline tables will include the following: demographic, medical history, laboratory parameters, vital signs, and baseline characteristics including weight, height, BMI, stratification factors, ECG (normal or abnormal), use of selected concomitant medications such as iron therapies and prior erythropoiesis stimulating agents. These baseline characteristics will be summarized for all randomized subjects, the full analysis set, and the completer set. In addition, baseline characteristics will be summarized for the initial Hb response analysis set by the initial Hb response subgroup.

10.5 Efficacy Analyses

The stratification factors from IVRS will be used for the analyses. Both the stratification factors and subgroups defined in Section 6.2 will be considered for subgroup analyses. Additional subgroup analyses may be performed if other prognostic factors emerge in this study or in this population.

10.5.1 Analyses of Primary Efficacy Endpoint(s)

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 will be described with 2-sided 95% CIs. Confidence intervals

will be derived using normal approximation. The relative risk ratio and its 95% CI will be described using the Cochran-Mantel-Haenszel statistic controlling for the stratification factors.

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, baseline eGFR and diabetes at baseline.

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 date (on-study approach).
- Completer analysis set with the evaluation period between the date of randomization and the end of study date

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.

The reason for IP discontinuation will be reviewed to evaluate its relationship and potential impact on the primary endpoint. Time to first RBC transfusion or discontinuing IP due to lack of efficacy using the on-treatment approach will be analyzed by each treatment group with Kaplan-Meier curves, Kaplan-Meier percentiles and estimates at 6, 12, 18, and 24 months, the number of subjects censored, and the number of subjects transfused or discontinuing IP due to lack of efficacy. 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.

Other sensitivity analyses may be performed as appropriate.

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 the clinical context surrounding transfusions. These summaries will be transfusion event incidence instead of subject incidence.

10.5.2 Analyses of Secondary Efficacy Endpoint(s)

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 approach with the full analysis set and on-study approach with all randomized subjects.

Time to first RBC transfusion will be analyzed using both on-treatment approach with the full analysis set and on-study approach with all randomized subjects. It will be analyzed by each treatment group with Kaplan-Meier curves, Kaplan-Meier percentiles and estimates at 6, 12, 18, and 24 months, 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 (Hollander and Wolfe, 1973). As a sensitivity analysis, the above analyses will be repeated excluding Hb concentrations measured within 3 months (84 days) from an RBC transfusion.

Cumulative doses of darbepoetin alfa adjusted for investigation product exposure time (eg, average cumulative darbepoetin alfa dose per 4 week) 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.

The descriptive summary of total number of RBC transfused, time to first RBC transfusion, average achieved Hb concentration while receiving IP and cumulative doses of darbepoetin alfa adjusted for IP exposure time by randomized treatment group, using the on-treatment approach, will be repeated by subgroups of stratification factors used at randomization, and also by subgroups of age, gender, race, baseline Hb concentrations baseline eGFR and diabetes at baseline.

10.5.3 Analyses of Exploratory Endpoints

The following exploratory endpoints will be summarized by each treatment group using the full analysis set:

- Darbepoetin alfa dose and weight-adjusted dose received at each study visit
- Hb concentration and its subgroup 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 at each study visit
- Anti-HLA antibodies as measured using panel reacted antibodies (PRA) over time based on both on-treatment and on-study approaches

Anti-HLA antibodies over time will be summarized by the transfusion subgroup (on-treatment approach) and by randomized treatment group using the full analysis set. The summary will be repeated by the transfusion subgroup (on-study approach) and by randomized treatment group using all randomized subjects.

Furthermore, the following Hb-related information will be evaluated and summarized by randomized treatment group using the full analysis set

- At least one Hb < 8.0 g/dL and the proportion of the Hb measurements < 8.0 g/dL
- At least one Hb < 9.0 g/dL and the proportion of the Hb measurements < 9.0 g/dL
- At least one Hb > 11.0 g/dL and the proportion of the Hb measurements > 11.0 g/dL
- At least one Hb > 12.0 g/ dL and the proportion of the Hb measurements > 12.0 g/dL
- At least one Hb > 13.0 g/dL and the proportion of the Hb measurements > 13.0 g/dL

Number of days hospitalized will be summarized by treatment group using the on-treatment approach and the full analysis set. As a sensitivity analysis, the number of days hospitalized will also be summarized by treatment group using the on-study approach and all randomized subjects.

Initial Hb response at Week 5 will be summarized by treatment group using initial Hb response analysis set. The following will be summarized by initial Hb-response subgroup and treatment group using the initial Hb response analysis set:

- Hb concentration at each study visit and the achieved Hb
- Darbepoetin alfa dose at each study visit and the cumulative dose

Subjects received ≥ 1 RBC transfusion and time to first RBC transfusion will be descriptively summarized by the initial Hb response subgroup using on-treatment approach.

10.6 Safety Analyses

10.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 or later will be used to code all adverse events to a system organ class and a preferred term. All adverse event tables will be summarized by the randomized treatment group. Treatment-emergent adverse events are events with an onset after the administration of the first dose of IP.

The subject incidence of adverse events will be summarized for all treatment-emergent, serious, treatment-related, serious treatment-related, those leading to withdrawal of investigational product, fatal, and special events of interest (EOI). Subject incidence of EOI will also be summarized according to their categories.

Subject incidence of all treatment-emergent, serious, treatment-related, serious treatment-related, those leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in descending order of frequency.

