Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Vadadustat

Phase 3b, Randomized, Open-label, Active-controlled Trial Evaluating the Efficacy and Safety of Oral Vadadustat Once Daily (QD) and Three Times Weekly (TIW) for the Maintenance Treatment of Anemia in Hemodialysis Subjects Converting from Erythropoiesis-stimulating Agents (ESAs)

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Statistical Analysis Plan

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Abbreviations

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
BP	Bodily Pain
CBC	Complete Blood Count
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiography
eCRF	electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
EPO	Erythropoietin
ESA	Erythropoiesis-Stimulating Agent
ET	Early Termination
EU	European Union
FAS	Full Analysis Set
FACT-An	Functional Assessment of Cancer Therapy-Anemia
FBR	Future Biospecimen Research
FDA	Food and Drug Administration

Abbreviation	Definition
FSC	Fully Conditional Specification
GH	General Health
Hb	Hemoglobin
HLGT	High-Level Group Term
HLT	High-Level Term
HRQOL	Health-Related Quality of Life
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ISS	Integrated Safety Summary
IV	Intravenous
IWR	Interactive Web Response
LLD	Lower Limits of Detection
MCS	Mental Summary Component
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mental Health
MMRM	Mixed Models for Repeated Measurements
NDA	New Drug Application
NEC	Not Elsewhere Classified
NYHA	New York Heart Association
PCS	Physical Summary Component
PD	Pharmacodynamic
PEP	Primary Efficacy Period
PF	Physical Functioning
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PGx	Pharmacogenomic
PI	Package Insert

Abbreviation	Definition
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
QD	Once Daily
RBC	Red Blood Cell
RE	Role-Emotional
RP	Role-Physical
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SEAC	Safety Event Adjudication Committee
SEP	Secondary Efficacy Period
SF	Social Functioning
SF-36v2	36-Item Short Form Version 2
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TIBC	Total Iron Binding Capacity
TIW	Three Times Weekly
TSAT	Transferrin saturation
ULN	Upper Limit of Normal
US	United States
[redacted]	[redacted]
VT	Vitality
WBC	White Blood Cells
WNL	Within Normal Limits

1 Introduction

This statistical analysis plan (SAP) covers the 404-201-00012 MO$_2$DIFY Study.

The SAP supports the Statistical Methods Section and documents the pre-planned statistical analyses plan of the clinical study report (CSR). It elaborates upon the protocol-specified endpoint definitions and the formal statistical methods that will be used in analyzing the study. Unless otherwise specified, all analyses will be conducted. If the analyses described in the protocols differ from those in this SAP, the methods of the SAP prevail.

2 Description of the Studies

This study is a phase 3b, randomized, open-label, active-controlled trial evaluating the efficacy and safety of oral vadadustat once daily (QD) and three times weekly (TIW) for the maintenance treatment of anemia in hemodialysis subjects converting from erythropoiesis-stimulating agents (ESAs).

2.1 Randomization and Stratification

Subjects who meet all eligibility criteria are randomized 1:1:1 to vadadustat QD, vadadustat TIW, or darbepoetin alfa. Randomization is stratified with respect to:

- Geographic region: United States (US) versus Europe, approximately 90 subjects in Europe.
- Mean weekly darbepoetin alfa dose (or ESA equivalent) calculated over a period of 8 weeks prior to Screening Visit 2:
    - Low darbepoetin alfa dose group (≤ 0.45 μg/kg/week).
    - High darbepoetin alfa dose group (> 0.45 and ≤ 1.5 μg/kg/week).

In each stratum, there are 3 arms: vadadustat QD, vadadustat TIW, and darbepoetin alfa.

2.2 Study Periods

Following randomization, the study has 2 study periods during the trial:

- **Conversion and Maintenance Treatment Period (Weeks 0 to 52):**
    - Weeks 0 to 20: conversion to investigational medicinal product (IMP) for maintaining hemoglobin (Hb).
    - Weeks 20 to 26: primary efficacy period (PEP).
    - Weeks 26 to 46: ongoing maintenance period.
    - Weeks 46 to 52: secondary efficacy period (SEP).

- **Safety Follow-up Period (Early Termination [ET] and Follow-up):** post-treatment Safety Follow-up Visit (ET/End of Treatment [EOT] + 4 weeks).

Individual subjects will participate in total trial duration of approximately 64 weeks. An exit interview will also be conducted at the EOT visit at a subset of sites. Subjects' end of study (EOS) will be their safety follow-up visit (ET/EOT+4 weeks) or if afterwards, the date of the determined survival status per documented attempt(s) as defined in the protocol.

The analysis time periods for efficacy divide the Conversion and Maintenance Treatment period into five windows (see Table 1).

2.3 Target Hb Ranges

Hb levels are to be maintained in the following target ranges:

- US: 10.0 to 11.0 g/dL, inclusive.
- Europe: 10.0 to 12.0 g/dL, inclusive.

2.4 Primary Objectives of the Trial

The primary objective of the trial is to demonstrate the efficacy and safety of vadadustat compared to darbepoetin alfa for the maintenance treatment of anemia in hemodialysis subjects after conversion from current ESA therapy.

2.5 Blinding

This is an open-label study.

Treatment assignment is done through the interactive web response (IWR) system and the investigator, sponsor, and contract research organization (CRO) study teams are not aware of which treatment will be assigned next. Treatments is administered in an open-label fashion. The sponsor and CRO study teams are blinded to "by treatment" aggregated analyses except for the unblinded personnel. Because Hb values are objective and will be measured via a central laboratory for all efficacy endpoints, efficacy assessments are not considered to be subject to bias with an open label design. In order to reduce potential execution bias further, special steps will be taken to restrict access to the study data. Please refer to a separate document, Blinding Procedures and Oversight Plan, for additional details.

Adjustments to doses for vadadustat are based on Hb concentration and Dose Adjustment Guideline, which was addressed in Protocol. Darbepoetin alfa dose adjustments are based on US package insert (PI), European Union (EU) Summary of Product Characteristics (SmPC), local prescribing information, or investigator's clinical discretion, incorporating the Dose

Adjustment Guideline as well as the subject's current Hb level, trajectory, variability, symptoms, cardiovascular risk, and other features of his/her clinical condition(s).

In addition, the study involves the use of an Independent Data Monitoring Committee (IDMC), and an identical schedule of visits, procedures, and assessments for all treatment groups in order to reduce the potential bias. An external independent group of unblinded biostatisticians and programmers will provide the support to IDMC.

The Safety Event Adjudication Committee (SEAC) remains blinded throughout the full course of the study.

An Independent Expert Panel Committee for Hepatic Events of Interest will also be formed prior to trial commencement to adjudicate hepatic events. An internal independent group of unblinded biostatisticians and programmers will provide the support to the Independent Hepatic Expert Panel.

2.6 Sample Size

For the primary efficacy analysis in this trial, it is assumed that the mean change from Baseline in Hb for vadadustat will be the same as for the active control darbepoetin alfa, and the common standard deviation for the mean change from Baseline is assumed to be 1.2 g/dL. Noninferiority will be established based on a 2-sided 95% confidence interval (CI) for the difference between vadadustat QD group and darbepoetin alfa group and using a noninferiority margin of -0.75 g/dL. With these assumptions and approximately 100 subjects per treatment group, the noninferiority test will have > 90% power with consideration of a 30% drop out rate. Same assumptions and sample size calculations will be applied to the difference between vadadustat TIW group and darbepoetin alfa group. After the noninferiority of vadadustat QD is demonstrated, the noninferiority of vadadustat TIW group to darbepoetin alfa group will be tested hierarchically with 2-sided significant level of 0.05.

2.7 Efficacy

Treatment comparisons in efficacy analyses are between vadadustat QD and darbepoetin alfa, and between vadadustat TIW and darbepoetin alfa.

For clarity, this SAP uses the word "mean" to refer to averages over the study groups and "average" to refer to the within-person average during specified evaluation periods.

The primary efficacy endpoint is defined as the Hb change from Baseline (average pretreatment Hb) to the average Hb from Weeks 20 to 26 (inclusive).

The primary efficacy objective is to first show that vadadustat QD is noninferior to darbepoetin alfa within the noninferiority margin. Noninferiority will be established based on a margin of -0.75g/dL (for vadadustat minus darbepoetin alfa). If vadadustat QD meets the noninferiority criterion, then the next objective is to show that vadadustat TIW is noninferior to darbepoetin alfa within the noninferiority margin.

If the lower limit of the 2-sided 95% confidence interval for the difference between the mean Hb change from baseline to Weeks 20 to 26 in the vadadustat group and the mean Hb change from baseline in the darbepoetin alfa group is above zero, superiority will have been established and the finding will be interpreted as providing evidence of a greater change from baseline in Hb for vadadustat relative to the control arm. Because the same 95% confidence interval is used to the superiority test, no adjust of multiplicity is needed.

2.8 Safety

Safety analyses include adverse events (AEs), serious adverse events (SAEs) and Hb-related safety endpoints. Additional safety presentations are described below (Section 7 and Section 10).

3 Analysis Populations

3.1 The Analysis Populations

The following analysis populations are used in this trial:

- Randomized population: defined as all subjects randomized. Analyses of this population will be based on the randomized treatment.
- Full Analysis Set (FAS) population: defined as all subjects in the randomized population who received at least 1 dose of study medication and had at least 1 post dose Hb. Analyses of this population will be based on the randomized treatment.
- Per protocol (PP) population: defined as all randomized subjects who received study medication during the primary evaluation period, had at least 1 Hb assessments during the primary evaluation period, and had no critical or major protocol deviation affecting the primary endpoint analyses (ie, prior to Week 26). Analyses of this population will be based on actual treatment received, as described for the Safety population.
- Safety population: defined as all subjects in the randomized population who received at least 1 dose of study treatment. Analysis of this population will be based on the actual treatment received. Subjects who received in error some vadadustat and some

darbepoetin alfa (excluding rescue therapy) will be classified by the more frequently received drug.

- Pharmacokinetic (PK) population: defined as all subjects in the safety population who have at least 1 measurable vadadustat plasma concentration.

Efficacy analyses will utilize the randomized, FAS, and PP populations while safety analyses will utilize the safety population. PK analyses will utilize the PK population.

3.2 Characterization of the Analysis Population

Number and percent of subjects included in the analysis sets will be summarized.

4 Quality of the Trials

4.1 Study Drug Dosing and Compliance

The IMP (vadadustat or darbepoetin alfa) dosing electronic case report forms (eCRFs) will collect study drug dosing information and whether they have experienced any problems related to the dosing of IMP.

The study drug compliance rate for a given time period will be derived from exposure data as the number of days on dosing period collected on eCRFs divided by the number of days in that time period.

The average weekly dosages and the proportion of subjects who have at least 80% compliance will be tabulated and summarized by treatment group and analysis period for safety and FAS populations. The number and percentage of subjects with any study medication interruptions and their reasons for interruption, collected in eCRF, will be summarized as well.

4.2 Protocol Deviations

Protocol deviations will be summarized in the randomized population as the number and percentage of subjects with a protocol deviation by treatment group. A by-subject listing of protocol deviations will be provided. Protocol deviations due to coronavirus disease 2019 (COVID-19) will be summarized as well.

