NCT02453334

ID: 1VIT14039

# IRON CLAD: Can Iron Lessen Anemia Due to Cancer and Chemotherapy: A Study to Investigate the Efficacy and Safety of Injectafer®

# Statistical Analysis Plan

## Protocol No.: 1VIT14039

## IRON CLAD: Can Iron Lessen Anemia Due to cancer and chemotherapy: A multi-center, randomized, double-blinded, controlled study to investigate the efficacy and safety of Injectafer® (ferric carboxymaltose injection) in adults

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| Sponsor: | Luitpold Pharmaceuticals, Inc. |
| Version: | Version Final 1.0 |
| Issue Date: | January 03, 2018 |

**STATISTICAL ANALYSIS PLAN APPROVAL**

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## ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| ALT | Alanine Aminotransferase |
| ANCOVA | Analysis Of Covariance |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BP | Blood Pressure |
| CI | Confidence Intervals |
| CMH | Cochran-Mantel-Haenszel |
| CRA | Cancer- and Chemotherapy-related Anemia |
| DDE | Drug Dictionary Enhanced |
| eCRF | Electronic Case Report Form |
| ECOG | Eastern Cooperative Oncology Group |
| ESA | Erythropoiesis stimulating agents |
| FACIT | Functional Assessment of Chronic Illness Therapy |
| HR | Heart Rate |
| IRT | Interactive Response Technology |
| ITT | Intent-to-Treat |
| IV | Intravenous |
| LLN | Lower Limit of Normal |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | Modified Intent-to-Treat |
| MMRM | Mixed-effect model for repeated measures |
| MAR | Missing at Random |
| OC | Observed Cases |
| PCS | Potentially Clinically Significant |
| PT | Preferred Term |
| RBC | Red Blood Cell |
| ROS | Rest of World |
| SAEs | Serious AEs |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Organ Class |
| TEAE | Treatment-Emergent Adverse Event |
| WHO | World Health Organization |
| WNL | Within Normal Limits |

# 1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Protocol 1VIT14039 (Administrative Amendment 1, 02 November 2017).

## 1.1 STUDY OBJECTIVES

### 1.1.1 Primary Objective(s)

The primary objective of this study is to compare the efficacy and safety of ferric carboxymaltose (FCM) versus placebo as monotherapy for maintaining hemoglobin (Hgb) levels in participants with cancer- and chemotherapy-related anemia (CRA).

### 1.1.2 Secondary Objective(s)

Secondary objectives include:

- To evaluate the safety and tolerability of FCM
  - Percentage of adverse events and serious adverse events
- To evaluate the percentage of participants with a hemoglobin stabilized throughout the study
- To evaluate transfusion rate (The decision of when to transfuse will be at the discretion of the Investigator and treating physicians. However, Investigators and treating physicians will be encouraged not to transfuse patients whose measured Hgb is greater than 7.0 g/dL in absence of any evidence of inadequate oxygen delivery to organs that could be due to Hgb).
  - Percentage of participants receiving a transfusion
- To evaluate quality of life
  - Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale
- To evaluate efficacy response based on hepcidin levels

## 1.2 STUDY ENDPOINTS

### 1.2.1 Primary Endpoint

Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from Week 3 to Week 18. The following participants will be considered to have met the primary endpoints:

- Participants with observed Hgb decrease from baseline between 0.5 – 1.0 g/dL on two consecutive visits between Weeks 3 and 18.
- Participants with observed Hgb decrease from baseline >= 1.0 g/dL at one visit (i.e. any post-baseline visit).
- Participants who have a non-study intervention prior to Week 18.

- Participants who discontinue prior to Week 18 for lack of efficacy or adverse events.