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class, high level group term, and preferred term. Summaries of treatment-emergent, serious, treatment-related, and serious treatment-related adverse events occurring in at least 5% of the subjects by preferred term in any treatment arm will be provided in descending order of frequency of the Hb-based titration group. Risk difference and its 95% CI of each preferred term of AE and SAE will be tabulated in descending order of the risk difference.

Subgroup analyses for stratification factors, age group, race, gender, baseline Hb, baseline eGFR and diabetes at baseline will be presented by system organ class and preferred term in descending order of frequency.

10.6.2 Major Clinical Events

Time to adjudicated major clinical events (as specified in Section 4.3), 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, using both on-treatment approach with the full analysis set, and on-study approach with

all randomized subjects. Subgroup analyses for the initial Hb response subgroup will be presented using both on-treatment and on-study approaches and the initial Hb response analysis set.

10.6.3 Laboratory Test Results

Results of laboratory parameters including serum creatinine, eGFR, spot urine albumin and creatinine ratio, complete blood count, reticulocytes, ferritin, iron, TIBC, transferrin saturation (TSAT), serum albumin, high sensitivity C-reactive protein (CRP), Troponin-T will be summarized by treatment group and the protocol-specified scheduled visit. For the summary purpose, the analytical window specified in Appendix A will be used. Change from baseline will also be presented. Shift tables will be provided by treatment group which will be based on CTCAE version 3 toxicity grading and will compare baseline laboratory values with the most extreme post-baseline values. Summaries of subjects with post-baseline laboratory values with a CTC grade ≥ 3 by treatment group will be provided.

10.6.4 Vital Signs and Weights

Systolic blood pressure, diastolic blood pressure, and pulse will be summarized descriptively by treatment group at each study visit using the full analysis set. Summaries of change from baseline at each scheduled visit will also be presented. Average systolic and diastolic blood pressure on treatment will be described as average value using the AUC method.

Summary statistics for weight will be produced for the data recorded at baseline and at end of study / early termination using the full analysis set.

10.6.5 Antibody Formation

A list of anti-erythropoietic antibodies results using the full analysis set will be provided. The list will include subject number, treatment group, baseline binding antibody status, post baseline binding antibody status, binding antibody classification, baseline neutralizing anti-erythropoietic antibody status, post baseline neutralizing anti-erythropoietic antibody status, neutralizing anti-erythropoietic antibody classification.

The percentage of seroreactive subjects at each time assayed will be summarized. Subjects with positive results for anti-erythropoietic antibodies in both immunoassay and bioassay will be summarized.

10.6.6 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group. Cumulative dose received up to a specific study visit, the corresponding cumulative weight-adjusted dose received, average cumulative dose per 4-week and average cumulative weight-adjusted dose per 4-week will be summarized by randomized treatment group at each study visit.

The number and percentage of subjects with dose not administered and its reason will be summarized at each study visit by treatment group.

10.6.7 Exposure to Concomitant Medication

The number and proportion of subjects receiving selected concomitant medications, such as iron therapies and other erythropoietic agents, will be summarized by preferred term for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary. Summaries will be provided for baseline use and use after Study Day 1. See Appendix C for a list of selected medications and their groupings.

11. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There are no changes to the protocol-specified analyses.

12. LIST OF PLANNED TABLES, FIGURES AND LISTINGS [TFLs]

12.1 Planned Tables

Category	Data/ Endpoint	Description
1. Disposition and Analyzed Datasets	Subject Disposition - All Enrolled Subjects	Tabulates the disposition of all enrolled subjects, including the number of subjects screened, the number of subjects enrolled, the number of subjects who received or did not receive investigational product by treatment group. The number of subjects discontinue investigational product and discontinue study will also be summarized by treatment group. This table will contain content to create the diagram summarizing the disposition of subjects.
	Investigational Product Completion and Discontinuation - All Enrolled Subjects	Tabulates the number of subjects who received or did not receive investigational product, the number of subjects who completed or discontinued investigational product, and the reason for investigational product discontinuation by treatment group.
	Study Completion and Discontinuation - All Enrolled Subjects	Tabulates the number of subjects who completed or discontinued study, and the reason for study discontinuation by treatment group.
	Summary of Study Reporting Period - All Enrolled Subjects	Include the date of the first subject enrollment, last subject enrollment, last subject end of investigational product, and last subject end of study.
	Analysis Sets	Tabulation of all subjects included and excluded from each analysis set, and reasons for exclusion by treatment group.
2. Demographic and Baseline Characteristics	Baseline Demographics – <<Full Analysis Set>>	Summarize the demographic data (sex, race, age, and age subgroup) for all subjects in the <<Full Analysis Set>> by treatment group. Repeat for all randomized subjects, the completer set and the initial Hb response analysis set.
	Baseline Subject Characteristics – <<all analysis sets>>	Summarize the baseline subject characteristics for subjects in the <<Full Analysis Set >> by treatment group. Repeat for all randomized subjects, the completer set and the initial Hb response analysis set.
	Baseline Medical History – <<Full Analysis Set>>	Summarize the medical histories for subjects in the <<Full Analysis Set>> by treatment group. Repeat for all randomized subjects, the completer set and the initial Hb response analysis set.