4.3 Baseline Characteristics, Exposure, and Retention by Treatment Group

Descriptive statistics will be generated by treatment group for demographic and pretreatment variables for each analysis population.

The total number of randomized subjects, treated subjects, and randomized but not treated subjects will be tabulated by treatment group in the randomized population.

The number of subjects who discontinued the study and the reason for discontinuation will be summarized for randomized population.

Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) for each treatment group based on the safety population.

5 General Conventions

Study days are defined as follows:

Study Day = [Event date – First dosing date + 1] if on or after first dosing date

[Event date – First dosing date] if before first dosing date.

Note that with the definition above, days of "0" will not be used. As such, the study day can be interpreted as the number of days before or after first day of dosing. Event date refers to the date associated with the result being summarized. In some cases, this is the date of an assessment or measurement; in other cases, this is the onset date of an adverse or outcome event.

For subjects whose reference date is missing, the study day will also be categorized as missing.

5.1 Visit and Analysis Time Period Classification

The time windows in this section reflect the administrative range around each visit for analysis. They are wider than those stated in the protocol to reduce missing values by capturing as many observation dates as possible. Table 1. provides the convention to classify assessment dates into protocol-defined visits and analysis time periods for assessments conducted at every visit, such as Hb value.

Unless otherwise specified, all assessments will be mapped to visit windows based on the date of the assessment relative to the first dose date, regardless of subject disposition or the CRF page completed, e.g., "Unscheduled", "End of Treatment", etc. Similarly, all values collected within a reporting period will be considered for identification of safety events of interest.

If more than 1 Hb value is available in an analysis time period post-baseline, the average of all observed values (at most 1 per day) will be assigned to that period. For example, the

window for the primary efficacy outcome, analysis time period 3, includes any Hb value (at most 1 per day) assessed between Study Days 127 to 196, corresponding to Weeks 20, 24 and 26.

Efficacy evaluations will use Hb values as assessed by the central laboratory.

When more than 1 assessment is made for other measures (not Hb) within a given visit window post-baseline, the value of the assessment closest to the end of the window is the value associated with that visit for summaries over time. Most summaries of results by visit (e.g., laboratory or vital sign results) will use the single value for each visit determined by this convention. Notable exceptions to this convention are the primary efficacy outcome and clinically significant changes.

If no assessment is available within a time window, then the associated visit and week classifications will be missing.

Table 1. Classification of Assessments at Every Visit

Time Period	Visit/Week	Target Day	Actual Study Day of Visit
Baseline	Screening Visit 1	-	-
	Screening Visit 2	-	-
	Baseline Visit	Day 1	Day 1 (first dose date)[a]
1) Weeks 2-8	Week 2	Day 14	Day 2-21
	Week 4	Day 28	Day 22-35
	Week 6	Day 42	Day 36-49
	Week 8	Day 56	Day 50-63
2) Weeks 10-16	Week 10	Day 70	Day 64-77
	Week 12	Day 84	Day 78-98
	Week 16	Day 112	Day 99-126
3) Primary Efficacy Period (PEP) (Weeks 20-26)	Week 20	Day 140	Day 127-154
	Week 24	Day 168	Day 155-175
	Week 26	Day 182	Day 176-196
4) Weeks 30-42	Week 30	Day 210	Day 197-224
	Week 34	Day 238	Day 225-252
	Week 38	Day 266	Day 253-280
	Week 42	Day 294	Day 281-308
5) Secondary Efficacy Period (SEP) (Weeks 46-52)	Week 46	Day 322	Day 309-336
	Week 50	Day 350	Day 337-357
	Week 52	Day 364	Day 358-378
Safety Follow-up	Follow-up	ET/EOT + 4 Weeks	ET/EOT+15 Days – ET/EOT+42 Days

ET=Early Termination; EOT=End of Treatment.

[a] If patient has no first dose date, day 1 will be the randomization date.

5.2 Definition of Baseline

The baseline value must be assessed prior to initiation of study treatment. For Hb, baseline will be calculated as an average of the last 2 values prior to or on the first dose date, as specified in Section 9.2.1. For other parameters, unless otherwise specified, baseline will be defined as the last available value prior to the first dose of IMP.

5.3 Prior and Concomitant Medication

Prior medication is defined as any medications taken before the date of the first dose of IMP. Concomitant medication is defined as any medications taken at any time from the date of the first dose of IMP through the date of the last dose of the IMP.

Prior and concomitant medications will be coded using World Health Organization Drug dictionary and summarized for each treatment group based on the safety population. Prior and concomitant ESA medications and their reasons of usage will be summarized by treatment group. Number of subjects taking concomitant anti-hypertensive medications, and number of concomitant anti-hypertensive medications taken will be summarized by study period for each treatment group as well.

5.4 Handling of Missing Data

Missing data will be handled using a procedure specific to each variable and analysis as described in the sections relevant to each endpoint. If no method for missing data is discussed, descriptive analyses will be based upon observed data without imputation.

For the analysis of safety variables, only partial dates will be imputed unless otherwise specified. The algorithms for imputation of partial dates depend upon the parameter, as follows.

Adverse event onset

- If onset date is completely missing, date is set to date of first dose.
- If year is present and month and day are missing, or year and day are present, but month is missing:
    - If year = year of first dose, then set month and day to month and day of first dose.
    - If year < year of first dose, then set month and day to December 31.
    - If year > year of first dose, then set month and day to January 1.
- If month and year are present and day is missing:

  - If year = year of first dose and
    - month = month of first dose, then set day to day of first dose date.
    - month < month of first dose, then set day to last day of month.
    - month > month of first dose, then set day to first day of month.
  - If year < year of first dose, then set day to last day of month.
  - If year > year of first dose, then set day to first day of month.
- For all other cases, set date to date of first dose.

Adverse event end date

- If year is present and month and day are missing, or year and day are present and month is missing, set end month and day to December 31.
- If month and year are present and day is missing, set the day to last day of the month.
- If fatal event, date is set to minimum of imputed end date and death date.
- For all other cases, set date to missing.

Concomitant medication

- If start date is completely missing, start date will not be imputed.
- If start year is present and month and day are missing, or year and day are present and month is missing, set start month and day to January 1.
- If start year and month are present and day is missing, set start day to 1st day of month.
- If end date is completely missing, end date will not be imputed.
- If end year is present and month and day are missing, or year and day are present and month is missing, set end month and day to December 31.
- If end year and month are present and day is missing, set end day to last day of the month.
- The imputed dates must be logical, ensuring that no end date is after database lock or death or before the start date.

If site queries fail to resolve partial dates for laboratory values and vital signs, including for efficacy, the date is missing and will not be imputed.

6 Efficacy Endpoints

This section lists the efficacy endpoints; Section 9 describes their definitions and the plans for the analysis of each endpoint.

6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in Hb between Baseline (average pretreatment Hb) and the primary evaluation period (average Hb from Weeks 20 to 26, inclusive).

6.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoint is the change in Hb between Baseline and the secondary evaluation period (average Hb from Weeks 46 to 52).

6.3 Other Efficacy Endpoints

Other efficacy endpoints include the following:

- Proportion of subjects having average Hb values within the target range during the primary evaluation period (Weeks 20 to 26).
- Proportion of subjects having average Hb values within the target range during the secondary evaluation period (Weeks 46 to 52).
- Proportion of subjects receiving intravenous (IV) iron therapy from Baseline to Week 52.
- Average weekly dose of IV elemental iron administered from Baseline to Week 52 in subjects who have received IV elemental iron.
- Receipt of ESA rescue.
- Proportion of subjects receiving red blood cell (RBC) transfusions from Baseline to Week 26.
- Proportion of subjects receiving RBC transfusions from Baseline to Week 52.
- Change from baseline in 36-Item Short Form Version 2 (SF-36v2) Health-Related Quality of Life (HRQOL) scores.
- Change from baseline to the average value in Anemia Subscale ("Additional Concerns") of Functional Assessment of Cancer Therapy-Anemia (FACT-An) Score.
- Change from baseline to the average value in Total FACT-An Score.
- Change from baseline in score of Patient Global Impression of Severity (PGI-S).
- Score of Patient Global Impression of Change (PGI-C).

6.4 Rescue Therapy

The narrow and broad-on-treatment rescue therapies are defined as follows:

- Narrow: For all treatment arms, narrow rescue therapy is defined as rescue for worsening anemia with ESA medication or RBC transfusion, not starting after permanent study treatment discontinuation. Reason includes “Hb <9.5 g/dL”. For

darbepoetin alfa arm, darbepoetin alfa with increases in dose ≥50% or ≥100% will be considered as ESA rescue medication.

- Broad-on-treatment: For all treatment arms, broad-on-treatment rescue therapy is defined as any exposure to ESA medication (aside from darbepoetin alfa not designated as rescue in the control arm) or RBC transfusion for any reason not starting after permanent study treatment discontinuation. For darbepoetin alfa arm, darbepoetin alfa with increases in dose ≥50% or ≥100% will be considered as ESA rescue medication.

Reasons for ESA medication and RBC transfusion will be collected in eCRF. If a given therapy starts the same day as permanent discontinuation of study drug, then that therapy will be considered on treatment for rescue definitions.

In vadadustat arms, any use of ESA may be considered rescue. In darbepoetin alfa arm, since the study drug itself is an ESA, the use of another ESA may be considered rescue, and the increase dose in darbepoetin alfa may be planned titration or a rescue. Subjects treated darbepoetin alfa with increases in dose relative to last dose by percentage of <50%, ≥50% and <100%, and ≥100%. Darbepoetin alfa treatment with ≥50% or ≥100% dose increases from last dose will be considered as rescue therapies. Subjects will be presented by their maximum category of increase within each of the five analysis time periods (see Section 5.1).

The time to the first ESA medication or RBC transfusion (narrow or broad-on-treatment therapy with ≥50% or ≥100% dose increase in darbepoetin alfa) will be analyzed by Cox regression model for treatment comparison in the randomized population. The estimated hazard ratio and its 95% CI will be performed. Kaplan-Meier curve will be displayed as well.

Analyzing the impact of pre-baseline or post-baseline ESA on vadadustat efficacy requires conversion of ESA dose into common units. The epoetin alfa analogues, darbepoetin alfa and methoxy polyethylene glycol epoetin beta (Mircera), will be converted to IV epoetin equivalent units per kilogram per week (U/kg/week). The following conversions have been derived from published literature and input from clinical experts [Paganini, 1995; Kaufman, 1998; Cremieux, 2006; Gosselin, 2006; Levin, 2008; FDA, 2011; Jordan, 2012; Choi, 2013; Vega, 2014; Wright, 2015]:

Table 2. ESA Unit Conversion

	SC Epoetin	IV Epoetin
Darbepoetin alfa to epoetin	1:160	1:200
Methoxy polyethylene glycol-epoetin beta to epoetin	1:176	1:220

Subcutaneous (SC) epoetin to intravenous (IV) epoetin is 1:1.25.

