AstraZeneca

Clinical Study Protocol

Drug Substance	Roxadustat
Study Code	D5740C00001
Version	6.0
Date	31 August 2018

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis

Sponsor: AstraZeneca AB, S-151 85 Södertälje, Sweden

VERSION HISTORY

Clinical Study Protocol version 6.0 (current version)

Rationale for protocol amendment:

A primary efficacy objective has been added, with specification of accompanying variables and analyses, in order to harmonize D5740C00001 with the other phase 3 trials in the roxadustat CKD non-dialysis program (FG-4592-060 and 1517-CL-0608). This will allow D5740C00001 to serve as a pivotal study to support both efficacy and safety of roxadustat for the treatment of CKD anemia. Furthermore, additional secondary efficacy objectives, with specification of accompanying variables and analyses, have been added and the corresponding ordering of secondary endpoints has been updated.

Adjudicated CV events from this study will be part of the pooled analysis across the study program. This strategy was adopted to ensure that the overall number of events is high enough to provide adequate power to address CV No harm. Thus, all analyses of CV safety will be conducted in accordance with the Pooled SAP (PSAP), and will not be reported in the individual CSR. However, all these analyses of adjudicated CV events will be made by individual study and then pooled and analyzed, as described in the PSAP, adopting meta-analysis techniques. Hence, all analyses of CV safety for this study will be reported in conjunction with the pooled analyses. Consequently, these analyses will not be duplicated separately for this individual study.

Summary of changes from Revised Clinical Study Protocol Edition 1.0 (Version 5.0), 21 December 2015 to version 6.0:

All below changes are updated in relevant sections of the study protocol.

Throughout the document:
Hematopoiesis changed to erythropoiesis.
Rationale:
Clarification.

Synopsis and section 2.1. Primary Objectives
Here are the changes as follows:

1. Previous primary objective is now specified as primary safety objective.
2. Primary efficacy objective and its two outcome measures, one for US FDA and one for EU health authority, are added.
3. The previous texts on primary objective are moved to the section on primary safety objective. New texts stating that pooled CV safety analyses are now described in the PSAP.

Rationale:
Harmonizes D5740C00001 with the other phase 3 trials in the roxadustat CKD non-dialysis program, to serve as a pivotal study for confirming efficacy and safety, and facilitates assessement of pooled efficacy and safety across the phase 3 trials.

Synopsis and section 2.2. Secondary objectives
Here are the changes as follows:

1. The secondary objectives are split into the secondary efficacy and secondary safety objectives.
2. The two previous CV-related secondary objectives (MACE+ and CSE) are removed as all analyses of CV safety will be conducted in accordance with the Pooled SAP (PSAP), and will not be done for the individual CSRs.
3. The previous secondary objective with its outcome measures related to anaemia symptoms using FACT-An is removed.
4. The previous secondary objective with its outcome measures related to self-reported health status using EQ-5D-5L and PGIC is removed.
5. "Proportion of total time of Hb ≥ 10 g/dL from week 28 to week 52", is added for the secondary efficacy objective based on Hb response and level during the study.
6. The time-frame to evaluate the proportion of total time of Hb measurements within the interval of 11±1 g/dL is changed from "from week 28 until end of treatment visit" to "from Week 28 to week 52".
7. The efficacy of roxadustat based on the change from baseline in Hb averaged over Week 28-52 in inflamed subjects is added as a secondary efficacy objective.
8. The previous rescue therapy related secondary objective is moved to the secondary efficacy objective together with its corresponding composite outcome measures, including IV, RBC or ESA as rescue therapy. Also, additional outcome measure, including RBC only as rescue therapy, is added to this secondary objective. Proportion and number of subjects receiving rescue therapy (composite or RBC only) are aslo reported.
9. The previous health-related quality of life related secondary objective is moved to the secondary efficacy objective together with its outcome measure.
10. The previous secondary objective related to CKD progression is moved to the secondary efficacy objective. Its outcome measure is the annual rate of eGFR change in log scale, calculated as the linear slope of log (eGFR values) to prior to initiation of dialysis/kidney transplant
11. The secondary efficacy objectives with its outcome measure related to LDL cholesterol is added.

Rationale for change:
To harmonize with the secondary objectives of the other phase 3 studies in the program.

Synopsis, Study Period and Treatment Period
Expansion of the study duration. Enrollment is anticipated to occur over approximately a 3 year period followed by an additional 1-2 year treatment period.
Rationale:
Study duration prolonged to observe requisite number of patients with adjudicated CV endpoint events in the phase 3 study program.

Synopsis, Sample Size Determination and 8.2 Sample Size estimate

The sample size determination has been revised, allowing now also for primary efficacy objective.
Rationale for change:
Harmonization with the strategy for the analyses of efficacy and CV safety for the study program as described in the PSAP.

Synopsis and 9.3 Study timetable and end of study
Extension of study in Q3 2018.
Rationale:
The study end date has been changed to reflect a common study end date across the phase 3 trials when the requisite number of patients with adjudicated CV endpoints is anticipated.

Section 1.4.1 Treatment duration and dosing and 4.2 Treatment period
Removal of the statement, "Treatment duration is expected to vary between 1 and 2 years.
Rationale:
Some patients will be treated for up to 4 years.

Section 1.4.4 Visits
Change from "During the treatment period, patients will be contacted by telephone at week 1, and will attend study visits every two weeks from week 2 to 20." To "During the treatment period, patients will be contacted by telephone at week 1, and will attend study visits every two weeks from weeks 0 to 20."
Rationale: Clarification.

Section 3.9.1 Temporary discontinuation from investigational product
Added statement clarifying that study drug should be withheld for subjects receiving erythropoietin analogue rescue therapy.
Rationale: Clarification

Section 3.9.2 Permanent discontinuation from investigational product
Added the following:

- *Patients who have received two courses of erythropoietin analogue rescue therapy, and for whom there is a need for a third course of rescue with erythropoietin analogue*
- *For patients initiating dialysis during the study; and for whom there is a need for rescue with erythropoietin analogue*

Rationale:
Clarification to make this section of the protocol consistent with section 7.7.4.3 which states that the above are reasons for permanent discontinuation from investigational product.

Section 3.9.3 Procedures for discontinuation of a patient from investigational product
Added statements clarifying that subjects who are permanently discontinued from study drug prior to study closure, should be followed until study closure; and that subjects who permanenty discontinue study drug prior to study closure may be followed via modified

follow-up schedules.
Rationale: Clarification

Section 3.9.3.2 Patient refuses to continue in-person study visits but agrees to undergo modified follow-up
Entire section clarified and elaborated.
Rationale: Clarification.

Section 3.9.3.3 Patient refuses any form of follow-up
Entire section clarified and elaborated.
Rationale: Clarification.

Section 3.10: Criteria for withdrawal
Entire section clarified and elaborated.
Rationale: Clarification.

Section 3.10.2: Withdrawal of the informed consent
Added: "Patients who agree to continued study participation following investigational product discontinuation, including modified follow-up such as telephone calls or medical record review, have not withdrawn consent."
Rationale: Clarification

Section 3.11 Discontinuation of the study and Section 4 Study Plan and timing of procedures
"The independent DSMB will monitor the study to ensure patient safety" moved from section 4 to section 3.11.
Rationale:
To improve clarity.

Table 1 Study Plan
Randomization visit footnote removed.
Rationale:
Error correction.

Table 1 Laboratory Values table from Section 5.2, and Section 5.7.1
Added that hepcidin and hsCRP will be analyzed from biomarker samples
Rationale: To enable evaluation of hepcidin and hsCRP in the clinical program.