Category	Data/ Endpoint	Description
	Baseline Concomitant Medications – <<Full Analysis Set>>	Summarize baseline concomitant medications for subjects in the <<Full Analysis Set>> by treatment group. Repeat for all randomized subjects, the completer set and the initial Hb response analysis set.
	Baseline Laboratory Parameters – <<Full Analysis Set>>	Summarize baseline laboratory values for subjects in the <<Full Analysis Set>> by treatment group. Repeat for all randomized subjects, the completer set and the initial Hb response analysis set.
	Baseline Vital Signs – <<Full Analysis Set>>	Summarize baseline vital signs for subjects in the <<Full Analysis Set>> by treatment group. Repeat for all randomized subjects, the completer set and the initial Hb response analysis set.
3. Measurements of Treatment Compliance	Summary of Important Protocol Deviations	Tabulation of important protocol deviations by category and sub-category codes and descriptions by treatment group. The distribution of the subjects across all the sub-categories with respect to the entire subject population will be calculated.
4. Efficacy	Proportion of Subjects Receiving at least 1 RBC Transfusion during the Evaluation Period – <<Full Analysis Set>>	Summary of the proportion of subjects receiving at least 1 RBC transfusion during the evaluation period (on-treatment approach) by treatment group, the difference in proportions between treatment groups, and relative risk ratio using the Cochran-Mantel-Haenszel statistics controlling for the stratification factors.
	Proportion of Subjects Receiving at least 1 RBC Transfusion during the Evaluation Period by <<Subgroup>> – <<Full Analysis Set>>	Repeat the primary analysis above by stratification factors, age, gender, race, baseline Hb concentrations, baseline eGFR and diabetes at baseline.
	Proportion of Subjects Receiving at least 1 RBC Transfusion during the Evaluation Period – <<All Randomized Subjects, Completer Analysis Set>>	Repeat the primary analysis above using all randomized subjects (on-study approach) and the completer analysis set.
	Exposure-adjusted Subject Incidence of Receiving at least 1 RBC Transfusion during the Evaluation Period – <<Full Analysis Set>>	Summary of the exposure-adjusted subject incidence of receiving at least 1 RBC transfusion and 95% CI using Chi-square approximation to the Poisson distribution with on-treatment approach.

Category	Data/ Endpoint	Description
	Exposure-adjusted Subject Incidence of Receiving at least 1 RBC Transfusion during the Study – << All Randomized Subjects>>	Summary of the exposure-adjusted subject incidence of receiving at least 1 RBC transfusion and 95% CI using Chi-square approximation to the Poisson distribution with on-study approach.
	Time to First RBC Transfusion or Discontinuing IP due to Lack of Efficacy – <<Full Analysis Set>>	Summary of time to first RBC transfusion or IP discontinuation due to lack of efficacy, including the number of subjects with events and censored, Kaplan-Meier curves, Kaplan-Meier estimates, with hazard ratio estimates by stratified Cox proportional hazards using on-treatment approach.
	Clinical Context Around Transfusion – <<Full Analysis Set>>	Summary of additional transfusion related information including the transfusion setting and the clinical context surrounding transfusions using on-treatment approach.
	Clinical Context Around Transfusion – <<All Randomized Subjects>>	Summary of additional transfusion related information including the transfusion setting and the clinical context surrounding transfusions using on-study approach.
	Total Number of Units of RBC Transfused – <<Full Analysis Set>>	Summarize the total number of units of RBC transfused per subject by treatment group using on-treatment approach.
	Total Number of Units of RBC Transfused by <<Subgroup>>– <<Full Analysis Set>>	Repeat the above analysis by stratification factors, age, gender, race, baseline Hb concentrations, baseline eGFR and diabetes at baseline.
	Total Number of Units of RBC Transfused – <<All Randomized Subjects>>	Repeat the above analysis using on-study approach.
	Exposure Adjusted Event Incidence of Total Number of Units of RBC Transfused – <<Full Analysis Set >>	Summarize the exposure adjusted event incidence of total RBC units transfused using on-treatment approach.
	Exposure Adjusted Event Incidence of Total Number of Units of RBC Transfused – <<All Randomized Subjects>>	Summarize the exposure adjusted event incidence of total RBC units transfused using on-study approach.
	Time to First RBC Transfusion – <<Full Analysis Set>>	Summary of time to first RBC transfusion including the number of subjects with events and censored, Kaplan-Meier curves and estimates, the difference between the treatment groups estimating using stratified Cox proportional hazards model (on-treatment approach).