7 Safety Endpoints

The following safety endpoints will be summarized by treatment groups:

- Adverse events (AEs) and serious adverse events (SAEs).
- Treatment-emergent adverse events (TEAEs) and treatment-emergent SAEs.
- Adverse events of special interest (AESI).
- Vital signs, ECGs and clinical laboratory values.
- Episodes of Hb >11.0 g/dL for US, > 12.0 g/dL, > 13.0 g/dL, > 14.0 g/dL, < 8.0 g/dL, or < 9.0 g/dL.
- Number of episodes of Hb increase > 1.0 g/dL within any 2-week interval or > 2.0 g/dL within any 4-week interval.

8 Pharmacokinetic (PK)/ Pharmacodynamic (PD)/ Pharmacogenomic (PGx) Analysis

8.1 Pharmacokinetic Analysis

Plasma concentrations, time of sample collection and time post-dose calculations will be listed. Concentrations may be part of a population PK analysis that will be reported separately.

8.2 Pharmacodynamic Analysis

A by-subject listing of all PD variables, including erythropoietin (EPO), reticulocytes, and iron indices (iron, ferritin, TIBC, and TSAT), will be provided including the changes from Baseline/Day 1. The observed and change from Baseline/Day 1 values of all PD assessments will be summarized using descriptive statistics. For PD variables analyzed after database lock, values will be reported separately.

8.3 Pharmacogenomic Analysis

No PGx analysis is planned.

9 Efficacy Endpoints and Analyses

The general approach for analysis of continuous outcomes will be analysis of covariance (ANCOVA) with multiple imputation for missing data or mixed models for repeated measurements (MMRM) on observed data.

For binary variables, the general approach will be Mantel-Haenszel estimation of risk difference stratified by the baseline strata with (or without) multiple imputation for handling missing data [Mantel, 1959].

9.1 Primary Estimand

The primary estimand defining the treatment effect of interest in this trial uses the treatment policy strategy specified in the ICH E9 (R1) Addendum [FDA 2021b]. In this trial, the research question is to compare the assignment of darbepoetin alfa to vadadustat, regardless of intercurrent events. The primary analysis will be performed in the randomized population in accordance with intent-to-treat. This means the analysis will include individuals who never received treatment, discontinued treatment, were rescued with any therapy, and withdrew consent. The estimate of the treatment effect of interest will be the one regardless of whether the intercurrent event occurred.

The primary estimand for this trial is defined by the following components:

- Treatment: vadadustat with rescue therapy as needed versus darbepoetin alfa with rescue therapy as needed.
- Population: randomized population.
- Variable: change in Hb from Baseline to the primary evaluation period (average Hb from Weeks 20 to 26, inclusive).
- Intercurrent event: never received treatment, discontinued treatment, rescued with any therapy or withdrew consent.
- Population-level summary: difference in mean change in Hb from baseline to the primary evaluation period between the vadadustat groups and darbepoetin alfa control group.

9.2 Definition of Primary Efficacy Endpoint: Change from Baseline in Hb

The primary efficacy endpoint is the change in average Hb between baseline and the PEP (Weeks 20 to 26, inclusive).

The primary analysis will use the randomized population with an ANCOVA, with randomization stratification factors and baseline Hb as covariates.

A 2-sided, 95% CI will be calculated for the difference in mean change in Hb from baseline to the PEP between the vadadustat group and darbepoetin alfa control group. Noninferiority of vadadustat will be established if the lower limit of this CI is ≥ -0.75 g/dL.

A hierarchical testing scheme will be used to correct for the multiplicity of the 2 primary endpoints: comparison between vadadustat QD vs. darbepoetin alfa and comparison between vadadustat TIW vs. darbepoetin alfa.

- Step 1: comparison between vadadustat QD vs. darbepoetin alfa.
- If the noninferiority of vadadustat is established in step 1, then move to the step 2;
- Step 2: comparison between vadadustat TIW vs. darbepoetin alfa.

9.2.1 Baseline Hb

Baseline Hb will be calculated as the average of the last 2 central laboratory Hb measurements of samples taken at the visits prior to or on the date of first dose date. If there is only one available Hb value prior to or on the date of first dose date, then it will be used for the calculation of baseline. If there is more than one available Hb values, the last 2 Hb values prior to or on the date of first dose date will be used.

9.2.2 Hb in the Primary Efficacy Period

Hb for the PEP will be calculated as the average of all Hb measurements from the central laboratory within the three visit windows during Weeks 20 through 26, regardless of intercurrent events. At least 1 Hb measurement is required for the calculation; otherwise, the value will be missing and therefore imputed. The PEP is also called analysis time period 3 (see Table 1).

9.2.3 Change in Hb from Baseline to the Primary Efficacy Period

The change from baseline will be calculated for each subject as the PEP value minus the baseline value.

9.2.4 Analysis of Change from Baseline in Hb to the Primary Efficacy Period

The primary analysis will use multiple imputation with ANCOVA as the substantive model and will be performed in the randomized population.

All intercurrent events will be handled by treatment policy strategy (see Section 9.1). Unobserved data after intercurrent events, including hemoglobin outcomes and any covariates to be used in the models, will be imputed with randomized subjects using multiple imputation under fully conditional specification (FSC) method. Under the assumption of FSC, data for each variable with missing values will be imputed with a separate regression model allowing for all available data to be used in the imputation process. For continuous variables, the regression method will be used for imputations. For categorical variables, logistic regression models will be used for binary outcomes, and nominal response logistic regression for nominal responses.

An ANCOVA model will be used to compare the mean change from baseline in Hb between 2 treatment groups with the complete dataset from multiple imputation. The ANCOVA model will contain treatment group, baseline Hb level, and the 2 stratification factors (geographic region and mean weekly darbepoetin alfa dose prior to Screening Visit 2) as predictor variables. The stratification factor assignments at randomization will be used in the analysis.

The data will have shown noninferiority of vadadustat if the lower bound of the 95% confidence interval for the difference in estimated change from baseline in the 2 groups (vadadustat minus darbepoetin) exceeds the noninferiority margin of -0.75g/dL. This ensures a 1-sided alpha of 0.025 for the primary analysis. If the lower limit of the 2-sided 95% confidence interval for the difference between the mean in the vadadustat group and the mean in the darbepoetin alfa group is above zero, superiority will have been established and the finding will be interpreted as providing evidence of a greater change from baseline in Hb for vadadustat relative to the control arm.

The procedure of primary analysis follows these steps:

1) Missing data will be imputed separately for each treatment group using FSC method with 100 imputed datasets and 40 iterations from PROC MI. The SAS codes of PROC MI with outcome variables and covariates will be as follows. [redacted]

[redacted]

2) The output from the multiple imputation procedure 1) will be 100 imputed complete datasets. These 100 imputed complete datasets will be used not only for primary efficacy analysis, but also secondary efficacy analysis and other efficacy analysis for proportion of subjects having average Hb values within target range.
3) An ANCOVA model will be used to compare the mean change from baseline in Hb between treatment groups with the complete dataset. [redacted]
4) The output from the ANCOVA model 3) will include the estimate (ESTIMATE) and standard error (STDERR) of change from baseline for each imputed complete dataset.
5) The overall results will be obtained using PROC MIANALYZE. [redacted]

9.2.5 Sensitivity Analyses to the Primary Efficacy Results

To assess the robustness of the findings from the primary analysis, the following set of sensitivity analyses will be performed:

- Primary analysis will be repeated using the FAS population.
- Primary analysis will be repeated using the PP population with the actual treatment received.
- Primary analysis will be repeated with imputation of data which may have been affected by a subject's having received any form of rescue (transfusion or ESA). All per-visit Hb values within four weeks of administration rescue therapy (narrow or broad-on-treatment defined in Section 6.4) will be set as missing prior to imputation. [redacted]

- A mixed model for repeated measures (MMRM) will be fit to the observed data only and will be performed in the randomized population.

[redacted]

In the MMRM model, the within-subject correlations will use an unstructured covariance structure (TYPE=UN). In the unlikely situation that this model does not converge, the following variance covariance matrix structures will be used in the order of 1) heterogeneous Toeplitz (TYPE=TOEPH), 2) homogeneous Toeplitz (TYPE=TOEP), and 3) compound symmetry (TYPE=CS).

9.3 Secondary Efficacy Endpoints: Definitions and Analyses

The key secondary efficacy endpoint will be formally analyzed once the non-inferiorities have been established in the primary endpoint for vadadustat QD and TIW regimens.

Mean change in Hb value between Baseline and the secondary evaluation period (average Hb from Weeks 46 to 52) will be analyzed using the same methodology as specified for the primary efficacy endpoint. Sensitivity analyses like those of the primary efficacy endpoint will be performed.

9.4 Other Efficacy Endpoints: Strategies for Analysis

Except for specifying the analysis population, other efficacy endpoints analyses will be performed using the randomized and full analysis population, with the assigned treatment as described in Section 3.1. There will be no correction for multiplicity for these endpoints.

9.4.1 Proportion of Subjects Having Average Hb Values within the Target Range during the PEP (Weeks 20 to 26)

All subjects will be defined as either being in their geography-specific target range (see Section 2.3) in Weeks 20 through 26 (“yes”) or not (“no”), based on the average Hb value during the three visit windows in Weeks 20 through 26. Subjects with no Hb value in the PEP value will be treated as missing. To ensure uniformity across all analyses, the missing binary outcomes will be computed from the imputed complete dataset in primary analysis (see Section 9.1.4) [Ratitch, 2013].

The proportion of subjects within target range will be calculated, and a 95% confidence interval of the proportion will be performed by treatment group.

A Mantel-Haenszel estimation of risk difference stratified by the baseline strata will be conducted, and the corresponding 2-sided 95% confidence interval for the risk difference will be calculated. Noninferiority will have been established if the lower limit of the confidence interval is above -15% when tested per the testing procedure (Section 9.5).

If the lower limit of the 2-sided confidence interval for the risk difference is above zero, superiority will have been established and the finding will be interpreted as providing evidence of a higher proportion of subjects being within the target range for vadadustat relative to the control arm when tested per the testing procedure (Section 9.5).

The associated odds ratio and corresponding 2-sided 95% confidence interval will also be calculated.

The analysis of proportion of subjects within target range follows these steps:

1) 100 imputed complete datasets will be obtained from the multiple imputation procedure 1) of Section 9.2.4.
2) The proportion of subjects within target range will be calculated based on the 100 imputed complete datasets. A Mantel-Haenszel estimation of risk difference stratified by the baseline strata will be conducted. [redacted]
3) The overall results from 2) will be obtained using PROC MIANALYZE. [redacted]

9.4.2 Proportion of Subjects Having Average Hb Values within the Target Range during the SEP (Weeks 46 to 52)

Proportion of subjects having average Hb values within the target range during the SEP (Weeks 46 to 52) will be analyzed using the same methodology as specified for the PEP (see Section 9.4.1).

9.4.3 Proportion of Subjects Receiving IV Iron Therapy from Baseline to Week 52

The proportion of subjects receiving at least one intravenous (IV) iron therapy from Baseline to Week 52 will be calculated, and a Mantel-Haenszel estimation of risk difference stratified by the baseline strata will be performed.