Section 4.1.2: Additional screening assessments
Deleted the following text, "unless the Investigator has a valid reason to believe that the original lab result is due to an error e.g. possible sample mix up). Such repeat should be communicated to the AstraZeneca study physician as soon as possible."
Rationale: Clarification

Section 5.1.1 Secondary efficacy assessments

The title of this section is changed to "Efficacy assessment".
Rationale:
Assement of Hemoglobin level specified in 5.1.1.1 is for both the primary and some of the secondary efficacy endpoints.

Section 5.1.1.2: **Use of rescue therapy**
Changed "Use of rescue medications" to "Use of rescue therapy"
Rationale: Section refers to rescue medications as well as red blood cell transfusion

Section 5.2.1: Cardiovascular events
The texts in this section are simplified, the function of IERC is emphasized and the subsections 5.2.1.1 to 5.2.1.9 are removed.
Rationale:
IERC contains more detail information on CV event adjudication.

Section 5.7.3: Chain of custody of biological samples
Added the following statement: "Samples retained for future use are registered within the relevant sample tracking system at AstraZeneca."

Section 5.7.4 Samples retained for future use are registered within the relevant sample tracking system at AstraZeneca. Withdrawal of informed consent for donated biological samples
Insertion of "However, this does not result in withdrawal of the patient from the study and patient should continue until the end of study".
Removal of "As collection of the biological samples is an optional part of the study, then the patient may continue in the study."
Rationale:
Clarification.

Section 6.1 Definition of adverse event
Addition of the following language defining Treatment Emergent Adverse Event:
"An AE (classified by preferred term) that occurs during the double-blind treatment period will be considered a TEAE (Treatment Emergent Adverse Event) if it was not present prior to the first dose of study drug, or it was present prior to the first dose of study drug but increased in severity during the double-blind treatment period. An AE that occurs more than 28 days after the last dose of study medication will not be counted as a TEAE."
Rationale:
Need for definition of TEAE (treatment emergent AE).

Section 6.3.1 Time period for collection of adverse events
Reference to section 3.9.3.2 added.
Rationale:
Clarification.

Section 6.3.8 Disease progression

Section reworded, to clarify that both worsening of anemia and CKD progression should be considered disease progression and not AEs. Also, added the following text at the end of the section: "Acute kidney injury, when meeting diagnostic criteria (i.e. based on serum creatinine values or urine output), can be considered an AE or SAE. AEs or SAEs that cause anemia should be recorded, but anemia for which no cause is found other than CKD should not be reported as an AE or SAE."
Rationale:
Clarification to disease progression and AE reporting.

Section 6.3.9 Patients initiating dialysis during the treatment period
Section reworded. Addition of protocol specific reasons. Removal of dose adjustment wording.
Rationale:
Clarification to be more specific.

Section 7.2.5 Patients initiating dialysis during the treatment period
Section reworded. Addition of protocol specific reasons. Removal of dose adjustment wording.
Rationale:
Clarification of language.

Section 7.7.4.3 Initiation of Rescue with an approved erythropoietin analogue
Deleted "For patients initiating dialysis, study drug should be permanently discontinued." and added, "Study drug should be permanently discontinued for subjects who initiate dialysis and who are clinically judged to require erythropoietin analogue therapy."
Rationale: Clarification

Statistical methods and Statistical analyses
Change to outcome measures and the evaluation of the data.
Rationale:
Harmonization of D5740C00001 with the other phase 3 trials in the roxadustat non-dialysis program.

Section 8.1 Statistical considerations

Change that preparation of a comprehensive SAP will take place before database lock, instead of before the first randomization.

Rationale: To align with the timing for SAP finalization in the other phase 3 trials.

Section 8.3.1 Full Analysis Set (FAS)
Here are the changes as follows:

1. This analysis set was previously termed as Full Analysis Set (FAS), this is now changed to Intention To Treat Analysis Set (ITT).
2. The word "patients" is changed to "subjects". This change is also for the rest of the section 8 where applicable.

3. Texts are updated to clarify how the event of interest will be counted in respect of study drug discontinuation according to ITT principle.

Rationale for change:
To align with the definitions adopted in the other phase 3 trials in the study program.

Section 8.3.2. Per Protocol Set (PPS)
Here are the changes as follows:

1. An additional criterion, "subjects receiving at least 8 weeks of study treatment", has been added.
2. Censoring rule for subjects with an important protocol deviation is clarified.
3. Treatment groups to which PPS subjects belong to is specified.

Rationale for change:
To align with the definitions adopted in the other phase 3 trials in the study program, and for clarification

Section 8.3.3 Safety Analysis Set (SAS)
Here are the changes as follows:

1. Treatment groups to which SAS subjects belong is further clarified.
2. The Censoring rule for SAS subjects is specified.

Rationale for change:
For clarification

Section 8.3.4 Full Analysis Set (FAS)
This section is newly added allowing for an additional analysis set.
Rationale for change:
To align with the definitions adopted in the other phase 3 trials in the study program, this analysis set will be required for some Ex-US submissions.

Section 8.3.5 Subjects who will not be included in any analysis sets
This section is newly added to specify subjects not in any of analysis sets and the reason of their exclusion is stated.
Rationale for change:
Not included in previous editions of the CSP.

Section 8.4 Outcome measures for analyses

Here are the changes as follows:

1. Texts under "primary endpoint" and "Additional safety composite endpoints" are replaced by new texts and moved under a new section, 8.5, entitled "Adjudicated composite safety endpoint events"

2. A subsection, 8.4.1, specific to the primary efficacy endpoint with two outcome measures, one for US and one for EU health authorities, is added.

3. Texts under "Secondary points" are re-structured with the following changes:

    a. "Efficacy related endpoints" are re-structured into five new subsections, 8.4.2-8.4.6, one related to Hb, one to lipid, one to rescue therapy, one to health-related quality of life by SF-36 (Version 2, standard) and one to CKD progression, each with corresponding outcome measures specified.
    b. "Mean change in Hb from baseline to the end of treatment period (EOT), utilizing all Hb values from week 28 until the EOT", is moved under the primary efficacy endpoint for US FDA, and its timeframe is changed from "Week 28 to EOT" to "Week 28 to Week 52". The missing value imputation is changed from MMRM to MI ANCOVA with its details in SAP.
    c. EU primary endpoint is added as a secondary endpoint for the analysis for FDA.
    d. Mean change in Hb from baseline to the subjects mean level between week 28 to week 52 in subjects with baseline high-sensitivity C-reactive protein (hsCRP) greater than the Upper Limit Normal (ULN) is added as Hb related secondary efficacy endpoint
    e. Proportion of total time of Hb ≥ 10 g/dL from week 28 to week 52 is added as Hb related secondary efficacy endpoint.
    f. "Proportion of total time of Hb measurements within the interval of 10-12 g/dL from week 28 until end of treatment visit", is moved under the Section 8.4.2, and its timeframe is changed from "Week 28 until end of treatment visit" to "Week 28 to Week 52".
    g. "Endpoints related to HRQoL and health status" except the one related to health-related quality of life by SF-36 (Version 2, standard) under Section 8.4.5, are moved from secondary endpoint to exploratory endpoint.
    h. "Evaluation of the need for rescue therapy" related to IV iron is removed. The other two points are moved under the section 8.4.4, with more details specified.

Rationale for change:
For structure clarification and to harmonize with the other phase III studies in the program.