Category	Data/ Endpoint	Description
	Time to First RBC Transfusion by <<Subgroup>>– <<Full Analysis Set>>	Repeat the above analysis by stratification factors, age, gender, race, baseline Hb concentrations, baseline eGFR and diabetes at baseline.
	Time to First RBC Transfusion – <<All Randomized Subjects >>	Repeat of the above analysis using on-study approach.
	Average Achieved Hb Concentration while Receiving Investigational Product – <<Full Analysis Set>>	Summary of the average achieved Hb using the area under the curve method with the median of the difference in achieved Hb concentration (Hodges–Lehmann estimate) between treatment groups, and 2-sided 95% confidence limits by using a nonparametric Wilcoxon rank-sum statistic.
	Average Achieved Hb Concentration while Receiving Investigational Product by <<Subgroup>> – <<Full Analysis Set>>	Repeat the above analysis by stratification factors, age, gender, race, baseline Hb concentrations, baseline eGFR and diabetes at baseline.
	Average Achieved Hb Concentration Excluding Hb within 3 Months from an RBC Transfusion – <<Full Analysis Set>>	Summary of the average achieved Hb using the area under the curve method with the median of the difference in achieved Hb concentration (Hodges–Lehmann estimate) between treatment groups, and 2-sided 95% confidence limits by using a nonparametric Wilcoxon rank-sum statistic. Hb within 3 months from an RBC transfusion will be excluded.
	Average Cumulative Dose of Darbepoetin alfa per 4 Week – <<Full Analysis Set>>	Summary of the average cumulative doses of darbepoetin alfa per 4 week with the median of the difference (Hodges–Lehmann estimate) between treatment groups, and 2-sided 95% confidence limits by using a nonparametric Wilcoxon rank-sum statistic.
	Average Cumulative Dose of Darbepoetin alfa per 4 Week by <<Subgroup>> – <<Full Analysis Set>>	Repeat the above analysis by subgroup of stratification factors, age, gender, race, baseline Hb concentrations, baseline eGFR and diabetes at baseline.
	Average Cumulative Dose of Darbepoetin alfa at Each Study Visit – <<Full Analysis Set>>	Summary of the average cumulative doses of darbepoetin alfa at each study visit.
	Average Cumulative Weight-Adjusted Dose of Darbepoetin alfa at Each Study Visit – <<Full Analysis Set>>	Summary of the average cumulative weight-adjusted doses of darbepoetin alfa at each study visit.

Category	Data/ Endpoint	Description
	Darbepoetin alfa Dose Received at Each Study Visit – <<Full Analysis Set>>	Summary of the darbepoetin alfa dose received at each study visit by treatment group.
	Darbepoetin alfa Weight-adjusted Dose Received at Each Study Visit – <<Full Analysis Set>>	Summary of the darbepoetin alfa weight-adjusted dose received at each study visit by treatment group.
	Hb Concentration at Each Study Visit – <<Full Analysis Set>>	Summarize the Hb concentration and its subgroup at each study visit by treatment group.
	Hb Concentration Change from Baseline at Each Study Visit – <<Full Analysis Set>>	Summarize the Hb concentration change from baseline at each study visit by treatment group.
	Time to First Hb Concentration ≥ 10.0 g/dL – <<Full Analysis Set>>	Summary of the time to first Hb concentration ≥ 10.0 g/dL by treatment group.
	Proportion of Hb Measurements ≥ 10.0 g/dL – <<Full Analysis Set>>	Summarize the proportion of Hb measurements ≥ 10.0 g/dL by treatment group in the <<Full Analysis Set>>.
	Hb Rate of Change in a 4 Week Interval at Each Study Visit – <<Full Analysis Set>>	Summary the Hb rate of change in a 4 week interval at each study visit by treatment group.
	Hb Variability at Each Study Visit – <<Full Analysis Set>>	Summary of the Hb variability at each study visit by treatment group.
	Anti-human Leukocyte Antigen (HLA) Antibodies over Time – <<Full Analysis Set>>	Summarize the anti-human leukocyte antigen (HLA) antibodies over time by treatment group using on-treatment approach.
	Anti-human Leukocyte Antigen (HLA) Antibodies over Time – <<All Randomized Subjects>>	Summarize the anti-human leukocyte antigen (HLA) antibodies over time by treatment group using on-study approach.
	Anti-human Leukocyte Antigen (HLA) Antibodies over Time by Transfusion Subgroup – <<Full Analysis Set>>	Summarize the anti-human leukocyte antigen (HLA) antibodies over time by transfusion subgroup and treatment group using on-treatment approach.
	Anti-human Leukocyte Antigen (HLA) Antibodies over Time by Transfusion Subgroup – << All Randomized Subjects >>	Summarize the anti-human leukocyte antigen (HLA) antibodies over time by transfusion subgroup and treatment group using on-study approach.

Category	Data/ Endpoint	Description
	Proportion of Subject with at least One Hb [< 8.0] g/dL and the proportion of the Hb measurements [< 8.0] g/dL – <<Full Analysis Set>>	Summary the proportion of subject with at least one Hb < 8.0 g/dL and the proportion of Hb measurements < 8.0 g/dL by treatment group. Repeat for < 9.0 g/dL, >11.0 g/dL, > 12.0 g/dL, > 13.0 g/dL.
	Number of Days Hospitalized – <<Full Analysis Set>>	Summary the number of days hospitalized using the on-treatment approach by treatment group.
	Number of Days Hospitalized – <<All Randomized Subjects>>	Summarize the number of days hospitalized using the on-study approach by treatment group.
	Initial Hb Response at Week 5 – <<Initial Hb Response Analysis Set>>	Summary of the initial Hb response at week 5 by treatment group.
	Hb Concentration at Each Study Visit by Initial Hb Response – <<Initial Hb Response Analysis Set >>	Summary of the Hb concentration at each study visit by treatment group and initial Hb.
	Achieved Hb by Initial Hb Response – <<Initial Hb Response Analysis Set >>	Summary of the achieved Hb at each study visit by treatment group and initial Hb response.
	Darbepoetin alfa Dose over Time by Initial Hb Response – <<Initial Hb Response Analysis Set >>	Summary the darbepoetin alfa dose at each study visit by treatment group and initial Hb response.
	Darbepoetin alfa Weight-Adjusted Dose over Time by Initial Hb Response – <<Initial Hb Response Analysis Set >>	Summary the darbepoetin alfa weight adjusted dose at each study visit by treatment group and initial Hb response.
	Average Cumulative Darbepoetin alfa Dose by Initial Hb Response – <<Initial Hb Response Analysis Set >>	Summarize the average cumulative darbepoetin alfa dose by treatment group and initial Hb response.
	Subjects Received ≥ 1 RBC Transfusion by Initial Hb Response – <<Initial Hb Response Analysis Set >>	Summary of the subjects received ≥ 1 RBC transfusion using on-treatment approach by treatment group and initial Hb response.