In addition, the following subgroups of baseline iron will be performed:

- Subjects not receiving any iron at baseline, and
- Subjects receiving IV or oral iron at baseline.

9.4.4 Average Weekly Dose of IV Elemental Iron Administered from Baseline to Week 52

Average weekly dose of IV elemental iron administered from Baseline to Week 52 in subjects who have received IV elemental iron will be calculated, and an analysis of variance (ANOVA) model with 2 stratification factors at randomization will be performed. If the distribution is highly skewed because of a long tail to the right, other methods may be considered.

9.4.5 Receipt of ESA Rescue

The proportion of subjects with any ESA rescue medications including narrow or broad-on-treatment therapies with ≥50% or ≥100% dose increase in darbepoetin alfa defined in Section 6.4 will be calculated. A Mantel-Haenszel estimation of risk difference stratified by the baseline strata for each study period will be performed.

The time to the first ESA rescue (narrow or broad-on-treatment therapies with ≥50% or ≥100% dose increase in darbepoetin alfa) will be analyzed by Cox regression model for treatment comparison in the randomized population. The estimated hazard ratio and its 95% CI will be performed. Kaplan-Meier curve will be displayed as well.

9.4.6 Proportion of Subjects Receiving Red Blood Cell (RBC) Transfusions

The proportion of subjects receiving RBC transfusions (narrow or broad-on-treatment therapy) will be calculated from Baseline to Week 26 and from Baseline to Week 52. A Mantel-Haenszel estimation of risk difference stratified by the baseline strata will be performed.

The time to the first RBC transfusion (narrow or broad-on-treatment therapy) will be analyzed by Cox regression model for treatment comparison in the randomized population. The

estimated hazard ratio and its 95% CI will be performed. Kaplan-Meier curve will be displayed as well.

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9.4.10 Score of Patient Global Impression of Change (PGI-C)

The PGI-C is a scale that evaluates all aspects of a subject's health and assesses if there has been an improvement or decline in clinical status. Subjects will answer the following question:

- How would you compare the impact of your anemia and its treatment on how you feel now to when you were on the previous treatment (or the period before your last visit)?

The question will be rated as “very much worsened”, “much worsened”, “minimally worsened”, “not changed”, “minimally improved”, “much improved”, or “very much improved”. PGI-C scale score will be summarized by visit and by treatment group.

9.5 Study Level Type I Error Control

The study-wise type I error control for multiple testing of efficacy endpoints is controlled at 0.05 level, two-sided by using hierarchical testing procedure. The order of hierarchy is listed below. Upon the demonstration of the non-inferiority of the primary endpoint of vadadustat QD vs. darbepoetin alfa for the change in average Hb between baseline and the PEP, the non-inferiority of the other primary endpoint of vadadustat TIW vs. darbepoetin alfa for the change in average Hb between baseline and the PEP will be examined with pre-specified margin. If it meets the noninferiority margin, the secondary efficacy endpoints in the list will be examined against the pre-specified statistical criteria and so on. In other words, an endpoint will only be tested against pre-specified statistical criteria when the previous endpoint meets statistical criteria. Once an endpoint did not meet the statistical criteria, any endpoints after it will not be formally tested. The hierarchical testing order will be as follows:

1. Noninferiority of vadadustat QD vs. darbepoetin alfa for the change in average Hb between baseline and the PEP (primary efficacy endpoint).
2. Noninferiority of vadadustat TIW vs. darbepoetin alfa for the change in average Hb between baseline and the PEP (primary efficacy endpoint).
3. Noninferiority of vadadustat QD vs. darbepoetin alfa for the change in average Hb between baseline and the SEP (secondary efficacy endpoint).
4. Noninferiority of vadadustat TIW vs. darbepoetin alfa for the change in average Hb between baseline and the SEP (secondary efficacy endpoint).
5. Noninferiority of vadadustat QD vs. darbepoetin alfa for the proportion of subjects having average Hb values within the target range during the PEP (other efficacy endpoint).
6. Noninferiority of vadadustat TIW vs. darbepoetin alfa for the proportion of subjects having average Hb values within the target range during the PEP (other efficacy endpoint).
7. Noninferiority of vadadustat QD vs. darbepoetin alfa for the proportion of subjects having average Hb values within the target range during the SEP (other efficacy endpoint).

8. Noninferiority of vadadustat TIW vs. darbepoetin alfa for the proportion of subjects having average Hb values within the target range during the SEP (other efficacy endpoint).

10 Safety Analyses

All analyses of safety data will use the safety population.

Most of the analysis of safety data will be descriptive without formal statistical testing. In some cases, 95% confidence intervals for the change from baseline as well as for the difference between the study groups will be reported.

10.1 Mortality

The number and cause of death will be reported and summarized by treatment arm.

10.2 Hb-related Safety Endpoints

Hb-related safety endpoints will be defined using data from the central laboratory. The analyses will use all central laboratory values in the database starting from randomization. No imputation will be performed for missing data.

Any post-baseline Hb value above a set threshold will be considered as a "yes" in the Hb related safety analysis. Subjects with no available post-baseline data will be excluded from this analysis. All other subjects will be classified to the "no" category.

The number and proportion of subjects with at least 1 of the following criteria at any post-baseline time point will be summarized by analysis time period. The denominator for calculating proportion is the total number of subjects with available post-baseline Hb values in each analysis time period. A 95% confidence interval of the proportion will be performed by treatment group using the Clopper-Pearson exact method [Clopper, 1934].

- Hb > 11.0 g/dL for US.
- Hb > 12.0 g/dL.
- Hb > 13.0 g/dL.
- Hb > 14.0 g/dL.
- Hb increase > 1.0 g/dL within any 2-week interval.
- Hb increase > 2.0 g/dL within any 4-week interval.
- Hb < 8.0 g/dL.
- Hb < 9.0 g/dL.

A Mantel-Haenszel estimation of risk difference stratified by the baseline strata will be conducted, and the corresponding 2-sided 95% confidence interval of the risk difference will be calculated. The associated odds ratio and corresponding 2-sided 95% confidence interval will also be calculated.

10.3 Adverse Events and Serious Adverse Events

The AE eCRF has been designed to capture all events from time of signing the informed consent through the Safety Follow-up visit. Subjects must be followed for AEs until the final required protocol visit or until all drug-related toxicities and serious adverse events (SAEs) have resolved (or are considered chronic/stable), whichever is later. All AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The MedDRA version used for reporting this study will be described in a footnote on AE related outputs.

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the start of IMP treatment. In more detail, TEAEs are all adverse events which started after start of IMP treatment; or if the event was continuous from baseline and was worsening, serious, IMP related, or resulted in death, discontinuation, interruption or reduction of IMP.

All TEAE summaries will provide the number of subjects reporting at least 1 TEAE. Tables will present the number and percentage of subjects by treatment group reporting at least 1 of the following:

- TEAE, SOC, and PT
    - TEAE leading to withdrawal of study medication, SOC, and PT
    - TEAE, severity, SOC and PT
    - Drug-related TEAE, SOC, and PT
    - Drug-related TEAE leading to withdrawal of study medication, SOC, and PT
- Treatment-emergent SAE, SOC, and PT
    - Drug-related treatment-emergent SAE, SOC, and PT
    - Fatal TEAE, SOC and PT.

A summary table will show number of subjects with at least 1 of each of the following:

- AE,
- SAE,
- TEAE,
- Severe TEAE
- TEAE leading to withdrawal of study treatment,

- Drug-related TEAE leading to withdrawal of study treatment,
- Drug-related TEAE,
- Treatment-emergent SAE,
- Drug-related treatment-emergent SAE,
- Fatal TEAE,
- All death.

TEAEs reported at least 5% of subjects in any treatment groups, and non-serious TEAEs reported at least 5% of subjects in any treatment groups will be summarized by SOC and PT for each treatment group.

TEAEs will be summarized by 1) worst severity, and 2) worst causality by SOC and PT. For each subject and each PT, the worst severity recorded will be used in the by-severity summaries. Similarly, the most conservative causality assessment (most related to treatment) will be attributed and used in the by-causality summaries. If severity or causality is missing, data will be imputed to the worst category.

A by-subject listing of all AEs will be provided. This listing will be presented by treatment group and will include center, subject identifier, age, sex, race, AE (SOC, PT, and verbatim term), flag of TEAE, study day of onset, study day of resolution, duration, severity, seriousness, relationship to the study medication, action taken, outcome and causality.

AEs of special interest (AESI) listed in Appendix D will be summarized by treatment group. The number and percentage of subjects reporting these AESI will be provided.

10.4 Major Adverse Cardiovascular Event (MACE)

Potential safety events will be collected in Safety Event Data Collection eCRF page. The occurrence of any potential safety events will be summarized by SOC and PT for each treatment group, and a by-subject listing will be provided.

An independent Safety Event Adjudication Committee (SEAC) that is composed of independent experts will be formed prior to trial commencement to adjudicate the MACE (all-cause mortality, non-fatal myocardial infarction (MI), and non-fatal stroke) plus hospitalization for heart failure (HF) or thromboembolic event excluding vascular access thrombosis. Adjudicated safety events will be summarized for each treatment group, and a by-subject listing will be provided.

10.5 Other Safety Endpoints

Observed values of continuous and categorical parameters and changes from baseline for continuous parameters to each trial visit will be summarized descriptively for vital signs and clinical laboratory results. Graphical displays of selected laboratory parameters will also be provided.

10.5.1 Clinical Laboratory Evaluation

Observed values and changes (absolute and percent) from baseline in continuous clinical laboratory results will be summarized by visit and by treatment group. If the central laboratory uses assays that have lower limits of detection (LLD), all laboratory results below the LLD will be imputed with the LLD. Results reported as greater than a value (i.e., "> value") will be imputed as 1.5 × that value.

A summary of liver function abnormalities will be provided by treatment group. Any subject with at least 1 of the following liver function abnormalities will be summarized:

- Alanine aminotransferase (ALT):
  - >2 × and ≤3 × upper limit of normal (ULN).
  - >3 × and ≤5 × ULN.
  - >5 × and ≤10× ULN.
  - >10 × ULN.
- Aspartate aminotransferase (AST):
  - >2 × and ≤3 × ULN.
  - > 3× and ≤ 5 × ULN.
  - >5 × and ≤10 × ULN.
  - >10 × ULN.
- Total bilirubin:
  - >2× and ≤3× ULN.
  - >3× ULN.

The occurrence of events that satisfy the following laboratory values fulfilling potential liver injury criteria will be summarized. For each subject, the worse laboratory results will be considered.

- (ALT or AST >3× ULN and <= 5xULN) and total bilirubin >2× ULN.
- (ALT or AST >5× ULN and <= 10xULN) and total bilirubin >2× ULN.
- ALT or AST >10× ULN and total bilirubin >2× ULN.

The number and percentage of subjects experiencing clinically significant values for Potassium >6.0 mmol/L will be presented by analysis time period.

10.5.2 Vital Signs, ECGs, and Physical Findings

Observed values and changes from baseline in vital signs and body weight will be summarized by visit and by treatment group. A summary of each electrocardiography (ECG) parameter will be provided by treatment group.