Section 8.5 Methods for statistical analyses
The section number is changed from 8.5 to 8.6, and all its subsection numbers are changed from 8.5.X to 8.6.X.
Rationale for change: For clarification, a new section, entitled "Adjudicated CV Events Analyses for Safety Assessments", is added as Section 8.5.

Change that finalization of the SAP will take place before database lock instead of the first subject in, which includes further details of the statistical analyses.
Rationale for change: To align with the timing for SAP finalization in the other phase 3 trials.

Section 8.5.1 Stratification variables

Here are the changes as follows:

1. The section number is changed to 8.6.1.
2. Baseline Hb is added to the list of "stratification variables".
3. How to handle baseline Hb in the analysis is specified.
4. CV history is defined in more details.

Rationale for change:

To be in agreement with the other studies in the program

Section 8.5.2. Analysis of the primary variable

Here are the changes as follows:

1. This section is split into two sections, 8.6.2 and 8.6.3, entitled "Analysis of primary efficacy endpoint for US" and "Analysis of primary efficacy endpoint for EU", respectively.
2. New texts on the analysis of the primary efficacy endpoint for US and EU are added.
3. Previous texts in this section are removed.

Rationale for change:

To be in agreement with the other studies in the program

Section 8.5.3 Analysis of the secondary variables

Here are the changes as follows:

1. The section number is changed to 8.6.4.
2. The title of this section is changed to "CV safety endpoint analyses".
3. New texts on CV safety endpoint analyses according to the PSAP using adjudicated pooled data across the study program are added.
4. Previous texts in this section are moved to the Section 8.6.5 with changes specified below.

Rationale for change:

Strategic change in the approach to address CV safety for the project.

Section 8.5.4 Additional Secondary Analyses

Here are the changes as follow:

1. The section number is changed to 8.6.5.
2. The title of this section is changed to "Analysis of the secondary efficacy endpoints".
3. Previous texts in this section are removed.
4. Previous texts in Section 8.5.3 were moved to this section with the following changes:
   a. ITT analysis date set is used for all the secondary efficacy endpoints except for the first secondary efficacy endpoint and the two rescue related endpoints.
   b. The secondary efficacy endpoint related to mean change in Hb from baseline to average Hb from week 28 until EOT is removed.

c. Time-to-event analyses including time-to-first MACE+ and time-to-first CSE are referred to the PSAP.
d. IV iron use is now an exploratory, rather than a secondary, efficacy endpoint (see SAP).
e. The erythropoietin analogues use as rescue therapy is now an exploratory, rather than a secondary, efficacy endpoint (see SAP).
f. The EU primary endpoint is added as a secondary endpoint for the analysis for FDA
g. The time-frame of the secondary efficacy endpoint related to the proportion of total time of Hb within the interval of 10-12 g/dL is changed, from "week 28 to EOT" to "week 28 to week 52".
h. The secondary efficacy endpoint related to FACT-An is moved to exploratory analyses (see SAP).
i. The secondary efficacy endpoints related to EQ-5D-5L and PGIC are moved to exploratory analyses (see SAP).
j. The secondary efficacy endpoint related to SF-36 is split into two secondary efficacy endpoints.
k. FAS will not be used for the secondary efficacy endpoint related to composite and RBC-only rescue therapy. Instead, the OT+28 censoring rule will be used.

5. Additional secondary efficacy endpoints are added, two related to Hb-response, one to LDL cholesterol, and one to CKD progression.
6. The list of the secondary endpoints is re-ordered.

Rationale for change:
To harmonize with the secondary efficacy endpoints of the other phase III studies in the program.

Section 8.5.5 Testing order
This section is removed.
Rationale for change:
To avoid repeating the related texts specified in "Analysis of the secondary efficacy endpoints".

Section 8.5.9 Exploratory analysis
The section number is changed to 8.6.9 and the previous texts in this section are changed to indicate that the analysis details are specified in SAP.
Rationale for change:
For clarificaction

Appendix E - National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
Removed and replaced by a reference to the document.

Revised Clinical Study Protocol Edition 1.0 (Version 5.0), 21 December 2015
An administrative change was approved (dated 21 December 2015), correcting errors and clarifying operational aspects of the protocol. Revised Clinical Study Protocol Edition 1.0 was the resulting version number, as this was the first revision of the protocol. History of the changes is included in the previous CSP versions.

Clinical Study Protocol Version 4.0, 26 September 2014
Edition 4.0 was the protocol submitted and approved globally. History of the changes is included in the previous CSP versions.

Clinical Study Protocol Version 3.0, 22 August 2014
Version 3.0 was finalized but never used. Czech Republic & Russia submitted this edition to HA, but have only enrolled patients on Edition 4.0. History of the changes is included in the previous CSP versions.

Clinical Study Protocol Version 2.0, 21 May 2014
Olympus protocol Edition 2.0 was submitted and approved in the United States only, as the study began in that market. History of the changes is included in the previous CSP versions.

Clinical Study Protocol Version 1.0, 25 March 2014
Initial creation. Was never submitted in any country.

PROTOCOL SYNOPSIS

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis

International Co-ordinating Investigator (ICI)

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Study site(s) and number of patients planned

Approximately 2600 patients will be randomized at approximately 400 study centers worldwide.

Study period		Phase of development
Date of first patient enrolled	Q2 2014	III
Estimated date of last subject completed	Q3 2018	

Study design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate efficacy and safety in anemic patients with Stage 3, 4 or 5 chronic kidney disease (CKD) who are not on dialysis.

Study Objectives

Primary Efficacy Objective:	Outcome Measure:
Evaluate the efficacy of roxadustat compared to placebo for the treatment of anemia in CKD subjects not on dialysis.	**US FDA:** The primary efficacy endpoint for the US is the mean change from baseline in Hb averaged over week 28 to week 52. **EU health authorities:** The primary efficacy endpoint is whether patients achieved Hb response (Yes/No) where Yes is defined as: o Hb ≥ 11.0 g/dL and Hb increase from baseline by ≥ 1.0 g/dL, for subjects with baseline Hb > 8.0 g/dL; or o Hb increase from baseline by ≥ 2.0 g/dL, for subjects with baseline Hb ≤ 8.0 g/dL at two consecutive visits [dates] (with available data) separated at least 5 days during the first 24 weeks of treatment without having received rescue therapy (RBC transfusion, ESA, or IV iron) prior to Hb response.

Primary Safety Objective:	Outcome Measure:
Contribute CV safety data to pooled safety analyses across the phase 3 program	Adjudicated CV safety data. Analyses of the adjudicated events are described in a separate pooled statistical analysis plan.

Secondary Efficacy Objectives:	Outcome Measure:
The efficacy of roxadustat compared to placebo based on Hb response and level during the study	Proportion of total time of Hb ≥ 10 g/dL from week 28 to week 52. Proportion of total time of Hb within the interval of 10-12 g/dL from week 28 to week 52
The efficacy of roxadustat compared to placebo based on Hb response in inflamed subjects	Mean change in Hb from baseline to the subjects mean level between week 28 to week 52 in subjects with baseline high-sensitivity C-reactive protein (hsCRP) greater than the Upper Limit Normal (ULN)
The effect of roxadustat compared to placebo on Low-density lipoprotein (LDL) cholesterol	Mean change in LDL cholesterol from baseline to week 24

Secondary Efficacy Objectives:	Outcome Measure:
The need for rescue therapy in subjects treated with roxadustat compared to placebo	Time-to-first (and proportion of subjects receiving) instance of receiving intravenous (IV) iron, red blood cell (RBC) transfusions, or erythropoietin analogue as rescue therapy. Time-to-first (and proportion of subjects receiving) instance of receiving red blood cell (RBC) transfusions as rescue therapy.
The effect of roxadustat on anemia symptoms and health-related quality of life (HRQoL) based on comparison with placebo	Changes in generic HRQoL as measured by the SF-36 (Vital Status and Physical Functioning)
The effect on the CKD progression of roxadustat as compared to placebo	Annual rate of eGFR change in log scale, calculated as the linear slope of log (eGFR values) to prior to initiation of dialysis/kidney transplant

Secondary Safety Objectives:	Outcome Measure:
To evaluate the safety and tolerability of roxadustat.	Adverse events (AEs), serious adverse events (SAEs). Changes in vital signs, electrocardiogram (ECG) and laboratory values.