Category	Data/ Endpoint	Description
	Time to First RBC Transfusion during the Evaluation Period by Initial Hb Response – <<Initial Hb Response Analysis Set >>	Summary of the time to first RBC transfusion using on-treatment approach by treatment group and initial Hb response.
5. Extent of Exposure	Exposure to Investigational Product – <<Full Analysis Set>>	Summary of the number of subjects exposed to investigational product and duration of exposure to investigational product by treatment group.
	Cumulative Darbepoetin alfa Dose over Time – <<Full Analysis Set>>	Summary of the cumulative darbepoetin alfa dose received up to specific study visit by treatment group.
	Cumulative Darbepoetin alfa Weight-adjusted Dose over Time – <<Full Analysis Set>>	Summary of the cumulative weight-adjusted darbepoetin alfa dose received up to specific study visit by treatment group.
	Average Cumulative Darbepoetin alfa Dose per 4 Week Over Time <<Full Analysis Set>>	Summary of the average cumulative darbepoetin alfa dose per 4 week at each study visit by treatment group.
	Average Cumulative Weight-adjusted Darbepoetin alfa Dose per 4-week – <<Full Analysis Set>>	Summary of the average cumulative weight-adjusted darbepoetin alfa dose per 4 week at each study visit by treatment group.
	Summary of Concomitant Medications – <<Full Analysis Set>>	Tabulation of subjects receiving concomitant medication by WHODRUG preferred term by treatment group in the <<Full Analysis Set>>.
6. Adverse Events	Overall Summary of Treatment-emergent Adverse Events – <<Full Analysis Set>>	Tabulation of subjects experiencing the following types of summary of treatment-emergent adverse events: all, serious, treatment-related, serious treatment-related, those leading to withdrawal of investigational product, events of special interest, and fatal and by treatment group in the <<Full Analysis Set>>.
	Summary of Treatment-emergent Adverse Events – <<Full Analysis Set>>	Tabulation of subjects experiencing any treatment-emergent adverse events by system organ class and preferred term and by treatment group in descending order of frequency in the <<Full Analysis Set>>.
	Summary of Serious Treatment-emergent Adverse Events – <<Full Analysis Set>>	Tabulation of subjects experiencing serious treatment-emergent adverse events by system organ class and preferred term and by treatment group in descending order of frequency in the <<Full Analysis Set>>.

Category	Data/ Endpoint	Description
	Summary of Treatment-related Treatment-emergent Adverse Events – <<Full Analysis Set>>	Tabulation of subjects experiencing treatment-related treatment-emergent adverse events by system organ class and preferred term and by treatment group in descending order of frequency in the <<Full Analysis Set>>.
	Summary of Serious Treatment-related Treatment-emergent Adverse Events – <<Full Analysis Set>>	Tabulation of subjects experiencing serious treatment-related treatment-emergent adverse events by system organ class and preferred term and by treatment group in descending order of frequency in the <<Full Analysis Set>>.
	Summary of Treatment-emergent Adverse Events Leading to Withdrawal of Investigational Product – <<Full Analysis Set>>	Tabulation of subjects experiencing treatment-emergent adverse events leading to withdrawal of investigational product by system organ class and preferred term and by treatment group in descending order of frequency in the <<Full Analysis Set>>.
	Summary of Fatal Treatment-emergent Adverse Events – <<Full Analysis Set>>	Tabulation of subjects experiencing fatal treatment-emergent adverse events by system organ class and preferred term and by treatment group in descending order of frequency in the <<Full Analysis Set>>.
	Summary of Treatment-emergent Adverse Events by System Organ Class, High Level Group Term, and Preferred Term – <<Full Analysis Set>>	Tabulation of subjects experiencing any treatment-emergent adverse events by system organ class, high level group term, and preferred term and by treatment group.
	Summary of Serious Treatment-emergent Adverse Events by System Organ Class, High Level Group Term, and Preferred Term – <<Full Analysis Set>>	Tabulation of subjects experiencing serious treatment-emergent adverse events by system organ class, high level group term, and preferred term and by treatment group.
	Summary of Treatment-emergent Adverse Events of Special Interest – <<Full Analysis Set>>	Tabulation of subjects experiencing treatment-emergent adverse events of special interest by categories of events and by treatment group in descending order of frequency in the <<Full Analysis Set>>.
	Summary of Treatment-emergent Adverse Events Occurring in ≥ 5% – <<Full Analysis Set>>	Tabulation of subjects experiencing any treatment-emergent adverse events occurring ≥ 5% in any treatment group by preferred term and by treatment group in descending order of frequency in the <<Full Analysis Set>>.