The number and percentage of subjects experiencing the following findings will be summarized by treatment group and by analysis time periods. The denominator for calculating percentage is the total number of subjects with available values in each analysis time period.

- Systolic blood pressure (SBP):
  - ≥ 180 mmHg.
  - ≥ 160 mmHg.
  - ≤ 90 mmHg.
  - Increase from Baseline ≥ 20 mmHg.
  - Decrease from Baseline ≥ 20 mmHg.
- Diastolic blood pressure (DBP):
  - ≥ 110 mmHg.
  - ≤ 50 mmHg.
  - Increase from Baseline ≥ 20 mmHg.
  - Decrease from Baseline ≥ 20 mmHg.
- QTc interval: > 450 msec (males); >470 msec (females).

11 Subgroups

Analyses of the primary efficacy endpoint and key secondary efficacy endpoint will also be performed using the randomized and FAS populations, using the assigned treatment, for subgroups based on the following:

- Low darbepoetin alfa dose group (≤ 0.45 μg/kg/week) or High darbepoetin alfa dose group (> 0.45 and ≤ 1.5 μg/kg/week).

Due to use of different target Hb levels in the US versus non-US, the endpoints will also be analyzed for subsets based on the target Hb level:

- The US subset will be assessed due to the target Hb range being 10.0 to 11.0 g/dL in the US.

- The European subset will be assessed since the target Hb range is 10.0 to 12.0 g/dL in the Europe.
- Geographic region (US, Europe).
- Age (<65 years, ≥65 years).
- Sex (Male, Female).
- Race (White, Black or Other).
- Baseline Hb (<10.0 g/dL, ≥10.0 g/dL).

Subgroup analyses will be performed only if the total number of outcomes in a subgroup, combined over the two compared treatment groups, is at least 30.

[redacted]

13 Interim Analysis

No interim analyses will be performed. No analyses of the primary efficacy endpoint will be conducted when all randomized subjects complete their Week 26 evaluations. .

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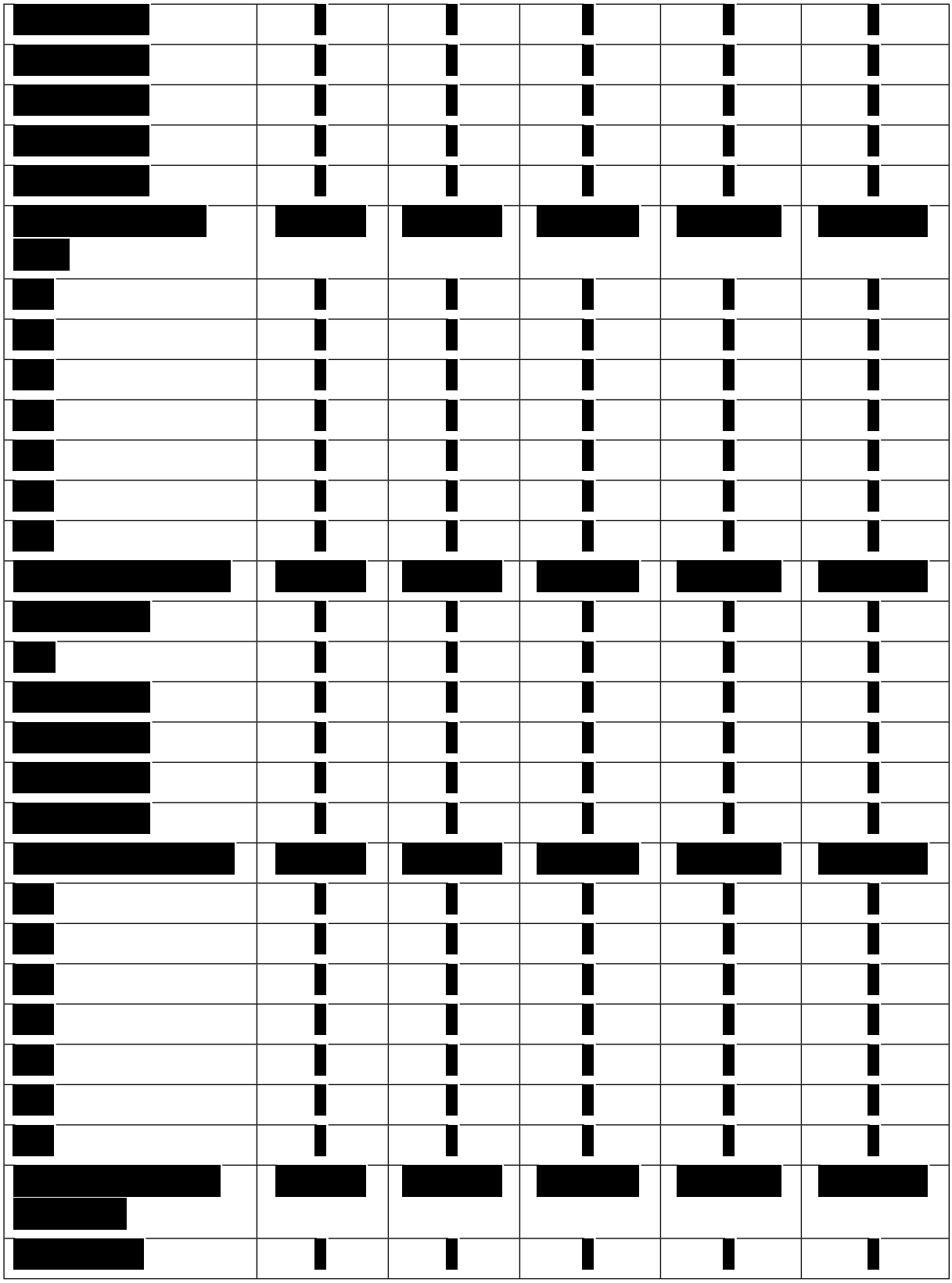

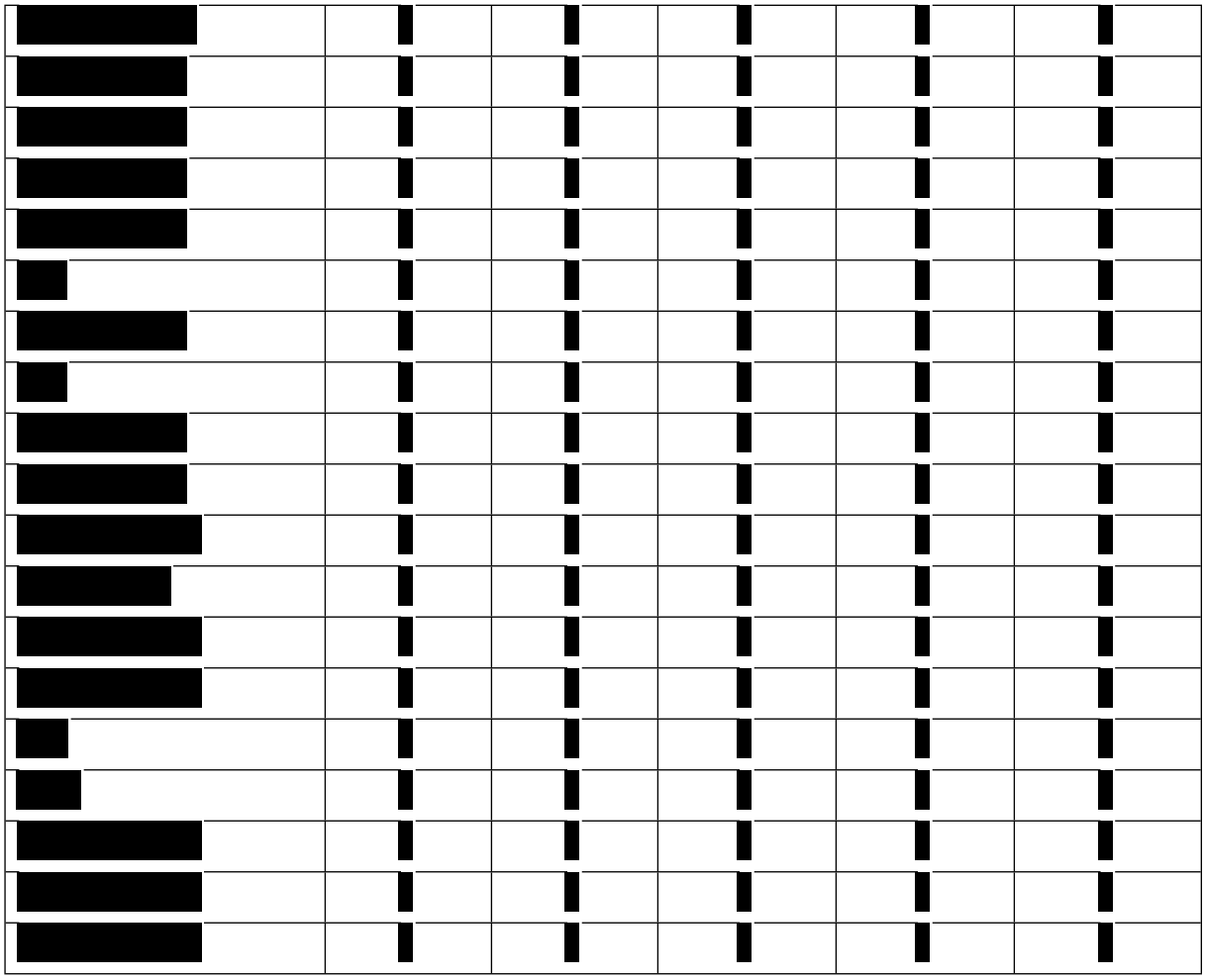

17 Appendix D Adverse Event of Special Interest

The list of adverse events of special interest (AESI) in the following is from Vadadustat Adverse Events of Special Interest Version 2 Final.

- Worsening of Hypertension: Hypertension MedDRA SMQ Narrow.
- Hepatotoxicity: Drug related hepatic disorders Comprehensive SMQ.
- Pulmonary Hypertension: Pulmonary Hypertension SMQ Narrow.
- Adrenal disorder: MedDRA HLGT Adrenal gland disorders and the MedDRA HLT Adrenal cortex tests.
- Malignancies including renal cell carcinoma: Malignant or unspecified tumors (SMQ) Broad.
- Congestive heart failure: Cardiac failure MedDRA SMQ Narrow.

Adverse event preferred terms used in key queries from Food and Drug Administration (FDA) [FDA, 2021a] are listed below.