Target patient population

Anemic patients (Hb <10 g/dL) with Stage 3, 4 or 5 CKD who are not on dialysis.

Duration of treatment

This study will consist of three study periods as follows:

- **Screening Period**: Up to 6 weeks
- **Treatment Period:** Patients will be randomized (1:1) to double-blind treatment with roxadustat or placebo. A study end date will be declared and common closeout will occur when the target number of CV events has been accrued. It is anticipated that enrollment will occur over approximately a 3 year period and that an additional 1 to 2years may be required to accumulate the requisite number of patients with positively adjudicated endpoint events.
- **Post-Treatment Follow-Up Period:** 4 weeks.

Investigational product, dosage and mode of administration

The initial study drug dose is 70 mg three times a week (TIW). The dose is subsequently adjusted to achieve and maintain Hb 11±1 g/dL. Study drug doses must be administered at least 2 days apart and no more than 4 days apart, except in subjects who require dose hold or dose reduction to 20 mg once weekly.

Dose adjustments are permitted starting at week 4 and at intervals of every 4 weeks until week 52, every 8 weeks thereafter, unless a dose reduction is required for excessive erythropoiesis (see Table 4). Study drug will be dosed TIW throughout the study treatment period unless downward dose adjustment requires a change to twice or once weekly.

Rescue therapy guidelines are provided to optimize standardization of the use of rescue therapy by investigators and to ensure safety of the individual study patients.

Statistical methods

Sample Size Determination

Primary efficacy endpoint: A sample size of 450 subjects will have > 99% power to detect a 0.75 g/dL difference in mean Hb values between the two treatment groups, assuming that the common standard deviation is 1.2 g/dL, using an analysis of variance (ANOVA) test with a 0.05 two-sided significance level.

To contribute adjudicated CV safety events for the pooled CV analyses across the phase 3 program: approximately 2600 subjects are planned to be randomized in a 1:1 ratio to either roxadustat or placebo. The sample size in this study is driven by the overall requirement of adjudicated CV events for the phase 3 program in CKD-NDD (which consists of 3 studies in total targeting 465 subjects with MACE events). The two other placebo-controlled studies in the study program are FGCL-4592-060 and 1517-CL-0608.

Further information related to the sample size determination can be found in the study statistical analysis plan and the pooled statistical analysis plan.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance model
Anti-HCV antibody	Anti-hepatitis C virus antibody
AST	Aspartate aminotransferase
BP	Blood pressure
CABG	Coronary artery bypass graft surgery
CBC	Complete Blood Count
CKD	Chronic kidney disease
CKD-NDD	Chronic kidney disease-non-dialysis dependent
CSA	Clinical Study Agreement
CSE	Composite safety endpoint
CSR	Clinical Study Report
CMH	Cochran-Mantel-Haenszel
CTCAE	Common Terminology Criteria for Adverse Event
CV	Cardiovascular
DSMB	Data and Safety Monitoring Board
DVT	Deep vein thrombosis
EC	Ethics committee, synonymous to Institutional Review Board(IRB)
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
EQ-5D-5L	EuroQol Health Utility Index
FACT-An	Functional Assessment of Cancer Therapy-Anemia
ESRD	End-stage Renal Disease
FAS	Full Analysis Set
GGT	Gamma-glutamyl transferase
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice

Abbreviation or special term	Explanation
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIF	Hypoxia-inducible factor
HIF-PHI	HIF prolyl hydroxylase inhibitor
HIV	Human immunodeficiency virus
HR	Heart rate
HRQoL	Health Related Quality of Life
hsCRP	High-sensitivity C-reactive protein
IB	Investigator's brochure
ICF	Informed consent form
ICI	International Co-ordinating Investigator, If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IERC	Independent Endpoint Review Committee
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention To Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL	Low-density lipoprotein
LFT	Liver function test
LLN	Lower limit of normal
MACE	Major adverse cardiovascular events; defined as a composite endpoint of death from any cause, non-fatal myocardial infarction or non-fatal stroke
MACE+	Major adverse cardiovascular events+; A composite endpoint of death from any cause, non-fatal MI, non-fatal stroke, congestive heart failure requiring hospitalization and unstable angina requiring hospitalization.
MI	Myocardial Infarction
NCI	National Cancer Institute
OT+28	On treatment plus 28 days

Abbreviation or special term	Explanation
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PEY	Person Exposure Year
PF	Physical Functioning subscale component of SF-36
PGIC	Patients' Global Impression of Change
PI	Principal Investigator
PK	Pharmacokinetics
PPS	Per Protocol Set
PRO	Patient-reported outcome
PSAP	Pooled statistical analysis plan
PTDV	Premature Treatment Discontinuation Visit
QoL	Quality of life
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SF-36	Short Form 36
Tbili	Total bilirubin
TIBC	Total iron binding capacity
TIW	Three times a week
TSAT	Transferrin saturation
ULN	Upper limit of normal
URL	Upper reference limit
VAT	Vascular Access Thrombosis
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Roxadustat is an orally administered investigational novel drug in development for the treatment of anemia associated with chronic kidney disease (CKD). It is currently in global Phase 3 clinical development and has not been marketed in any country. Roxadustat is a potent and reversible active hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) (Semenza 1998, Peyssonnaux et al 2008) that transiently induces hypoxia- inducible factor (HIF) stabilization and leads to a functional HIF transcriptional response that mimics the erythropoietic response associated with exposure of humans to intermittent hypoxia. HIF induces expression of not only erythropoietin, but also the erythropoietin receptor and proteins that promote iron absorption and recycling (Peyssonnaux et al 2008). Thus, roxadustat pharmacologically stimulates erythropoiesis via the HIF pathway and in a manner consistent with the body's normal homeostatic response to hypoxia, but under normoxic conditions. Potential advantages of roxadustat compared with erythropoietin analogues for treatment of anemia in patients with CKD include oral administration, greater cardiovascular (CV) safety and reduced need for intravenous (IV) iron therapy. The clinical data collected thus far suggest that roxadustat is generally safe and well tolerated in healthy adult subjects and in dialysis and non-dialysis CKD patients with anemia treated up to 60 weeks. Information from the clinical studies conducted with roxadustat can be found in the Investigator's Brochure.

The key objective of the study is to assess the efficacy and CV safety of roxadustat in patients with stage 3, 4, or 5 CKD who are anemic and not on dialysis.