### 1.2.2 Secondary Endpoint(s)

Key secondary endpoint:

- Change in Hgb from baseline to Week 18 or to non-study intervention.
  **Non-study intervention is defined as initiation of erythropoiesis-stimulating agents (ESAs), red blood cell (RBC) transfusion, and additional intravenous (IV) or oral iron.**

Other secondary endpoints:

- Percentage of participants who receive non-study intervention.
- Percentage of participants with Hgb ≥1 g/dL increase (change from baseline) in the absence of non-study intervention.
- Percentage of participants with Hgb >12 g/dL in the absence of non-study intervention.
- Time to hemoglobin increase ≥1 g/dL (change from baseline) in the absence of non-study intervention.
- Percentage of participants requiring a blood transfusion.
- Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from their baseline between Day 0 to each study visit. The following participants will be considered to have met this endpoint:
  - with observed Hgb decrease ≥ 0.5 g/dL from baseline to the particular visit.
  - have a non-study intervention between the previous and the particular visit.
  - discontinue for lack of efficacy or adverse events between the previous and the particular visit.
- Time to a decrease in Hgb ≥ 0.5 g/dL from their baseline between Day 0 to Week 18.
- Correlation of change in hemoglobin with Day 0 hepcidin level.
- Total score of the FACIT-Fatigue
- Adverse Events

## 1.3 SUMMARY OF THE STUDY DESIGN

### 1.3.1 General Study Design and Plan

This is a Phase III, multicenter, randomized, double-blinded, prospective study with two parallel treatment groups. FCM is a non-dextran IV iron recently approved by the Food and Drug

Administration (FDA). Approximately 222 patients who meet all the inclusion and no exclusion criteria will be randomized in a 1:1 ratio via the Interactive Response Technology (IRT) system to either group A or B as listed below.

**Group A participants** will receive 2 doses of FCM, at 15 mg/kg for a maximum single dose of 750 mg given 7 days apart for a total of up to 1500 mg. It will be diluted in no more than 250 mL of normal saline and infused over 15 minutes. **Note: FCM should not be diluted to concentrations less than 2 mg/mL.**

**Group B participants** will receive placebo, which will be normal saline. It will be administered as an infusion of no more than 250 mL infused over 15 minutes.

The trial duration is 18 weeks. Scheduled study visits will occur on Day -14 to -2 (screening), Day 0 (randomization/first treatment day), Day 7 (second treatment day), Week 2, Week 3, Week 6, Week 9, Week 12, Week 15 and Week 18. (Also presented in Table 1). Study participants can withdraw at any time during the trial. At the time of withdrawal, procedures for the Week 18 visit must be immediately performed regardless of whether the subject has completed study drug treatment.

Table 1 Schedule of Event

| VISIT DAY | SCREENING[1] | Day 0 | Day 7 | Week 2 | Week 3 | Week 6 | Week 9 | Week 12 | Week 15 | Week 18 |
|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | | | |
| Inclusion/exclusion | X | X | | | | | | | | |
| IRT | X[2] | X[3] | | | | | | | | |
| Medical History | X | X | | | | | | | | |
| FACIT-Fatigue Scale | | X | X | X | X | X | X | X | X | X |
| Physical Exam[4] | X | | | | | | | | | X |
| Vital Signs[5] | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | |
| Weight | X | | | | | | | | | |
| Hematology, chemistry, and iron indices | X | X | X | X | X | X | X | X | X | X[6] |
| Hepcidin | | X | | X | | | | | | X |
| Serum pregnancy test[7] | X | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| Adverse events assessments | | X | X | X | X | X | X | X | X | X |
| Randomization | | X | | | | | | | | |
| FCM administration | | X | X | | | | | | | |
| Placebo administration | | X | X | | | | | | | |

1. Screening period can occur 2 to 14 days prior to Day 0, in order to obtain all clinical assessments needed to qualify the subject.

2. Contact the IRT system for subject screening number
3. Contact the IRT system for randomization
4. Includes clinical assessment of skin, cardiovascular, pulmonary, abdominal and central nervous system.
5. Vital signs include sitting blood pressure (BP) and heart rate (HR). On dosing days BP and HR will be collected, pre, immediately post and 30 minutes post dosing.
6. If the participants phosphorous is below the lower limit of Normal (LLN) at Week 18 the subject should return (as directed by the Investigator) for repeat phosphorous until the value is back within normal Limits (WNLs) or the subject's baseline.
7. Serum pregnancy test will be performed for all women of childbearing potential.