- Thrombosis (FDA):

Cerebral infarction
Embolic cerebral infarction
Ischaemic stroke
Cerebellar infarction
Lacunar stroke
Embolic stroke
Brain stem stroke
Lacunar infarction
Thrombosis in device
Arteriovenous fistula thrombosis
Arteriovenous graft thrombosis
Vascular access site thrombosis
Vascular graft thrombosis
Graft thrombosis
Shunt thrombosis
Acute myocardial infarction
Myocardial infarction
Deep vein thrombosis
Thrombosis
Atrial thrombosis
Peripheral artery thrombosis
Subclavian vein thrombosis
Brachiocephalic vein thrombosis
Subclavian artery thrombosis
Vena cava thrombosis
Thrombophlebitis superficial

Arterial thrombosis
Thrombophlebitis
Jugular vein thrombosis
Venous thrombosis
Pelvic venous thrombosis
Venous thrombosis limb
Cardiac ventricular thrombosis
Intracardiac thrombus

- Device/shunt thrombosis/occlusion/malfunction/Stenosis (FDA):

Thrombosis in device
Arteriovenous fistula thrombosis
Arteriovenous graft thrombosis
Vascular access site thrombosis
Vascular graft thrombosis
Medical device site thrombosis
Device occlusion
Arteriovenous fistula occlusion
Vascular access site occlusion
Vascular access complication
Vascular access malfunction
Arteriovenous graft site stenosis
Shunt occlusion
Shunt malfunction
Vascular graft stenosis
Anastomotic stenosis
Vascular access site complication
Vascular graft occlusion

- Device/shunt thrombosis (FDA):

Thrombosis in device
Arteriovenous fistula thrombosis
Arteriovenous graft thrombosis
Vascular access site thrombosis
Vascular graft thrombosis
Graft thrombosis
Shunt thrombosis
Medical device site thrombosis
Device related thrombosis
Injection site thrombosis

- Seizure (FDA):

Epilepsy
Epileptic encephalopathy
Seizure
Generalised tonic-clonic seizure
Idiopathic partial epilepsy
Partial seizures
Tonic convulsion

- Stroke (FDA):

Cerebral infarction
Embolic cerebral infarction
Ischaemic stroke
Cerebellar infarction
Lacunar stroke
Embolic stroke
Brain stem stroke
Lacunar infarction

Cerebrovascular accident
Haemorrhagic stroke
Brain stem haemorrhage

- Sepsis/septic shock (FDA):

Device related sepsis
Enterococcal sepsis
Sepsis
Urosepsis
Streptococcal sepsis
Pseudomonal sepsis
Staphylococcal sepsis
Septic shock
Sepsis syndrome
Biliary sepsis
Bacterial sepsis
Fungal sepsis
Citrobacter sepsis
Listeria sepsis
Abdominal sepsis
Septic encephalopathy
Escherichia sepsis

18 References

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19 Proposed List of Summary Tables

Table Number	Table Title	Population
14.1.1	Subject Disposition	All Subjects
14.1.2.1	Analysis Population	Randomized Population
14.1.2.2	Clinical Study Report (CSR) Reportable Protocol Deviation	Randomized Population
14.1.3.1	Demographics	Randomized Population
14.1.3.2	Demographics	Safety Population
14.1.3.3	Demographics	Full Analysis Set Population
14.1.3.4	Demographics	Per Protocol Population
14.1.4.1	Baseline Characteristics	Randomized Population
14.1.4.2	Baseline Characteristics	Safety Population
14.1.4.3	Baseline Characteristics	Full Analysis Set Population
14.1.4.4	Baseline Characteristics	Per Protocol Population
14.1.5.1	Baseline Laboratory Measurements	Randomized Population
14.1.5.2	Baseline Laboratory Measurements	Safety Population
14.1.5.3	Baseline Laboratory Measurements	Full Analysis Set Population
14.1.5.4	Baseline Laboratory Measurements	Per Protocol Population
14.1.6.1	Etiology of CKD	Randomized Population
14.1.6.2.1	Medical History	Randomized Population
14.1.6.2.2	Other Medical History	Randomized Population
14.1.7.1	Prior Medications	Safety Population
14.1.7.2	Concomitant Medications	Safety Population
14.1.7.3	Prior ESA Medications	Safety Population
14.1.7.4	Concomitant ESA Medications	Safety Population
14.1.7.5.1	Concomitant Procedures	Safety Population
14.1.7.5.2	Concomitant Procedures - Transfusion	Safety Population
14.1.7.5.3	Concomitant Procedures - Phlebotomy	Safety Population

Table Number	Table Title	Population
14.1.7.6.1	Summary of COVID 19 Vaccines	Safety Population
14.1.7.6.2	Listing of COVID 19 Vaccines	Safety Population
14.1.8.1	Number of Subjects Taking Concomitant Anti-Hypertensive Medications	Safety Population
14.1.8.2	Number of Concomitant Anti-Hypertensive Medications Taken Per Subject	Safety Population
14.1.9.1.1	Study Treatment Compliance Rate by Study Period	Safety Population
14.1.9.1.2	Study Treatment Compliance Rate by Study Period	Full Analysis Set Population
14.1.9.2.1	Study Treatment Compliance Rate by Visit	Safety Population
14.1.9.2.2	Study Treatment Compliance Rate by Visit	Full Analysis Set Population
14.1.9.3.1	Average Weekly Dose of Study Treatment	Safety Population
14.1.9.3.2	Average Weekly Dose of Study Treatment	Full Analysis Set Population
14.1.9.3.3.1	Average Weekly Dose of Study Treatment by Baseline Hb Category	Safety Population
14.1.9.3.3.2	Average Weekly Dose of Study Treatment by Baseline ESA Type	Safety Population
14.1.9.3.3.3	Average Weekly Dose of Study Treatment by Baseline ESA Dose Group	Safety Population
14.1.9.4.1	Number of Subjects by Vadadustat Dose Level	Safety Population
14.1.9.4.2	Number of Subjects by Vadadustat Dose Level	Full Analysis Set Population
14.1.9.5.1	Summary of Maximum Increase in Dose Amount of Darbepoetin Alfa	Safety Population
14.1.9.5.2	Summary of Maximum Increase in Dose Amount of Darbepoetin Alfa	Full Analysis Set Population
14.1.9.6.1	Total Duration of Exposure (Week) to Study Treatment During the Study	Safety Population

Table Number	Table Title	Population
14.1.9.6.2	Total Duration of Exposure (Week) to Study Treatment During the Study	Full Analysis Set Population
14.1.9.7.1	Reason for Study Drug Change and Interruption	Safety Population
14.1.9.7.2	Reason for Study Drug Change and Interruption	Full Analysis Set Population
14.2.1.1	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 20-26 (ANCOVA with Multiple Imputations)	Randomized Population
14.2.1.2.1	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 20-26 (ANCOVA with Multiple Imputations)	Full Analysis Set Population
14.2.1.2.2	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 20-26 (ANCOVA with Multiple Imputations)	Per Protocol Population
14.2.1.2.3.1	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 20-26 (ANCOVA with Multiple Imputations of Data Affected by any Rescue - Narrow Therapy with ≥50% Increases in Darbepoetin Alfa Treatment)	Randomized Population
14.2.1.2.3.2	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 20-26 (ANCOVA with Multiple Imputations of Data Affected by any Rescue - Narrow Therapy with ≥100% Increases in Darbepoetin Alfa Treatment)	Randomized Population
14.2.1.2.4.1	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 20-26 (ANCOVA with Multiple Imputations of Data Affected by any Rescue - Broad-on-treatment Therapy with ≥50% Increases in Darbepoetin Alfa Treatment)	Randomized Population

Table Number	Table Title	Population
14.2.1.2.4.2	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 20-26 (ANCOVA with Multiple Imputations of Data Affected by any Rescue - Broad-on-treatment Therapy with ≥100% Increases in Darbepoetin Alfa Treatment)	Randomized Population
14.2.1.3	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 20-26 (MMRM)	Randomized Population
14.2.2.1	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 46-52 (ANCOVA with Multiple Imputations)	Randomized Population
14.2.2.2.1	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 46-52 (ANCOVA with Multiple Imputations)	Full Analysis Set Population
14.2.2.2.2	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 46-52 (ANCOVA with Multiple Imputations)	Per Protocol Population
14.2.2.2.3.1	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 46-52 (ANCOVA with Multiple Imputations of Data Affected by any Rescue - Narrow Therapy with ≥50% Increases in Darbepoetin Alfa Treatment)	Randomized Population
14.2.2.2.3.2	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 46-52 (ANCOVA with Multiple Imputations of Data Affected by any Rescue - Narrow Therapy with ≥100% Increases in Darbepoetin Alfa Treatment)	Randomized Population
14.2.2.2.4.1	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 46-52 (ANCOVA with Multiple Imputations of Data Affected by any Rescue - Broad-on-treatment	Randomized Population

Table Number	Table Title	Population
	Therapy with ≥50% Increases in Darbepoetin Alfa Treatment)	
14.2.2.2.4.2	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 46-52 (ANCOVA with Multiple Imputations of Data Affected by any Rescue - Broad-on-treatment Therapy with ≥100% Increases in Darbepoetin Alfa Treatment)	Randomized Population
14.2.2.3	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 46-52 (MMRM)	Randomized Population
14.2.3.1.1	Proportion of Subjects Having Average Hb Values within the Target Range during Primary Efficacy Period (Weeks 20 to 26)	Randomized Population
14.2.3.1.2	Proportion of Subjects Having Average Hb Values within the Target Range during Primary Efficacy Period (Weeks 20 to 26)	Full Analysis Set Population
14.2.3.2.1	Proportion of Subjects Having Average Hb Values within the Target Range during Secondary Efficacy Period (Weeks 46 to 52)	Randomized Population
14.2.3.2.2	Proportion of Subjects Having Average Hb Values within the Target Range during Secondary Efficacy Period (Weeks 46 to 52)	Full Analysis Set Population
14.2.4.1.1	Proportion of Subjects Receiving IV Iron Therapy by Baseline Iron Group	Randomized Population
14.2.4.1.2	Proportion of Subjects Receiving IV Iron Therapy by Baseline Iron Group	Full Analysis Set Population
14.2.4.2.1	Average Weekly Dose (mg) of IV Elemental Iron Administered in Subjects Who Have Received IV Elemental Iron	Randomized Population
14.2.4.2.2	Average Weekly Dose (mg) of IV Elemental Iron Administered in Subjects Who Have Received IV Elemental Iron	Full Analysis Set Population

Table Number	Table Title	Population
14.2.4.3.1.1	Proportion of Subjects with any ESA Rescue Medications - Narrow Therapy with ≥50% Increases in Darbepoetin Alfa Treatment	Randomized Population
14.2.4.3.1.2	Proportion of Subjects with any ESA Rescue Medications - Narrow Therapy with ≥50% Increases in Darbepoetin Alfa Treatment	Full Analysis Set Population
14.2.4.3.2.1	Proportion of Subjects with any ESA Rescue Medications - Narrow Therapy with ≥100% Increases in Darbepoetin Alfa Treatment	Randomized Population
14.2.4.3.2.2	Proportion of Subjects with any ESA Rescue Medications - Narrow Therapy with ≥100% Increases in Darbepoetin Alfa Treatment	Full Analysis Set Population
14.2.4.3.3.1	Proportion of Subjects with any ESA Rescue Medications - Broad-on-treatment Therapy with ≥50% Increases in Darbepoetin Alfa Treatment	Randomized Population
14.2.4.3.3.2	Proportion of Subjects with any ESA Rescue Medications - Broad-on-treatment Therapy ≥50% Increases in Darbepoetin Alfa Treatment	Full Analysis Set Population
14.2.4.3.4.1	Proportion of Subjects with any ESA Rescue Medications - Broad-on-treatment Therapy with ≥100% Increases in Darbepoetin Alfa Treatment	Randomized Population
14.2.4.3.4.2	Proportion of Subjects with any ESA Rescue Medications - Broad-on-treatment Therapy with ≥100% Increases in Darbepoetin Alfa Treatment	Full Analysis Set Population
14.2.4.4.1	Time to First ESA Rescue Medication - Narrow Therapy with ≥50% Increases in Darbepoetin Alfa Treatment	Randomized Population