1.2 Rationale for study design, doses and control groups

1.2.1 Rationale for control group

Currently available options for the treatment of anemia in patients with CKD and not on dialysis (erythropoietin analogues, IV iron, and red blood cell [RBC] transfusion) have significant disadvantages in terms of inconvenience to the patient, cost and adverse effects. Although clinical guidelines, e.g. KDIGO 2012 recommend the use of erythropoietin analogues in these patients if certain criteria are fulfilled, the use of these agents is still controversial (Breault 2011). The proportion of CKD patients with anemia who are treated with erythropoietin analogues was found to be about 8% (Veterans and Medicare data, Lawler et al 2011, Collins et al 2009, respectively). Thus, treatment with erythropoietin analogues is not considered a standard of care by the majority of practicing clinicians. Importantly, the use of erythropoietin analogues has been associated with increased CV risk (Besarab et al 1998, Drüeke et al 2006, Singh et al 2006) and this is likely to have hampered their broader use. Since it is still unclear whether this risk is due to a correction of Hb above a certain level, rate of Hb rise, toxic effects of erythropoietin analogues *per se* or a combination of these or other factors (Unger et al 2010), it is appropriate to investigate roxadustat, a compound with an entirely different mechanism of action, against placebo. Finally, no clinically justified anemia therapy will be withheld in patients on placebo for whom oral iron and, if necessary rescue therapy (erythropoietin analogue, IV iron, RBC transfusion) will be available. Thus, placebo is deemed to be the appropriate comparator in this study.

1.2.2 Rationale for doses

Starting doses of roxadustat were studied in three ways in the Phase 2 program: mg per kg weight-based dosing, tiered weight-based dosing (45 to 60 kg, >60 to 90 kg, >90 to 140 kg) or a fixed starting dose regardless of body weight.

Dose adjustments were allowed at regular 4-week intervals to maintain, increase or decrease the dose according to pre-specified rules based on absolute Hb levels and change of Hb in the previous 4 weeks. Additional rules were provided to minimize excessive erythropoiesis. These dose adjustments are adopted in this study with minor modifications.

The starting dose for this study will be 70mg TIW. Doses will be administered three times weekly throughout the study unless downward dose adjustment requires a change to twice or once weekly. Dose adjustment is allowed at 4-week intervals to achieve and maintain Hb 11±1 g/dLIn the event of excessive erythropoiesis, the dose may be adjusted at any time. The maximum dose allowed will be the lower of 3.0 mg/kg or 300 mg per dose.

1.2.3 Rationale for hemoglobin level

This study seeks to achieve and maintain Hb 11±1 g/dLThis level is chosen to improve the clinical manifestations of anemia, reduce RBC transfusion and improve quality of life, without affecting CV risk. Systematic reviews have found that anemia correction in patients with CKD improved exercise tolerance, energy and physical functions (Gandra et al 2010, Johansen et al 2010). Also, a number of studies and meta analyses have addressed the issue of clinical benefit versus potential risk upon anemia correction in CKD (Phrommintikul et al 2010, Strippoli et al 2004). In a recent update, the KDIGO 2012 guidelines suggest that erythropoietin analogues to be started at Hb below 10 g/dL and should generally not be used to maintain Hb above 11.5 g/dL (KDIGO 2012). In contrast, the Cleveland Clinic recommends target hemoglobin level for both predialysis CKD and end-stage renal disease (ESRD) patients should be 11 to 12 g/dL (Lascano et al 2010).

Unlike Hb levels above 13 g/dL where the data indicate CV harm (Pfeffer et al 2009), there is a paucity of data on the potential risk of CV adverse events when Hb below 12 g/dL is achieved. Further, other factors than the exact Hb level may contribute to the CV risk associated with erythropoietin analogue use. These include toxic effects of higher doses of erythropoietin analogues (Andrews et al 2013) and a too rapid increase in hemoglobin upon anemia correction (Singh 2010).

Roxadustat acts via a different mechanism of action than erythropoietin analogues and supra-physiologic erythropoietin concentrations have not been observed in patients treated with roxadustat (Yu et al 2013). In clinical practice, it is difficult to maintain individual patient Hb values within a very narrow range and the proposed range (11±1 g/dL) is in line with achievable levels in practice.

1.3 Benefit/risk and ethical assessment

The primary benefit for patients randomized to roxadustat is expected to be the correction of anemia, including the relief of associated signs and symptoms and an improved quality of life. Roxadustat is expected to be at least as safe as parenteral erythropoietin analogues.

Patients treated with placebo may not obtain any benefit in terms of anemia correction, but may benefit from the closer follow-up and will receive alternative therapies whenever clinically indicated.

An established dose adjustment algorithm will be used during the study to titrate roxadustat doses to enable patients to achieve and maintain Hb levels, while closely monitoring the rate of rise of Hb levels. Roxadustat doses may be held and therapeutic phlebotomy is allowed in the event of excessive erythropoiesis.

In studies with healthy subjects, headache and dizziness were common events, which occurred at a higher frequency with roxadustat compared to placebo. An increased frequency of mild to moderate musculoskeletal pain was also noted with high doses of roxadustat. These findings were not observed at the usual therapeutic dose range in the Phase 2 studies in the target populations.

Treatment with roxadustat was associated with increases in heart rate which were most pronounced at supra-therapeutic doses (5 mg/kg). At the high clinical dose of 2.75 mg/kg, the increase was modest (about 10 bpm from baseline, placebo corrected). In the Phase 2 studies, there were no adverse effects on hemodynamics with repeated dose administration in the therapeutic dose range. The cumulative safety data to date have not identified any major risks related to roxadustat, which was well tolerated by healthy subjects and patients with CKD.

The safety of treatment with roxadustat and placebo will be carefully monitored and an independent Data Safety Monitoring Board (DSMB) will perform periodic assessments of safety data to detect any potential safety signals that may arise during the study and advise the International Coordinating Investigator and Sponsor accordingly. Based on data so far obtained, treatment with roxadustat is expected to be efficacious in treating anemia in patients with CKD. The safety profile of the compound, together with the safety monitoring implemented would minimize the risk to study participants. The benefit-risk in this study is therefore deemed acceptable.

More detailed information about the efficacy and safety profile of roxadustat is provided in the IB.

1.4 Study Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study in anemic patients with stage 3, 4 or 5 CKD who are not on dialysis. This study is planned to recruit approximately 2600 patients from approximately 400 centers worldwide.

1.4.1 Treatment duration and dosing

This study will consist of three study periods:

- **Screening Period**: Up to 6 weeks
- **Treatment Period**: Patients will be **randomized** (1:1) to double-blind treatment with roxadustat or placebo, started at 70mg TIW and titrated to achieve and maintain Hb 11±1 g/dL. Treatment duration is variable for individual patients. A study end date will be declared and common closeout will occur when the target number of CV events has been accrued.
- **Post-Treatment Follow-Up Period**: 4 weeks. Patients who discontinue study medication or protocol-specified study visits will be followed up for CV events, vital status and hospitalizations until the end of the study (EOS), unless consent to participate is withdrawn.

1.4.2 Randomization

A total of approximately 2600 patients will be randomized at 1:1 ratio to roxadustat or placebo via an Interactive Web Response System (IWRS)/ Interactive Voice Response System (IVRS).

1.4.3 Blinding

This is a double blind, placebo-controlled study. The investigator, study site staff and the patient, are blinded to study treatment, but not to the dose or dosing frequency. The Sponsor and designees except the personnel analyzing the pharmacokinetic (PK) samples are blinded to study treatment, dose and dosing frequency. Sponsor study team members responsible for IWRS system are blinded to study treatment and can in special cases be unblinded to dose and dosing frequency.

Roxadustat tablets and matching placebo tablets will be identical in appearance, packaging and labelling in order to maintain the blind. Treatment assignments will be unblinded after database lock.