### 1.3.2 Randomization and Blinding

Patients will be randomized on Day 0 to FCM or placebo in a 1:1 ratio. The randomization will be stratified by study site and the randomization schedule will be generated prior to study initiation. The schedule was approved by Sponsor before being loaded into the IRT system. All participants, investigators and study personnel will be blinded to the content of study drug with the exception of the un-blinded study personnel who will be responsible for randomizing the subject on Day 0, preparing, concealing and administering the study drug on Day 0 and 7, and completing the Study Drug Accountability Form, study drug dosing record and applicable case report form pages.

### 1.3.3 Sample Size and Statistical Power Considerations

The study is powered to demonstrate a clinically meaningful difference between FCM and placebo with respect to the percentage with decrease in Hgb $\geq$0.5 g/dL (i.e., with respect maintenance of Hgb levels) from Week 3 to Week 18. Determination of sample size was based on the following assumptions:

- The proportion of placebo participants not maintaining Hgb levels will be 65%.[1]
- A relative reduction of 35%, i.e., a reduction from 65% with placebo to 42% with FCM, would be clinically meaningful.[2]
- The study would have 90% power to detect a clinically meaningful treatment difference at two sided $\alpha$ =0.05.
- Test statistic is continuity corrected chi-squared test.
- Treatments will be allocated on a 1:1 ratio.

Then a sample size of 106 participants per treatment group is required. Assuming 5% of participants will not meeting the definition of modified Intent-to-Treat (mITT), 111 participants per treatment group (222 participants in total) should be randomized.

The key secondary efficacy endpoint is the change in Hgb from baseline to Week 18 or to non-study intervention. This sample size of 106 participants per treatment group will have 99% power to demonstrate superiority of FCM over placebo in the mean change in Hgb from baseline to Week 18 in the absence of non-study intervention, using a t-test at two-sided $\alpha$=0.05. This assumes a difference in means of Hgb of 1.0 g/dL with common standard deviation = 1.5 g/dL.

# 2. STATISTICAL METHODS

## 2.1 GENERAL CONSIDERATIONS

In general, continuous variables will be summarized by number of participants, mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants in each category. If applicable, hypothesis testing will be carried out at the two-sided $\alpha$=0.05 level unless otherwise specified; 2-sided 95% confidence intervals (CIs) will be presented, where specified.

In general, summary tables will present data by treatment group. Source data for the summary tables and statistical analyses will be presented as subject data listings, which include data collected on the electronic case report forms (eCRFs) as well as any derived variables for all enrolled participants.

Baseline will be defined as the last non-missing value obtained prior to the first dose of study drug.

### 2.1.1 Reporting Precision

Summary statistics will be presented to the following degree of precision, unless otherwise specified:

| Statistics | Degree of Precision |
|---|---|
| Mean, Geometric mean, Median, Quartiles, Confidence limit boundaries | One decimal place more than the raw data. |
| Standard deviation, Standard error | Two decimal places more than the raw data. |
| Minimum, Maximum | The same as the raw data. |
| p-value | Rounded to 4 decimal places and therefore presented as 0.xxxx; p-values smaller than 0.0001 as '<0.0001'; p-values greater than 0.9999 as '>0.9999'. |
| Percentage | One decimal place. A percentage of 100% will be reported as 100%. Percentages of zero will be reported as 0. |

For weight and height, one decimal place will be used for summary statistics. Fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12 – 0.30).

## 2.2 DEFINITIONS OF ANALYSIS POPULATIONS

### 2.2.1 Intent-to-Treat Population (ITT)

The ITT population will comprise all randomized participants. Participants will be evaluated according to the treatment to which they were randomized. Any participant who receives a treatment randomization number will be considered to have been randomized.

### 2.2.2 Modified Intent-to-Treat Population (mITT)

The mITT population will comprise all participants in the ITT population who receive at least one dose of study drug, have a baseline Hgb measurement, and at least one corresponding post-baseline measurement. Participants will be evaluated according to the treatment to which they were randomized. The primary population for the assessing efficacy will be the mITT population.