Category	Data/ Endpoint	Description
	Summary of Serious Treatment-emergent Adverse Events Occurring in ≥ <<5%>> – <<Full Analysis Set>>	Tabulation of subjects experiencing serious treatment-emergent adverse events occurring ≥ 5% in any treatment group by preferred term and by treatment group in descending order of frequency in the <<Full Analysis Set>>.
	Summary of Treatment-related Treatment-emergent Adverse Events Occurring in ≥ 5% – <<Full Analysis Set>>	Tabulation of subjects experiencing treatment-related treatment-emergent adverse events occurring ≥ 5% in any treatment group by preferred term and by treatment group in descending order of frequency in the <<Full Analysis Set>>.
	Summary of Serious Treatment-related Treatment-emergent Adverse Events Occurring in ≥ 5% – <<Full Analysis Set>>	Tabulation of subjects experiencing serious treatment-related treatment-emergent adverse events occurring ≥ 5% in any treatment group by preferred term and by treatment group in descending order of frequency in the <<Full Analysis Set>>.
	Summary of Treatment-emergent Adverse Events by Stratification Factors – <<Full Analysis Set>>	Tabulation of subjects experiencing any treatment-emergent adverse events by system organ class and preferred term and by treatment group in descending order of frequency by stratification factor in the <<Full Analysis Set>>.
	Summary of Treatment-emergent Adverse Events by Age Subgroup – <<Full Analysis Set>>	Tabulation of subjects experiencing any treatment-emergent adverse events by system organ class and preferred term and by treatment group in descending order of frequency by age subgroup in the <<Full Analysis Set>>.
	Summary of Treatment-emergent Adverse Events by Race Subgroup – <<Full Analysis Set>>	Tabulation of subjects experiencing any treatment-emergent adverse events by system organ class and preferred term and by treatment group in descending order of frequency by race subgroup. Note that races with < 5% will be pooled in the <<Full Analysis Set>>.
	Summary of Treatment-emergent Adverse Events by Gender – <<Full Analysis Set>>	Tabulation of subjects experiencing any treatment-emergent adverse events by system organ class and preferred term and by treatment group in descending order of frequency by gender in the <<Full Analysis Set>>.

Category	Data/ Endpoint	Description
	Summary of Treatment-emergent Adverse Events by Baseline Hb Subgroup – <<Full Analysis Set>>	Tabulation of subjects experiencing any treatment-emergent adverse events by system organ class and preferred term and by treatment group in descending order of frequency, for each baseline Hb subgroup in the <<Full Analysis Set>>.
	Summary of Treatment-emergent Adverse Events by Baseline eGFR Subgroup – <<Full Analysis Set>>	Tabulation of subjects experiencing any treatment-emergent adverse events by system organ class and preferred term and by treatment group in descending order of frequency, for each baseline eGFR subgroup in the <<Full Analysis Set>>.
	Summary of Treatment-emergent Adverse Events by Diabetes at baseline Subgroup – <<Full Analysis Set>>	Tabulation of subjects experiencing any treatment-emergent adverse events by system organ class and preferred term and by treatment group in descending order of frequency, by subgroup of diabetes at baseline in the <<Full Analysis Set>>.
7. Major Clinical Events	Summary of Time to First <Major Clinical Events> - <<Full Analysis Set>>	Summary by each treatment group with Kaplan-Meier curves, Kaplan-Meier percentiles, the number of subjects censored, and the number of subjects with events using on-treatment approach. Major clinical events include 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, and vascular access thrombosis
	Summary of Time to First <Major Clinical Events> - <<All Randomized Subjects>>	Repeat the above analysis with all randomized subjects using on-study approach.
	Summary of Time to First <Major Clinical Events> by Initial Hb Response Subgroup - <<Initial Hb Response Analysis Set>>	Repeat the above analysis with the initial Hb response analysis set using on-treatment approach by initial Hb response subgroup.
	Summary of Time to First <Major Clinical Events> by Initial Hb Response Subgroup - <<Initial Hb Response Analysis Set>>	Repeat the above analysis with the initial Hb response analysis set using on-study approach by initial Hb response subgroup.

Category	Data/ Endpoint	Description
8. Clinical Laboratory	Summary of <<lab test name>> – <<Full Analysis Set>>	Summary of <<lab test name>> by treatment group. It will include eGFR, serum creatinine, complete blood count, TSAT, ferritin, iron, TIBC.
	Clinical Laboratory Change from Baseline over Time – <<Full Analysis Set>>	Summary of laboratory parameters changes from baseline at each protocol-specified scheduled visit by treatment group. It will include eGFR, serum creatinine, complete blood count, TSAT, ferritin, iron, TIBC.
	Shifts Table of CTC between Baseline and the Worst-case – <<Full Analysis Set>>	Shifts from baseline in CTC grades with the most extreme post-baseline values by treatment group in the <<Full Analysis Set>>.
	Summary of Subjects with Post-baseline Laboratory Values with CTC Grade ≥ 3 – <<Full Analysis Set>>	Summarize the subjects with post-baseline laboratory values with CTC Grade ≥ 3 by treatment group in the <<Full Analysis Set>>.
9. Vital Signs and Weight	Summary of [Systolic Blood Pressure] – <<Full Analysis Set>>	Summary of systolic blood pressure over time and the average systolic blood pressure by treatment group. Repeat for diastolic BP and pulse
	Change from Baseline in [Systolic Blood Pressure] – <<Full Analysis Set>>	Summary of systolic blood pressure change from baseline over time and the average systolic blood pressure change from baseline by treatment group. Repeat for diastolic BP and pulse
	Summary of Weight – <<Full Analysis Set>>	Summary of weight at baseline and at the end of study / early termination by treatment group.
10. Immunogenicity	Summary of Anti-Erythropoietic Antibodies – <<Full Analysis Set>>	Summary of anti-erythropoietic antibodies results by treatment group in the <<Full Analysis Set>>.
11. Concomitant Medications	Summary of Commercial Erythropoiesis Stimulating Agent – <<Full Analysis Set>>	Tabulation of subjects receiving commercial ESA during the study by treatment group.
	Summary of Iron Medication – <<Full Analysis Set>>	Tabulation of subjects receiving iron medication during the study by treatment group.
	Summary of Concomitant Medications – <<Full Analysis Set>>	Tabulation of subjects receiving concomitant medication by WHODRUG preferred term by treatment group.