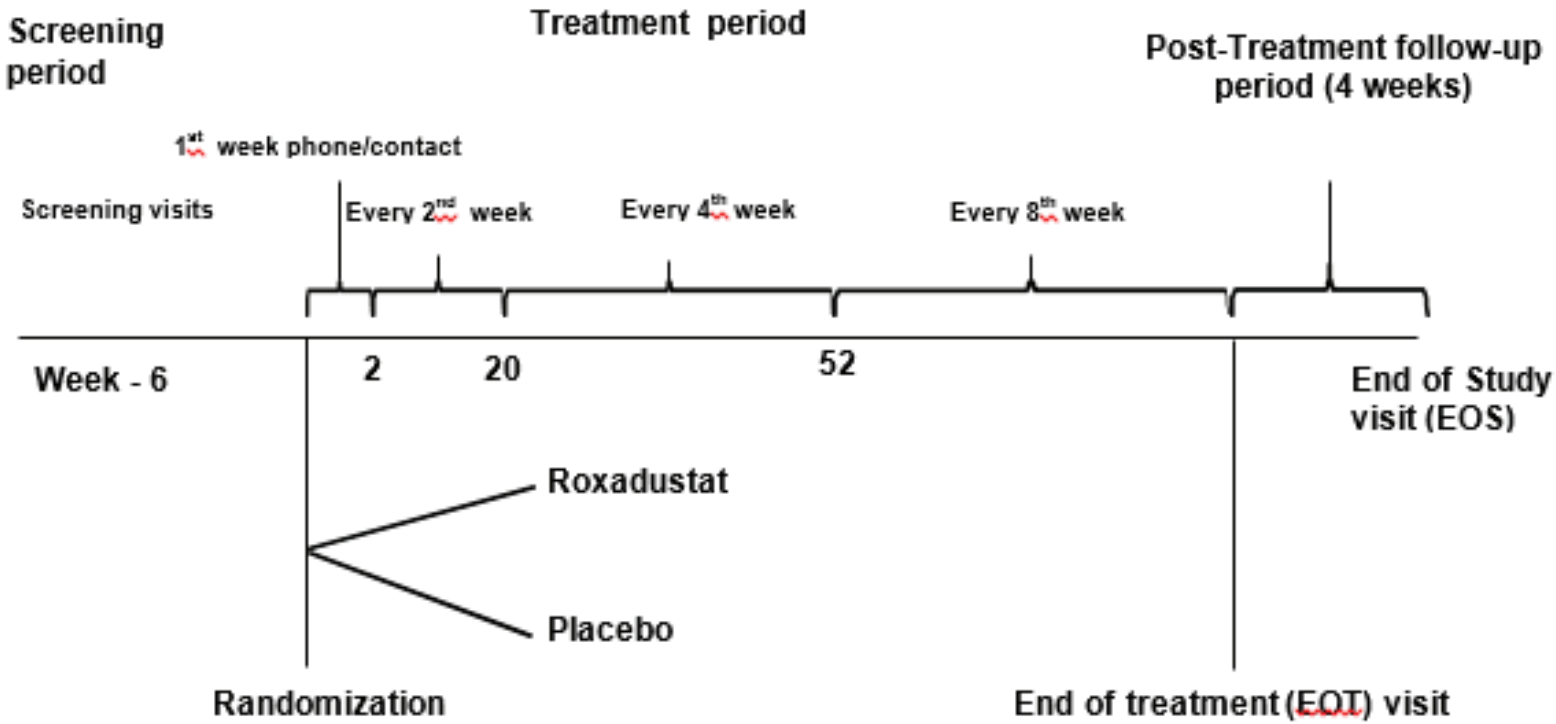
Any intentional or unintentional breaking of the blind should be reported and documented. Breaking the blind (for a single patient) should be considered only when knowledge of the treatment assignment is deemed essential by the investigator for the patient's care. Unplanned unblinding will result in the discontinuation of patient participation from the study treatment but follow up for CV events will continue until the study closes.

1.4.4 Visits

During the screening period, eligibility will be confirmed at a minimum of 2 screening visits. During the treatment period, patients will be contacted by telephone at week 1, and will attend study visits every two weeks from weeks 0 to 20. After week 20, study visits will occur every four weeks until week 52, then every 8 weeks until the end of the treatment period. A study end date will be defined based on when the planned number of events are estimated to be accrued, and the end of treatment (EOT) visit will occur as soon as possible after that date. An

EOS visit will be performed 4 weeks after the EOT. Detailed information about study visits and assessments is found in Section 4.

Figure 1 Study flow chart



2. STUDY OBJECTIVES

2.1 Primary objectives

Primary Efficacy Objective:	**Outcome Measure:**
Evaluate the efficacy of roxadustat compared to placebo for the treatment of anemia in CKD subjects not on dialysis.	**US FDA:** The primary efficacy endpoint for the US is the mean change from baseline in Hb averaged over week 28 to week 52. **EU health authorities:** The primary efficacy endpoint is whether patients achieved Hb response (Yes/No) where Yes is defined as: o Hb ≥ 11.0 g/dL and Hb increase from baseline by ≥ 1.0 g/dL, for subjects with baseline Hb > 8.0 g/dL; or o Hb increase from baseline by ≥ 2.0 g/dL, for subjects with baseline Hb ≤ 8.0 g/dL at two consecutive visits [dates] (with available data) separated at least 5 days during the first 24 weeks of treatment without having received rescue therapy (RBC transfusion, ESA, or IV iron) prior to Hb response.
Primary Safety Objective:	**Outcome Measure:**
Contribute CV safety data to pooled safety analyses across the phase 3 program	Adjudicated CV safety data. Analyses of the adjudicated events are described in a separate pooled statistical analysis plan.

2.2 Secondary objectives

Secondary Efficacy Objectives:	Outcome Measure:
The efficacy of roxadustat compared to placebo based on Hb response and level during the study	Proportion of total time of Hb ≥ 10 g/dL from week 28 to week 52. Proportion of total time of Hb within the interval of 10-12 g/dL from week 28 to week 52
The efficacy of roxadustat compared to placebo based on Hb response in inflamed subjects	Mean change in Hb from baseline to the subjects mean level between week 28 to week 52 in subjects with baseline high-sensitivity C-reactive protein (hsCRP) greater than the Upper Limit Normal (ULN)
The effect of roxadustat compared to placebo on Low-density lipoprotein (LDL) cholesterol	Mean change in LDL cholesterol from baseline to week 24
The need for rescue therapy in subjects treated with roxadustat as compared to placebo	Time-to-first (and proportion of subjects receiving) instance of receiving intravenous (IV) iron, red blood cell (RBC) transfusions, or erythropoietin analogue as rescue therapy. Time-to-first (and proportion of subjects receiving) instance of receiving red blood cell (RBC) transfusions as rescue therapy.
The effect of roxadustat on anemia symptoms and health-related quality of life (HRQoL) based on comparison with placebo	Changes in generic HRQoL as measured by the SF-36 (Version 2, standard)
The effect on the CKD progression of roxadustat as compared to placebo	Annual rate of eGFR change in log scale, calculated as the linear slope of log (eGFR values) to prior to initiation of dialysis/kidney transplant

Secondary Safety Objectives:	Outcome Measure:
To evaluate the safety and tolerability of roxadustat.	Adverse events (AEs), serious adverse events (SAEs). Changes in vital signs, electrocardiogram (ECG) and laboratory values.