### 2.2.3 Safety Population

The Safety population will consist of all participants in the ITT population who received at least one dose of study drug. Participants will be evaluated according to treatment received. This population will be used for assessing safety.

## 2.3 TIME WINDOWS FOR ANALYSIS

No visit window will be constructed. For safety analyses (including clinical lab and vital signs), only scheduled visits will be summarized. For efficacy, unscheduled visit will be included for analyses that are not summarized by visit. For FACIT-Fatigue, only scheduled visits will be summarized. Data of unscheduled visits will be presented in listings.

## 2.4 EXAMINATION OF SUBGROUPS

The following subgroup analysis will be performed for the primary and key secondary efficacy endpoints. Subgroup results need to be interpreted with caution if there are insufficient number of participants in a subgroup.

- Geographic region: United States, Europe
- Cancer Stage
- Baseline hemoglobin: <10 g/dL, ≥10 g/dL

## 2.5 POOLING OF CENTERS

This study was a multi-center study. For statistical inferences (models), sites will be pooled by country. Criteria will be documented prior to unblinding and database lock.

## 2.6 HANDLING OF DROPOUTS AND MISSING DATA

The handling of dropouts and missing data will be addressed as described in section 6.2.1.

### 2.7 ANALYSIS SOFTWARE

All summaries and statistical analyses will be generated using SAS® version 9.4.

## 3. STUDY PARTICIPANTS

### 3.1 DISPOSITION OF PARTICIPANTS

Disposition will be summarized by treatment group and overall for all enrolled participants.

The disposition will include the following:

- Participants who are randomized
- Participant who are in ITT population
- Participants who are in mITT population
- Participants who are in Safety population
- Participants who complete the study
- Participants who discontinue the study

The number and percent of participants will be summarized for each reason for premature discontinuation.

A listing of dispositions will be provided for all participants.

### 3.2 PROTOCOL DEVIATIONS

The clinical team will identify deviations and the deviations will be identified and classified into types in the database. The number and percent of participants will be summarized for each type of deviation by treatment group and overall. A participant data listing of clinically important protocol deviations will be listed.

## 4. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

### 4.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics (e.g. gender, age, race, ethnicity, body height, weight, Eastern Cooperative Oncology Group [ECOG] grade, cancer type, number of participants enrolled per site/country and cancer stage) will be summarized with descriptive statistics by treatment group and overall for the ITT Population.

A subject data listing of demographics and baseline characteristics will be provided.

### 4.2 MEDICAL HISTORY

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology. The number and percent of participants with clinically significant medical history at screening will be summarized by system organ class (SOC) and preferred term (PT) by treatment group and overall for Safety Population.

## 5. STUDY DRUG AND EXPOSURE

### 5.1 TREATMENT COMPLIANCE AND EXTENT OF EXPOSURE

Treatment compliance will not be summarized, as each participant will receive a single dose of study drug on Day 0 and Day 7 in an inpatient setting.

Extent of exposure will be summarized by the number of doses of study drug received by treatment group in the full analysis population.

A participant data listing of treatment exposure will be provided by treatment.

### 5.2 CONCOMITANT THERAPY

Concomitant medications are defined as medications (other than the study drug) taken on or after the first does of the study drug during the study.

All investigator terms for medications recorded on the CRF will be coded using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) drug dictionary (Version WHO Drug Dictionary Enhanced, WHO DDE March 2014). The number (percentage) of participants who took concomitant medications will be summarized by treatment group, ATC level 3 Classification, and WHO Drug preferred term in the full analysis population.

A subject data listing of concomitant therapy will be provided by treatment.

## 6. EFFICACY ANALYSES

All efficacy analyses will be based on the mITT Population. A participant listing will be provided for each efficacy endpoint.

Efficacy data collected after receiving the non-study intervention will not be summarized in tables, but will be included in data listing. Non-study intervention is defined as initiation of

ESAs, RBC transfusion, and additional IV or oral iron.