12.2 Planned Listings

Data/ Endpoint	Description
Subject Listing of Important Protocol Deviations	Listing of the Important Protocol Deviations with category and sub-category codes, and descriptions for each subject, grouped by site.
Subject Listing of Randomized Treatment Assignments	Listing of randomized treatment assignments for each subject grouped by stratification factors
Listing of Unique Manufacturing Lot Numbers	Listing of the unique Manufacturing Lot Numbers used in the study, grouped by treatment group (investigational product name and concentration).
Subject Listing of Manufacturing Lot Numbers	Listing of the subjects administered each Manufacturing Lot Number grouped by treatment group (investigational product name and concentration).

12.3 Planned Figures

Data/ Endpoint	Description
Cumulative Distribution Function of IP Discontinuation <<Full Analysis Set>>	Cumulative distribution of time to IP discontinuation over time by randomized treatment group with reasons for ending IP noted.
Time to First RBC Transfusion <<Full Analysis Set>>	Time to first RBC transfusion by treatment group using on-treatment approach. Repeat with all randomized subjects using on-study approach.
Time to First RBC Transfusion or Ending Investigational Product due to Lack of Efficacy <<Full Analysis Set>>	Time to first RBC transfusion or ending IP due to lack of efficacy using on-treatment approach
[Hemoglobin] Over Time <<Full Analysis Set>>	Mean ± SE [hemoglobin] over time. Repeat for all other laboratory parameters, SBP and DBP
Change from Baseline [Hemoglobin] Over Time <<Full Analysis Set>>	Mean ± SE change from baseline [hemoglobin] over time. Repeat for all other laboratory parameters, SBP and DBP
Hemoglobin Rate of Change Over Time <<Full Analysis Set>>	Mean ± SE hemoglobin rate of change over time.
Hemoglobin Variability Over Time <<Full Analysis Set>>	Mean ± SE hemoglobin variabillity over time.
Darbepoetin alfa Dose Over Time <<Full Analysis Set>>	Median (IQR) darbepoetin alfa dose over time.
Darbepoetin alfa Weight-adjusted Dose Over Time <<Full Analysis Set>>	Median (IQR) darbepoetin alfa weight-adjusted dose over time.
[Hemoglobin] Over Time by Initial Hb Response <<Initial Hb Response Analysis Set>>	Mean ± SE hemoglobin over time by initial Hb response and treatment group.

Darbepoetin alfa Dose Over Time <<Initial Hb Response Analysis Set>>	Median (IQR) darbepoetin alfa dose over time by initial Hb response and treatment group.
Darbepoetin alfa Weight-adjusted Dose Over Time <<Initial Hb Response Analysis Set>>	Median (IQR) darbepoetin alfa weight-adjusted dose over time by initial Hb response and treatment group.
Time to First RBC Transfusion <<Initial Hb Response Analysis Set>>	Time to first RBC transfusion by initial Hb response and treatment group using on-treatment approach.
Time to First <Major Clinical Event> - <<Full Analysis Set>>	Kaplan-Meier curves of time to first <major clinical event> using on-treatment approach. Major clinical events include 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, and vascular access thrombosis.
Time to First <Major Clinical Event> - <<All Randomized Subjects>>	Kaplan-Meier curves of time to first <major clinical event> using on-study approach. Major clinical events include 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, and vascular access thrombosis.

13. LITERATURE CITATIONS / REFERENCES

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14. DATA NOT COVERED BY THIS PLAN

Currently there are no pre-planned analyses for the biomarker objective.

15. APPENDICES

Appendix A. Analytical Study Week Assignments

Selected endpoints will be summarized by scheduled study visits. Since the actual visits may not exactly coincide with their scheduled visit day, the actual visit day is mapped to the study visit generally by non-overlapping consecutive intervals covering the entire time continuum, with scheduled visit time being the center of each interval.

Such assignments will be based on the scheduled visits specified in the protocol. If there are more than 1 measurement taken during the specific study window, the measurement at that specific scheduled visit will be defined as the measurement taken closest to the planned visit day during that visit window. If 2 measurements are equidistant from the scheduled visit, then the earlier measurement will be chosen. If there are multiple values available on that same day, then the last record will be used.

- Schedule visit in RAVE will be used as the time point the measurement is taken.
- Except for the visit coded as "SCR" (screening and screening 1), "UNSCHED", "ET" and "EOS", the analytical study day will be used.