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Patients will be recruited from academic and community specialty and primary care practices. Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study patients should fulfill the following criteria:

1. Provision of informed consent prior to any study specific procedures.
2. Age ≥18 years at screening visit 1

2. 3. eGFR <60 mL/min/1.73 m^2, (calculated by central lab) corresponding to stage or 5CKD according to the Kidney Disease Outcomes Quality Initiative (KDOQI), not receiving dialysis (Levey et al 2006, National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

National Kidney Foundation 2002)

4. Mean of 2 most recent central laboratory Hb values during the screening period, obtained at least 7 days apart, must be <10.0 g/dL
5. Ferritin ≥50 ng/mL at randomization (obtained from screening visit)
6. TSAT ≥15 % at randomization (obtained from screening visit)
7. Serum folate level ≥ lower limit of normal (LLN) at randomization (obtained from screening visit)
8. Serum vitamin B12 level ≥LLN at randomization (obtained from screening visit)
9. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x upper limit of normal (ULN) and total bilirubin (Tbili) ≤1.5 x ULN at randomization (obtained from screening visit)
10. Body weight 45 to 160 kg

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
2. Previous randomization in the present study
3. Any erythropoietin analogue treatment within 6 weeks of randomization
4. New York Heart Association Class III or IV congestive heart failure at enrollment
5. Myocardial infarction (MI), acute coronary syndrome, stroke, seizure or a thrombotic/thromboembolic event (e.g., deep vein thrombosis or pulmonary embolism) within 12 weeks prior to randomization
6. History of chronic liver disease (e.g., chronic infectious hepatitis, chronic auto-immune liver disease, cirrhosis or fibrosis of the liver)
7. Known hereditary hematologic disease such as thalassemia, sickle cell anemia, a history of pure red cell aplasia or other known causes for anemia other than CKD
8. Known and untreated retinal vein occlusion or known and untreated proliferative diabetic retinopathy (risk for retinal vein thrombosis)

9. Diagnosis or suspicion (e.g. complex kidney cyst of Bosniak Category IIF, III or IV) of renal cell carcinoma on renal ultrasound (or other imaging procedure e.g. CT scan or MRI) conducted at screening or within 12 weeks prior to randomization
10. Systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg (confirmed by repeated measurement), within 2 weeks prior to randomization. Patients may be rescreened once BP controlled
11. History of prostate cancer, breast cancer or any other malignancy, except the following: cancers determined to be cured or in remission for ≥5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer *in situ*, or resected colonic polyps
12. Positive for any of the following: human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus antibody (anti-HCV Ab)
13. Chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE)ankylosing spondylitis, psoriatic arthritis or inflammatory bowel disease that is determined to be the principal cause of anemia
14. Known hemosiderosis, hemochromatosis or hypercoagulable condition
15. Any prior organ transplant or a **scheduled** organ transplantation date
16. Any red blood cell transfusion (RBC) during the screening period
17. Any current condition leading to active significant blood loss
18. Any treatment with roxadustat or a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI)
19. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within at least 1 month of the first administration of IP in this study. (Note: patients consented and screened, but not randomized in this study or a previous study are not excluded)
20. History of alcohol or drug abuse within 2 years prior to randomization
21. Females of childbearing potential, unless using contraception as detailed in the protocol or sexual abstinence (see Section 3.8)
22. Pregnant or breastfeeding females
23. Known allergy to the investigational product or any of its ingredients
24. Any medical condition, including active, clinically significant infection, that in the opinion of the investigator or Sponsor may pose a safety risk to a patient in this study, which may confound efficacy or safety assessment or may interfere with study participation

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrollment and randomization

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

The Investigator(s) will:

- Obtain signed informed consent from the potential patient before any study specific procedures are performed
- Assign potential patient a unique enrollment number, beginning with 'E#' through the IWRS/IVRS
- Determine patient eligibility, see Section 3.1 and 3.2
- Assign eligible patients unique randomization code through the IWRS/IVRS

If a patient withdraws from participation in the study, his/her enrollment/randomization code cannot be reused.

Randomization codes will be assigned strictly sequentially as patients become eligible for randomization. Randomization of qualified patients within the IVRS/IWRS system must take place, prior to administration of study drug. Randomization procedures must be completed within 72 hours. The first dose of study drug defines Day 1. The randomization visit should be scheduled after the study drug has arrived at the study site.

3.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Randomization schedules will be prospectively prepared. Automated randomization and treatment assignments will be provided by an IWRS /IVRS. The randomization codes will be computer generated by AstraZeneca R&D using GRand (AZ Global Randomization system) and loaded into the IVRS/IWRS database. A block randomization schedule by country will be produced.

3.6 Methods for ensuring blinding

The investigator, study site staff, and the patient are blinded to study treatment, but not to the dose or dosing frequency. The Sponsor and designees except the personnel analyzing the pharmacokinetic (PK) samples are blinded to study treatment, dose and dosing frequency. Sponsor study team members responsible for IWRS system are blinded to study treatment and can in special cases be unblinded to dose and dosing frequency. The patient will also be blinded to study Hb values. Neither the patients nor the investigators and their staff can distinguish the roxadustat tablets from the matching placebo tablets. Both will be identical in appearance, packaging and labeling in order to maintain the blind.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigators or pharmacists from the IWRS/ IVRS. Routines for this will be described in the IWRS/ IVRS user manual that will be provided to each center.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment assignment to the AstraZeneca staff.

3.8 Restrictions

The following restrictions apply in the study:

Female patients of childbearing potential and male patients (non-surgically sterile i.e., vasectomy) with a female partner of childbearing potential must, if not practicing complete sexual abstinence, agree to practice a dual method of contraception, for example, a combination of the following: (1) oral contraceptive, depo progesterone or intrauterine device; and (2) a barrier method (condom or diaphragm).

Contraceptive methods must be practiced upon being randomized to the study and through 12 weeks after the last dose of study treatment. If a patient discontinues prematurely, the contraceptive method must be practiced for 12 weeks following final administration of study drug.

Pregnancy, spontaneous or therapeutic abortion or events related to pregnancy must be reported (see Section 6.6).

For high dose statins use, see Section 7.7.1.1.

3.9 Discontinuation of investigational product

Patients should be discontinued from investigational product (IP) in the following situations:

3.9.1 Temporary discontinuation from investigational product

For patients needing treatment with prohibited concomitant medications or receiving erythropoietin analogue rescue therapy, study medication must be discontinued or interrupted temporarily.

The AstraZeneca study physician should be consulted for all decisions around IP discontinuation.

3.9.2 Permanent discontinuation from investigational product

1. Patient decision: The patient is at any time free to discontinue treatment, without prejudice to further treatment
2. Investigator's decision, including but not limited to these examples:
    - Incorrectly randomized patient in whom the inclusion/exclusion criteria violation would put the patient at undue risk
    - Adverse Event (AE) for which the investigator thinks continued treatment may put the patient at undue risk
    - Severe non-compliance to study protocol
    - Pregnancy
    - Patients who have received two courses of erythropoietin analogue rescue therapy, and for whom there is a need for a third course of rescue with erythropoietin analogue
    - For patients initiating dialysis during the study; and for whom there is a need for rescue with erythropoietin analogue

Each permanent discontinuation from study medication should be communicated to the study team. For decisions around permanent discontinuation the AstraZeneca study physician should be consulted. Study assessments or follow-up should be continued in all cases if possible (see Section 4).

3.9.3 Procedures for discontinuation of a patient from investigational product

Patients permanently discontinuing study medication should be given conventional therapy, if applicable and should always be asked to continue the regular study visits as described below.