## 6.1 PRIMARY EFFICACY ANALYSIS

### 6.1.1 Percentage of participants with Hgb decrease from baseline ≥ 0.5 g/dL from Weeks 3 to 18

The following participants will be considered to have met the primary endpoint:

- Participants with observed Hgb decrease from baseline between 0.5 g/dL to 1.0 g/dL on two consecutive visits between Weeks 3 and 18.
- Participants with observed Hgb decrease from baseline ≥1.0 g/dL at one visit.
- Participants who have a non-study intervention prior to Week 18.
- Participants who discontinue prior to Week 18 for lack of efficacy or adverse events.

All other randomized participants will be considered to have not met primary endpoint, i.e., will be considered to have maintained Hgb levels.

The primary endpoint will be analyzed using the Cochran-Mantel-Haenszel (CMH) chi-square test adjusting for country. Estimates of treatment effect will be presented via the test-based odds-ratio and 95% confidence interval. In addition, the absolute difference in the percentages between FCM and Placebo, and its associated 95% confidence intervals will be presented. The same analysis will be performed in by subgroup as specified in Section 2.4.

## 6.2 SECONDARY EFFICACY ANALYSES

### 6.2.1 Change in Hgb from baseline to Week 18 or to non-study intervention

The Hgb baseline, actual post-baseline and the change from baseline to end of study will be summarized via descriptive statistics by treatment group and visit. The end of study is defined as week 18 for participants completing the study without non-study intervention. For participants who receive non-study intervention or early withdraw from the study, the time of intervention or early withdrawal will be considered as end of study, respectively.

Mixed-effect model for repeated measures (MMRM) will be used to test the association between treatment and change from baseline value, assuming missing at random (MAR). The model will include terms of treatment, visit, visit and treatment interaction, country, and baseline Hgb. An unstructured covariance matrix will be used to allow for unequal variances between visits. If the model does not converge with unstructured variance – covariance matrix, then the Toeplitz, first-order autoregressive, compound symmetric, variance components structures will be tried and the covariance structure will be decided based on model convergence status and the AKaike information criterion. The Kenward-Roger approximation will be used to calculate the denominator of degrees of freedom for the fixed effect. If the interaction term is not significant, it will be dropped from the model. No imputation of missing data other than that inherent in the MMRM model will be performed. The least square treatment mean difference estimate, associated 95% confidence interval and p-values will be reported. The same analysis will be performed in by subgroup as specified in Section 2.4.

### 6.2.2 Percentage of participants who receive non-study intervention

The number and percentage of participants who receive non-study intervention will be summarized by treatment group. The treatment effect in this endpoint will be assessed using the CMH chi-square test adjusting for country. Estimates of treatment effect will be presented via the test-based odds-ratio and 95% confidence interval. In addition, the absolute difference in the percentages and associated 95% confidence intervals will be presented.

### 6.2.3 Percentage of participants with Hgb increase ≥ 1 g/dL in the absence of non-study intervention

The number and percentage of participants with Hgb increase ≥ 1 g/dL increase at any time point in the absence of non-study intervention will be summarized by treatment group. The treatment effect in this endpoint will be assessed using the CMH chi-square test adjusting for country. Estimates of treatment effect will be presented via the test-based odds-ratio and 95% confidence interval. In addition, the absolute difference in the percentages and associated 95% confidence intervals will be presented.

### 6.2.4 Percentage of participants with Hgb > 12 g/dL in the absence of non-study intervention

The number and percentage of participants with Hgb > 12 g/dL at any time point in the absence of non-study intervention will be summarized by treatment group. The treatment effect in this endpoint will be assessed using the CMH chi-square test adjusting for country. Estimates of treatment effect will be presented via the test-based odds-ratio and 95% confidence interval. In addition, the absolute difference in the percentages and associated 95% confidence intervals will be presented.