Table Number	Table Title	Population
14.2.4.4.2	Time to First ESA Rescue Medication - Narrow Therapy with ≥100% Increases in Darbepoetin Alfa Treatment	Randomized Population
14.2.4.4.3	Time to First ESA Rescue Medication - Broad-on-treatment Therapy with ≥50% Increases in Darbepoetin Alfa Treatment	Randomized Population
14.2.4.4.4	Time to First ESA Rescue Medication - Broad-on-treatment Therapy with ≥100% Increases in Darbepoetin Alfa Treatment	Randomized Population
14.2.4.5.1.1	Proportion of Subjects Receiving any Red Blood Cell (RBC) Transfusions - Narrow Therapy	Randomized Population
14.2.4.5.1.2	Proportion of Subjects Receiving any Red Blood Cell (RBC) Transfusions - Narrow Therapy	Full Analysis Set Population
14.2.4.5.2.1	Proportion of Subjects Receiving any Red Blood Cell (RBC) Transfusions - Broad-on-treatment Therapy	Randomized Population
14.2.4.5.2.2	Proportion of Subjects Receiving any Red Blood Cell (RBC) Transfusions - Broad-on-treatment Therapy	Full Analysis Set Population
14.2.4.6.1	Time to First Red Blood Cell (RBC) Transfusion - Narrow Therapy	Randomized Population
14.2.4.6.2	Time to First Red Blood Cell (RBC) Transfusion - Broad-on-treatment Therapy	Randomized Population
14.2.4.7.1	Time to First ESA Rescue Medication or RBC Transfusion - Narrow Therapy with ≥50% Increases in Darbepoetin Alfa Treatment	Randomized Population
14.2.4.7.2	Time to First ESA Rescue Medication or RBC Transfusion - Narrow Therapy with ≥100% Increases in Darbepoetin Alfa Treatment	Randomized Population
14.2.4.7.3	Time to First ESA Rescue Medication or RBC Transfusion - Broad-on-treatment Therapy	Randomized Population

Table Number	Table Title	Population
	with ≥50% Increases in Darbepoetin Alfa Treatment	
14.2.4.7.4	Time to First ESA Rescue Medication or RBC Transfusion - Broad-on-treatment Therapy with ≥100% Increases in Darbepoetin Alfa Treatment	Randomized Population
14.2.5.1.1	Change from Baseline in SF-36v2 Health-related Quality of Life (HRQOL) Score	Randomized Population
14.2.5.1.2	Change from Baseline in SF-36v2 Health-related Quality of Life (HRQOL) Score	Full Analysis Set Population
14.2.5.2.1	Change from Baseline to the Average Value in FACT-An Anemia Subscale Score and Total Score	Randomized Population
14.2.5.2.2	Change from Baseline to the Average Value in FACT-An Anemia Subscale Score and Total Score	Full Analysis Set Population
14.2.5.3.1	Change from Baseline in Patient Global Impression of Severity (PGI-S)	Randomized Population
14.2.5.3.2	Change from Baseline in Patient Global Impression of Severity (PGI-S)	Full Analysis Set Population
14.2.5.4.1	Summary of Patient Global Impression of Change (PGI-C)	Randomized Population
14.2.5.4.2	Summary of Patient Global Impression of Change (PGI-C)	Full Analysis Set Population
14.2.6.1.1	Subgroup Analysis of Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 20-26 (ANCOVA with Multiple Imputations)	Randomized Population
14.2.6.1.2	Subgroup Analysis of Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 20-26 (ANCOVA with Multiple Imputations)	Full Analysis Set Population

Table Number	Table Title	Population
14.2.6.2.1	Subgroup Analysis of Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 46-52 (ANCOVA with Multiple Imputations)	Randomized Population
14.2.6.2.2	Subgroup Analysis of Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 46-52 (ANCOVA with Multiple Imputations)	Full Analysis Set Population
14.3.1.1	Overall Summary of Adverse Events	Safety Population
14.3.1.2.1	Treatment-Emergent Adverse Events	Safety Population
14.3.1.2.2	Treatment-Emergent Adverse Events by Severity	Safety Population
14.3.1.2.3	Drug-Related Treatment-Emergent Adverse Events	Safety Population
14.3.1.3.1	Serious Treatment-Emergent Adverse Events	Safety Population
14.3.1.3.2	Drug-Related Serious Treatment-Emergent Adverse Events	Safety Population
14.3.1.4.1	Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation	Safety Population
14.3.1.4.2	Drug-Related Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation	Safety Population
14.3.1.5	Treatment-Emergent Adverse Events Resulting in Death	Safety Population
14.3.1.6.1	Treatment-Emergent Adverse Events Reported at least 5% of Subjects in Any Treatment Groups	Safety Population
14.3.1.6.2	Non-Serious Treatment-Emergent Adverse Events Reported at least 5% of Subjects in Any Treatment Groups	Safety Population
14.3.1.7	Treatment-Emergent Adverse Events of Special Interest	Safety Population

Table Number	Table Title	Population
14.3.1.8	Adjudicated Safety Events	Safety Population
14.3.2.1	Listing of Serious Adverse Events	Safety Population
14.3.2.2	Listing of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation	Safety Population
14.3.2.3	Listing of Treatment-Emergent Adverse Events Resulting in Death	Safety Population
14.3.2.4	Listing of All Deaths	Safety Population
14.3.2.5	Listing of Treatment-Emergent Adverse Events for Subjects Who Discontinued from Study Due to Withdrawal of Consent	Safety Population
14.3.2.6.1	Listing of Reported Safety Events	Safety Population
14.3.2.6.2	Listing of Adjudicated Safety Events	Safety Population
14.3.2.7.1	COVID 19 Related Adverse Events	Safety Population
14.3.2.7.2	Listing of COVID 19 Related Adverse Events	Safety Population
14.3.5.1.1.1	Change from Baseline in Laboratory Test Results by Visit -- Complete Blood Count (Conventional Unit)	Safety Population
14.3.5.1.1.2	Change from Baseline in Laboratory Test Results by Visit -- Complete Blood Count (SI Unit)	Safety Population
14.3.5.1.2.1	Percent Change from Baseline in Laboratory Test Results by Visit -- Complete Blood Count (Conventional Unit)	Safety Population
14.3.5.1.2.2	Percent Change from Baseline in Laboratory Test Results by Visit -- Complete Blood Count (SI Unit)	Safety Population
14.3.5.2.1.1	Change from Baseline in Laboratory Test Results by Visit -- Chemistry (Conventional Unit)	Safety Population

Table Number	Table Title	Population
14.3.5.2.1.2	Change from Baseline in Laboratory Test Results by Visit -- Chemistry (SI Unit)	Safety Population
14.3.5.2.2.1	Percent Change from Baseline in Laboratory Test Results by Visit -- Chemistry (Conventional Unit)	Safety Population
14.3.5.2.2.2	Percent Change from Baseline in Laboratory Test Results by Visit -- Chemistry (SI Unit)	Safety Population
14.3.5.3.1.1	Change from Baseline in Laboratory Test Results by Visit -- Liver Function Tests (Conventional Unit)	Safety Population
14.3.5.3.1.2	Change from Baseline in Laboratory Test Results by Visit -- Liver Function Tests (SI Unit)	Safety Population
14.3.5.3.2.1	Percent Change from Baseline in Laboratory Test Results by Visit -- Liver Function Tests (Conventional Unit)	Safety Population
14.3.5.3.2.2	Percent Change from Baseline in Laboratory Test Results by Visit -- Liver Function Tests (SI Unit)	Safety Population
14.3.5.4.1.1	Change from Baseline in Laboratory Test Results by Visit -- Iron indices (Conventional Unit)	Safety Population
14.3.5.4.1.2	Change from Baseline in Laboratory Test Results by Visit -- Iron indices (SI Unit)	Safety Population
14.3.5.4.2.1	Percent Change from Baseline in Laboratory Test Results by Visit -- Iron indices (Conventional Unit)	Safety Population
14.3.5.4.2.2	Percent Change from Baseline in Laboratory Test Results by Visit -- Iron indices (SI Unit)	Safety Population
14.3.5.5.1.1	Change from Baseline in Laboratory Test Results by Visit -- Lipids (Conventional Unit)	Safety Population

Table Number	Table Title	Population
14.3.5.5.1.2	Change from Baseline in Laboratory Test Results by Visit -- Lipids (SI Unit)	Safety Population
14.3.5.5.2.1	Percent Change from Baseline in Laboratory Test Results by Visit -- Lipids (Conventional Unit)	Safety Population
14.3.5.5.2.2	Percent Change from Baseline in Laboratory Test Results by Visit -- Lipids (SI Unit)	Safety Population
14.3.5.6.1.1	Change from Baseline in Laboratory Test Results by Visit -- C-reactive protein, Vascular Endothelial Growth Factor and Hepcidin (Conventional Unit)	Safety Population
14.3.5.6.1.2	Change from Baseline in Laboratory Test Results by Visit -- C-reactive protein, Vascular Endothelial Growth Factor and Hepcidin (SI Unit)	Safety Population
14.3.5.6.2.1	Percent Change from Baseline in Laboratory Test Results by Visit -- C-reactive protein, Vascular Endothelial Growth Factor and Hepcidin (Conventional Unit)	Safety Population
14.3.5.6.2.2	Percent Change from Baseline in Laboratory Test Results by Visit -- C-reactive protein, Vascular Endothelial Growth Factor and Hepcidin (SI Unit)	Safety Population
14.3.5.7.1	Change from Baseline in Laboratory Test Results by Visit -- Erythropoietin and Reticulocytes (Conventional Unit)	Safety Population
14.3.5.7.2	Change from Baseline in Laboratory Test Results by Visit -- Erythropoietin and Reticulocytes (SI Unit)	Safety Population
14.3.5.8.1	Cumulative Number (%) of Subjects with Abnormal Laboratory Test Results -- Potential Liver Injury	Safety Population

Table Number	Table Title	Population
14.3.5.8.2	Number (%) of Subjects with Abnormal Laboratory Test Results -- Liver Function and Potassium	Safety Population
14.3.5.9	Hemoglobin (Hb)-Related Safety Endpoints	Safety Population
14.3.6.1	Change from Baseline in Vital Signs and Body Weight by Visit	Safety Population
14.3.6.2	Number (%) of Subjects with Abnormal Findings in Vital Signs	Safety Population
14.3.7.1	Change from Baseline in ECG by Visit	Safety Population
14.3.7.2	Number (%) of Subjects with Abnormal Findings in ECG	Safety Population
14.3.8.1	Summary of Dialysis History and Details	Safety Population
14.3.8.2	Summary of Dialysis Adequacy	Safety Population
14.3.9	Summary of Special Situations	Safety Population