Measurements are categorized into 4 different schedules based on scheduled of assessments in the protocol. Over time summary on endpoint of interests will be completed only at scheduled time points. Post-baseline measurements will be summarized according to the following:

- For protocol-specified study assessment which occurred every 4 weeks (Hb through point of care device, systolic BP, diastolic BP and pulse), the planned study day and corresponding analytical study days to the scheduled study visit assignments are listed below

Scheduled Visit	Planned Study day	Analytical Study Days
Week 1	1	1 ≤ Study days ≤ 14
Week 5	29	15 ≤ Study days ≤ 42
Week 9	57	43 ≤ Study days ≤ 70
Week 13	85	71 ≤ Study days ≤ 98
Week 17	113	99 ≤ Study days ≤ 126
Week 21	141	127 ≤ Study days ≤ 154
Week 25	169	155 ≤ Study days ≤ 182
Week 29	197	183 ≤ Study days ≤ 210
Week 33	225	211 ≤ Study days ≤ 238
Week 37	253	239 ≤ Study days ≤ 266
Week 41	281	267 ≤ Study days ≤ 294
Week 45	309	295 ≤ Study days ≤ 322

Scheduled Visit	Planned Study day	Analytical Study Days		
Week 49	337	323	≤ Study days ≤	350
Week 53	365	351	≤ Study days ≤	378
Week 57	393	379	≤ Study days ≤	406
Week 61	421	407	≤ Study days ≤	434
Week 65	449	435	≤ Study days ≤	462
Week 69	477	463	≤ Study days ≤	490
Week 73	505	491	≤ Study days ≤	518
Week 77	533	519	≤ Study days ≤	546
Week 81	561	547	≤ Study days ≤	574
Week 85	589	575	≤ Study days ≤	602
Week 89	617	603	≤ Study days ≤	630
Week 93	645	631	≤ Study days ≤	658
Week 97	673	659	≤ Study days ≤	686
Week 101	701	687	≤ Study days	

- For protocol-specified study assessment occurred at Day 1, Weeks 5, 13 and every 12 weeks (CBC, TSAT, ferritin, iron, TIBC), the analytical windows are:

Scheduled Visit	Planned Study day	Analytical Study Days		
Week 1	1	1	≤ Study days ≤	14
Week 5	29	15	≤ Study days ≤	57
Week 13	85	57	≤ Study days ≤	126
Week 25	169	127	≤ Study days ≤	210
Week 37	253	211	≤ Study days ≤	294
Week 49	337	295	≤ Study days ≤	378
Week 61	421	379	≤ Study days ≤	462
Week 73	505	463	≤ Study days ≤	546
Week 85	589	547	≤ Study days ≤	630
Week 97	673	631	≤ Study days	

- For protocol-specified study assessment occurred at Day 1, Week 25 and every 24 weeks afterwards (eGFR and serum creatinine), the analytical windows are:

Scheduled Visit	Planned Study day	Analytical Study Days		
Week 1	1	1	≤ Study days ≤	85
Week 25	169	86	≤ Study days ≤	252
Week 49	337	253	≤ Study days ≤	420
Week 73	505	421	≤ Study days ≤	588
Week 97	673	589	≤ Study days ≤	686
Week 101	701	687	≤ Study days	

- For protocol-specified study assessment occurred at Day 1, Week 13 and every 12 weeks afterwards (Anti-HLA antibodies), the analytical windows are:

Scheduled Visit	Planned Study day	Analytical Study Days		
Week 1	1	1	≤ Study days ≤	43
Week 13	85	44	≤ Study days ≤	126
Week 25	169	127	≤ Study days ≤	210
Week 37	253	211	≤ Study days ≤	294
Week 49	337	295	≤ Study days ≤	378
Week 61	421	379	≤ Study days ≤	462
Week 73	505	463	≤ Study days ≤	546
Week 85	589	547	≤ Study days ≤	630
Week 97	673	631	≤ Study days	

Appendix B. Code Fragments

CCI

[redacted]

CCI

[redacted]

Appendix C. Concomitant Medications

Concomitant medications collected will be summarized by the following categories using the ATC codes and concomitant medication preferred term (CMPREF) based on the most updated version of WHODrug available prior to database lock.

Category	sub-categories
Anti-hypertensive	ACEi and/or ARB
	Renin inhibitor
	Antiadrenergic, peripheral or centrally acting
	Beta blockers (including Alpha/beta blockers)
	Arterial smooth muscle vasodilator
	Calcium channel blockers
	Diuretics
	Other anti-hypertensives
Statin or other lipid lowering agents	Statin
	Other lipid lowering agents
Drugs used in diabetes	Insulin
	Sulfonamides
	Biguanides
	Thiazolidinediones
	Other anti-diabetic agents
Anti-inflammatory agents	Systemic corticosteroids
	NSAIDS
	Other anti-inflammatory
Aspirin or other antiplatelet agents	Aspirin
	Other antiplatelet agents
Anticoagulant	Vitamin K antagonists (Coumadin)
	Direct thrombin inhibitors
	Other anticoagulant
Erythropoiesis stimulating agent	Darbepoetin alfa
	Epoetin alfa
	Other erythropoiesis stimulating agent
Iron medications	Iron medications – intramuscular
	Iron medications – intravenous
	Iron medications – oral