### 6.2.5 Time to Hgb increase ≥ 1 g/dL in the absence of non-study intervention

Time to Hgb increase (from baseline) ≥ 1 g/dL will be analyzed using a logrank test stratified by country. P-value of the treatment effect will be reported. Participants who discontinue or complete the study, or receive a non-study intervention before having an increase in Hgb ≥ 1 g/dL will be censored at last study visit or time of receiving non-study intervention, respectively. Kaplan-Meier curves will be presented for each of the treatment groups.

### 6.2.6 Percentage of participants requiring a blood transfusion

The number (percentage) of participants requiring a blood transfusion at any time during the trial will be summarized by treatment group. The treatment effect in this endpoint will be assessed using the CMH chi-square test adjusting for country. Estimates of treatment effect will be presented via the test-based odds-ratio and 95% confidence interval. In addition, the absolute difference in the percentages and associated 95% confidence intervals will be presented.

### 6.2.7 Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from baseline to each study visit

The number and percentage of participants with Hgb decrease (from baseline) ≥ 0.5 g/dL will be summarized by visit and treatment group. The treatment effect in this endpoint will be assessed using the Cochran-Mantel-Haenszel (CMH) chi-square test adjusting for country. Estimates of treatment effect will be presented via the test-based odds-ratio and 95% confidence interval. In addition, the absolute difference in the percentages and associated 95% confidence intervals will be presented.

### 6.2.8 Time to a decrease in Hgb ≥ 0.5 g/dL from baseline (Day 0) to week 18

Time to Hgb decrease ≥ 0.5 g/dL will be analyzed using a logrank test stratified by country. P-value of the treatment effect will be reported. Participants who discontinue or complete the study, or receive a non-study intervention before having a decrease in Hgb ≥ 0.5 g/dL will be censored at last study visit or time of receiving non-study intervention, respectively. Kaplan-Meier curves will be presented for each of the treatment groups. Kaplan-Meier curves will be presented for each of the treatment groups.

### 6.2.9 Correlation of change in hemoglobin with Day 0 hepcidin level

The correlation of baseline hepcidin with change in hemoglobin to end of study will be analyzed within each treatment group. The end of study is defined as week 18. For participants who receive non-study intervention or early withdraw from the study, the time of intervention or early withdrawal will be considered as end of study, respectively. Spearman rank correlation and Pearson product-moment correlation will be summarized, and p-values will be reported.

### 6.2.10 Total score of the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-Fatigue)

The actual value and change from baseline in total score of FACIT-Fatigue will be summarized via descriptive statistics by visit and by treatment group. Data collected after receiving non-study intervention will not be included in the summary.

Mixed-effect model for repeated measures (MMRM) will be used to test the association between treatment and change from baseline value. The model will include terms of treatment, visit, visit and treatment interaction, pooled site, and baseline score. An unstructured covariance matrix will be used to allow for unequal variances between visits. If the model does not converge with unstructured variance – covariance matrix, then the Toeplitz, first-order autoregressive, compound symmetric, variance components structures will be tried and the covariance structure will be decided based on model convergence status and the AKaike information criterion. The Kenward-Roger approximation will be used to calculate the denominator of degrees of freedom for the fixed effect. If the interaction term is not significant, it will be dropped from the model. No imputation of missing data other than that inherent in the MMRM model will be performed. The least square treatment mean difference estimate, associated 95% confidence interval and p-values will be reported.

# 7. SAFETY ANALYSIS

All safety analyses will be performed on the safety population. No formal statistical testing for treatment group differences will be performed for safety. Safety assessments include:

- Adverse events
- Clinical laboratory tests
- Vital signs

## 7.1.1 Adverse Events

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT) using the MedDRA (version 18.0/AECODE). The verbatim term will be included in the AE listings.

A treatment-emergent adverse event (TEAE) is defined as an AE that begins after receipt of randomized treatment. Only TEAEs will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The incidence of TEAEs will be summarized as the number (percentage) of participants with TEAEs within SOC and PT by treatment group. Participants who report the same PT on multiple occasions will be counted once for the PT: under the highest severity (severe > moderate > mild) when summarized by severity and under the closest relationship (probably related > possibly related > unlikely related > none) to study drug when summarized by relationship. If a subject reports multiple PT for a SOC, the subject will be counted only once for that SOC. Treatment related AEs are defined as those events recorded on the CRF as 'Probably Related' or 'Possibly Related', others will not be related AEs.