Listing Number	Listing Title	Population
16.2.1.1	Informed Consent	Randomized Population
16.2.1.2	Subject Disposition	Randomized Population
16.2.2	Protocol Deviations	Randomized Population
16.2.3.1	Subject Randomization	Randomized Population
16.2.3.2	Analysis Sets	Randomized Population
16.2.3.3	Subjects not Meet Inclusion/Exclusion Criteria	Randomized Population
16.2.4.1	Demography	Randomized Population
16.2.4.2	Etiology of CKD	Randomized Population
16.2.4.3.1	Medical History	Randomized Population
16.2.4.3.2	Other Medical History	Randomized Population
16.2.4.4	Iron Therapy and RBC Transfusion History	Randomized Population

Listing Number	Listing Title	Population
16.2.4.5	Prior and Concomitant Medications	Randomized Population
16.2.4.6.1	Prior ESA Administration	Randomized Population
16.2.4.6.2	ESA Administration	Randomized Population
16.2.4.7	Iron Supplementation	Randomized Population
16.2.4.8	Red Blood Cell (RBC) Transfusion	Randomized Population
16.2.4.9	Concomitant Procedures	Randomized Population
16.2.5.1	Study Drug Administration	Randomized Population
16.2.5.2	Subject Compliance	Randomized Population
16.2.5.3	Pharmacokinetic Plasma Concentrations	Pharmacokinetic Population
16.2.6.1	Change from Baseline in Hemoglobin (Hb, g/dL) to the Average Value in an Analysis Period	Randomized Population
16.2.6.2	Average Weekly Dose of IV Elemental Iron by Baseline Iron Group	Randomized Population
16.2.6.3	36-Item Short Form Version 2 (SF-36v2) Health-Related Quality of Life (HRQOL) Score	Randomized Population
16.2.6.4	Functional Assessment of Cancer Therapy-Anemia (FACT-An) Score	Randomized Population
16.2.6.5	Patient Global Impression of Severity (PGI-S)	Randomized Population
16.2.6.6	Patient Global Impression of Change (PGI-C)	Randomized Population
16.2.7	Adverse Events	Randomized Population
16.2.8.1.1	Laboratory Test Results -- Complete Blood Count	Randomized Population
16.2.8.1.2	Laboratory Test Results -- Chemistry	Randomized Population
16.2.8.1.3	Laboratory Test Results -- Liver Function Tests	Randomized Population
16.2.8.1.4	Laboratory Test Results -- Iron Indices	Randomized Population
16.2.8.1.5	Laboratory Test Results -- Lipids	Randomized Population

Listing Number	Listing Title	Population
16.2.8.1.6	Laboratory Test Results – Erythropoietin and Reticulocytes	Randomized Population
16.2.8.1.7	Laboratory Test Results -- Other Labs	Randomized Population
16.2.8.2	Physical Examination	Randomized Population
16.2.8.3	Vital Signs	Randomized Population
16.2.8.4	12-Lead Electrocardiogram	Randomized Population
16.2.8.5.1	Pregnancy Test	Randomized Population
16.2.8.5.2	Pregnancy Report	Randomized Population
16.2.8.6.1	Dialysis History	Randomized Population
16.2.8.6.2	Dialysis Details	Randomized Population
16.2.8.6.3	Dialysis Adequacy	Randomized Population
16.2.8.7	Special Situations	Randomized Population
16.2.8.8	Lost to Follow-up Status	Randomized Population
16.2.8.9	Screening Failures	Screening Failure Subjects

20 Revision Changes

The purpose of this SAP revision is to align with the Protocol Amendment 1 and to make clarifying changes. The description of changes is documented below.

Location	Description of Changes
Header	Corrected the protocol number.
Abbreviation	Added abbreviations.
Section 1 (Introduction)	Clarified that SAP documents the pre-planned statistical analyses plan of CSR.
Section 2.1 (Randomization and Stratification)	Added “approximately 90 subjects in Europe”.
Section 2.2 (Study Periods)	Changed “trial medication” to “investigational medicinal product (IMP)”.

Section 2.5 (Blinding)	Clarified that the group of unblinded biostatisticians and programmers are external/internal independent.
Section 2.6 (Sample Size)	Clarified that the sample size calculation between vadadustat QD and darbepoetin alfa is the same as the one between vadadustat TIW and darbepoetin alfa.
Section 2.7 (Efficacy)	Clarified the treatment groups in treatment comparison.
Section 4.1 (Study Drug Dosing and Compliance)	Clarified the dosing compliance. Moved sentences related to dosing from Section 4.3 to 4.1.
Section 4.2 (Protocol Deviations)	Clarified the protocol deviation listing and summary.
Section 4.3 (Baseline Characteristics, Exposure, and Retention by Treatment Group)	Moved sentences related to dosing from Section 4.3 to 4.1.
Section 5.1 (Visit and Analysis Time Period Classification)	Changed the relative date of visit windows from "Randomization date" to "first dose date". Added a footnote of "[a] If patient has no first dose date, day 1 will be the randomization date" for "Day 1 (first dose date)" at Table 1.
Section 5.2 (Definition of Baseline) Section 5.3 (Prior and Concomitant Medication)	Changed "trial medication" to "IMP".
Section 6.3 (Other Efficacy Endpoints)	Changed "average monthly dose of IV elemental iron" to "average weekly dose of IV elemental iron".
Section 6.4 (Rescue Therapy)	Changed the reason of narrow rescue therapy for all treatment arms to "Hb <9.5 g/dL" only. Added "For darbepoetin alfa arm, darbepoetin alfa with increases in dose ≥50% or ≥100%." in narrow and broad-on-treatment rescue therapies. Remove "phlebotomy" from broad-on-treatment rescue. Changed the category of darbepoetin alfa with increases in dose to <50%, ≥50% and <100%, and ≥100%, and removed "recorded in eCRF".

	Added time to first ESA medication and RBC transfusion analyses.
Section 7 (Safety Endpoints)	Clarified that safety endpoints will be summarized by treatment groups. Removed "Major Adverse Cardiovascular Event (MACE)".
Section 9.1 (Primary Estimand)	Added a section of primary estimand.
Section 9.2.1 (Baseline Hb)	Clarified the calculation of baseline Hb value.
Section 9.2.4 (Analysis of Change from Baseline in Hb to the Primary Efficacy Period)	Clarified intercurrent event data handling. [redacted] Clarified the 100 imputed complete datasets will be used not only for primary efficacy analysis, but also secondary efficacy analysis and other efficacy analysis. Added "ESTIMATE" and "STDERR" for estimate and standard error, respectively.
Section 9.2.5 (Sensitivity Analyses to the Primary Efficacy Results)	[redacted] Changed the FAS population to randomized population for mixed model for repeated measures (MMRM).
Section 9.4 (Other Efficacy Endpoints: Strategies for Analysis)	Clarified the analysis population used for other efficacy endpoints.
Section 9.4.1 (Proportion of Subjects Having Average Hb Values within the Target Range during the PEP (Weeks 20 to 26))	Added "when tested per the testing procedure (Section 9.5)". Clarified that Mantel-Haenszel method will be used for estimation of risk difference.
Section 9.4.3 (Proportion of Subjects Receiving IV Iron Therapy from Baseline to Week 52)	Clarified that Mantel-Haenszel method will be used for estimation of risk difference. Reduced the performed subgroups.
Section 9.4.4 (Average Weekly Dose of IV Elemental Iron Administered from Baseline to Week 52)	Removed the subgroup analyses. Removed the large spike at zero for the distribution of average weekly dose of IV elemental iron administered in subjects who have received IV elemental iron.

Section 9.4.5 (Receipt of ESA Rescue)	Clarified that ESA rescue medications include narrow or broad-on-treatment therapies with ≥50% or ≥100% dose increase in darbepoetin alfa. Clarified that Mantel-Haenszel method will be used for estimation of risk difference. Added time to first ESA rescue analyses.
Section 9.4.6 (Proportion of Subjects Receiving Red Blood Cell (RBC) Transfusions)	Clarified that RBC transfusions include narrow or broad-on-treatment. Clarified that Mantel-Haenszel method will be used for estimation of risk difference. Added time to first RBC transfusion analyses.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Section 9.5 (Study Level Type I Error Control)	Added a section of study level type I error control.

Section 10.2 (Hb-related Safety Endpoints)	Clarified that calculation of number and proportion of subjects in Hb-related safety endpoints.
Section 10.3 (Adverse Events and Serious Adverse Events)	Clarified that AE will be coded by SOC and PT, and MedDRA version will be shown in AE outputs. Clarified the definition of TEAE. Added AE, SAE and all death in the summary table. Removed the AE summary order statement. Clarified the most conservative causality AE assessment will be used in the by-causality summaries. Changed TEAE listing to AE listing and added a flag of TEAE in AE listing.
Section 10.4 (Major Adverse Cardiovascular Event)	Added “excluding vascular access thrombosis” to the “thromboembolic event”. Removed “by SOC and PT” from the summary of adjudicated safety events. Remove time to the first occurrence of MACE analyses.
Section 10.5.1 (Clinical Laboratory Evaluation)	Removed “by analysis period” from the summary of liver function abnormalities. Changed “versions of Hy’s Law” to “laboratory values fulfilling potential liver injury criteria”. Removed summary and shift from baseline of abnormal laboratory values in CTCAE grade. Removed summary of additional laboratory parameters listed in Appendix, and removed the corresponding Appendix.
Section 10.5.2 (Vital Signs, ECGs, and Physical Findings)	Clarified the calculation of percentage of subjects experiencing findings. Added “QTc interval” criteria. Removed “at baseline” from the ECG summary. Removed summary of potential clinical relevance listed in Appendix, and removed the corresponding Appendix.
Section 11 (Subgroups)	Combined the “Black” and “Other” in race to “Black or Other”.

	Added subgroup analyses of baseline Hb. Removed subgroup analyses of medical history of diabetes mellitus, hypertension and NYHA class, and baseline value of ESA dose, C-reactive protein, TSAT and ferritin. Clarified that subgroup analyses will be performed only if the total number of outcomes is at least 30. Remove subgroup analyses of AE and time to the first occurrence of MACE analyses.
Section 12 (Other Exploratory Analyses)	Clarified that exit interview data will be reported separately.
Section 13 (Interim Analysis)	Clarified that no interim analysis will be conducted, and no analyses of the primary efficacy endpoint will be conducted when all randomized subjects complete their Week 26 evaluations.
Section 14 (Description of Variables Used in SAS Codes)	Updated the description.
Section 15 (Random Seed Assignment)	Added a section to describe the assigned random seeds.
Section 17 (Adverse Event of Special Interest)	Removed thrombotic events SMQ. Added FDA key query adverse event preferred terms.
Original Appendix (Criteria for Identifying Measurements of Potential Clinical Relevance)	Removed.
Section 18 (References)	Updated the references.
Section 19 (Proposed List of Summary Tables)	Updated the list of summary tables and listings.
Section 20 (Revision Changes)	Added a section of revision changes.

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