TEAEs will be summarized as below.

- An overview table, including number of participants with
  - TEAEs
  - serious AEs (SAEs)
  - study drug related TEAEs
  - Study drug related SAEs
  - TEAEs by severity
  - TEAEs leading to study discontinuation
  - TEAEs leading to death
- TEAE by SOC and PT
- TEAE by SOC, PT, and Severity

- Study drug related TEAEs by SOC, PT
- SAEs by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT

All TEAE tables will be sorted by SOC and PT in decreasing frequency of the number and percentage of participants in the treatment group.

### 7.1.2 Deaths, Serious and Other Significant Adverse Events

The listings of serious AEs, AE leading to study discontinuation, and participants who died during the study will be listed.

## 7.2 Clinical Laboratory Parameters

Laboratory assessments include hematology, clinical chemistry, and iron indices.

All laboratory parameters will be presented in conventional units. Actual value and change from baseline to each scheduled study visit will be summarized using descriptive statistics by treatment, for each laboratory test group above. All laboratory data will be included in the listings.

The number and percent of participants with treatment-emergent potentially clinically significant (PCS) laboratory values after baseline will be summarized by visit and by treatment. The denominator is all participants with normal baseline and at least one post baseline assessment in the safety population and the numerator is the number of participants with PCS (i.e., meets Grade III or Grade IV toxicity criteria from the National Cancer Institute Common Terminology Criteria Version 4.03) at post-baseline.

Shift from baseline toxicity grade to maximum post-baseline grade, and shift from baseline to the last visit in terms of toxicity grade will be summarized by treatment, separately.

## 7.3 Vital Signs

Vital signs include BP and HR. On study drug dosing days BP and HR will be collected immediately pre dosing, immediately and 30 minutes post dosing.

All vital signs will be presented in conventional units as in Table 3. Frequency and percentage of participants with values considered PCS occurring at post-baseline in dosing days will be summarized by visit (and time point) and by treatment and overall. The denominator is all participants with a baseline assessment in the full analysis population and the numerator is the number of participants with PCS at post-baseline. Criteria for PCS are presented below Table 3.

**Table 3 Criteria for Potentially Clinically Significant Vital Signs**

| Vital Sign | Criterion | Definition of PCS at Any Post-baseline Time Point |
|---|---|---|
| Systolic blood pressure | Low | Value ≤90 mmHg and decreased ≥20 mmHg [1] |
| | High | Value ≥180 mmHg and increased ≥20 mmHg [1] |
| | | |
| Diastolic blood pressure | Low | Value ≤50 mmHg and decreased ≥15 mmHg [1] |
| | High | Value ≥105 mmHg and increased ≥15 mmHg [1] |
| | | |
| Pulse | Low | Value ≤50 bpm and decreased ≥15 bpm [1] |
| | High | Value ≥ 120 bpm and increased ≥15 bpm [1] |

[1] For immediately and 30 minutes post-dose assessments on Dosing Days, the change (decrease or increase) is based on the pre-dose value obtained on each corresponding dosing day.

All vital sign data will be included in the listings

### 7.4 PHYSICAL EXAMINATION

Physical examination (PE) results were collected at screening and week 18, including five body systems, i.e. skin, cardiovascular, pulmonary, abdominal, and central nervous system. Physical examination results will be listed.

### 7.5 OTHER ANALYSES

Pregnancy test result (assessed at screening) will be listed.

## 8. INTERIM ANALYSES AND DATA AND SAFETY MONITORING BOARD (DSMB)

### 8.1 INTERIM ANALYSES

No formal interim analysis is planned.

### 8.2 DATA AND SAFETY MONITORING BOARD (DSMB)

No formal DSMB meeting is planned. Safety data will be reported internally focusing on demographic, AE, SAE and AE leading to study discontinuation.

## 9. REFERENCES

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2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Cancer- and Chemotherapy-Induced Anemia. Version 3.2014.