A patient who decides to discontinue study medication will always be asked about the reason(s) to discontinue study medication and the presence of AEs (if any). These data will be ascertained and documented by the investigator and recorded in the eCRF as appropriate. AEs will be followed up (see Sections 4 and 6.4) and the patient should return all study medications.

Each patient who permanently discontinued study medication prior to closure of the study, should be followed up for vital status and hospitalizations until study closure (see Section

3.9.3.2), unless he/she decides to withdraw consent for the study completely (see Section 3.9.3.3).

Discontinuation from study medication is not the same as complete withdrawal from the study (withdrawal of consent), which has a direct impact on the potential validity of all study data and should be avoided wherever possible. It is essential to collect as much data as possible for all patients throughout the study and especially all potential endpoint events.

There are several different options (methods of follow-up) for the continuation in the study as described below.

3.9.3.1 Patient agrees to undergo the Premature Treatment Discontinuation Visit and then continue in-person study visits

The patient agrees to undergo the Premature Treatment Discontinuation Visit (PTDV) and then continue in-person study visits according to plan. This is the **preferred** option and patients who discontinue study medication will always be asked if they agree to this approach. If agreed, as above, the patient will undergo their PTDV within 15 days after the study medication is stopped. The PTDV includes the same assessments as the EOT visit. The patient will continue attending subsequent study visits according to schedule (see Table 1) until end of study is declared (i.e., when the prespecified number of primary events has been reached).

At PTDV, the physicians caring for the patient will decide upon treatment the patient should receive as part of his/her ongoing clinical care. Patients who have permanently discontinued study drug may receive prohibited concomitant medications such as erythropoietin analogues.

3.9.3.2 Patient refuses to continue in-person study visits but agrees to undergo modified follow-up

If the patient agrees, the PTDV should be done. In all subjects permanently discontinuing study drug, all adverse events and potential endpoints should be captured during the 28 days following study drug discontinuation. Beyond 28 days following study drug discontinuation, for subjects who refuse to continue in-person study visits but agree to modified follow-up, all SAEs should be captured as well as any information (for example, hospitalization records) relevant to the following adjudicated events:

- Death
- Non-fatal MI
- Non-fatal stroke
- Heart failure requiring hospitalization
- Unstable angina leading to hospitalization
- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)

- Vascular access thrombosis (VAT)
- Hypertensive emergency

Additionally, information about anemia treatment following study drug discontinuation (for example, erythropoietin analogue use) should be documented in the eCRF.

Examples of modified follow-up include in-person study visits occurring at a different frequency and/or with fewer study procedures (for example, without laboratory assessments) than that listed in Table 1; periodic telephone contact with the subject, subject's spouse, or the subject's treating physician; and periodic medical record review.

3.9.3.3 Patient refuses any form of follow-up

If the patient refuses any form of follow-up, he/she officially withdraws from the study and withdraws consent. This approach should be avoided if possible and is further described in Section 3.10. All available follow-up options (including modified follow-up as described in section 3.9.3.2) should be discussed with the patient, and the patient's refusal of all follow-up options should be documented. Patients who agree to any form of follow-up or contact with the site (for example, one phone call during the study closeout period), have not withdrawn consent. At the end of the study, vital status on all withdrawal of consentpatients will be collected from publicly available sources, in accordance with local regulations.

3.9.3.4 Restart of study medication

Whenever possible, restart of randomized study medication should be encouraged.

If patient has been treated with erythropoietin analogues as rescue therapy, see Section 7.7.4 for guidance on when study drug can be restarted.

3.9.3.5 End of study procedures

If a patient is unable to attend the EOS visit in person, telephone contact for CSE events, hospitalization, SAEs and vital status should be made to ascertain endpoint and AE information.

3.10 Criteria for withdrawal

Patients are at any time free to discontinue investigational product and/or withdraw consent for participation in the study, without prejudice to further treatment. Whether or not withdrawal of consent from the study has occurred must be ascertained in subjects for whom investigational product is permanently discontinued, and this must be documented by the investigator and recorded in the eCRF as well as in the withdrawal addendum to the informed consent form (ICF). The withdrawal addendum to ICF should be signed and dated by both the patient and the investigator, if possible. Such patients will always be asked about the reason(s) and the presence of any AEs. The reason for permanent discontinuation of treatment with the study medication and the date of the last intake of the study medication must be documented in the eCRF.

To ensure validity of study data, it is very important to collect as much data as possible throughout the study and especially vital status (dead or alive) at the EOS visit. The investigator or delegate will therefore attempt to collect information on all patients' vital status from publicly available sources at the EOS visit, **in accordance with local regulations,** even if informed consent has been withdrawn completely.

3.10.1 Screen failures

Screening failures are patients who do not fulfill the eligibility criteria for the study and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as Incorrect Enrollment' (i.e. patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs the Investigator will follow up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced. **Patients who agree to continued study participation following investigational product discontinuation, including modified follow-up such as telephone calls or medical record review, have not withdrawn consent.**

3.11 Discontinuation of the study

A study end date will be defined based on when the planned number of events are estimated to be accrued.

The study may be stopped earlier if, in the judgment of AstraZeneca, the patients are placed at undue risk because of clinically significant findings or for other reasons.

Regardless of the reason for study termination, all data available for the patient at the time of discontinuation and follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

If terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests. The independent DSMB will monitor the study to ensure patient safety.

4. STUDY PLAN AND TIMING OF PROCEDURES

Study assessments and procedures are summarized in Study Plan, Table 1. At visits when PRO questionnaires (SF-36, FACT-An, EQ-5D-5L and PGIC) are scheduled, they should be completed prior to any other intervention. Blood samples for Hb measurement, safety laboratory tests and other laboratory assessments will be obtained according to the Study plan, Table 1.

Table 1 Study Plan

	Screening[a]		Treatment (-4d to +2d)																					EOT (-4d to +2d)	EOS (4wks after EOT+4d)
	Up to 6 wks		Rand (wk 0)	wk 1 ☎	wk 2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	60	every 8 wks		
Visit[b]	*1*	*2*	*3*	*4*	*5*	*7*	*9*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*23*	*24*	*25*	*27*	*29, 31, 33, 35, 37, 39 etc…*		
Written informed consent	X																									
Eligibility criteria	X	X	X																							
Demographics and medical history	X																									
Physical examination	X[c]		X							X[c]					X[c]										X	
Height[d], weight	X		X							X					X			X				X		every 24 wk	X	
12-lead ECG			X							X					X										X	
Blood pressure, Heart rate	X[e]	X[o]	X[e]			X		X		X[e]		X		X	X[e]	X	X	X	X	X	X	X[e]	X	, every 24 wks X[e]	X[e]	
Renal ultrasound if none performed within 12 weeks prior to randomization		X																								
Serum hCG pregnancy test[f]	X		X							X				X		X		X		X		X	X	every 8 wks	X	
Serology (HIV, Hepatitis B and C), Vitamin B12, folate	X																									
Hemocue assessment[g]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hemoglobin (Central lab)		X			X		X	X	X		X	X	X	X		X	X	X	X	X	X		X	X	X	
Complete blood count (CBC)[h]	X		X			X				X					X							X		every 24 wks	X	
Clinical chemistry	X		X			X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	
Iron, Ferritin, TIBC, TSAT	X		X					X				X			X			X				X			X	
Lipids (non fasting)			X												X										X	
Population PK sampling						X[i]		X																		
Pharmacogenetic sampling(optional)			X																							
Biomarker sampling (optional) hsCRP, hepcidin			X[j]												X											
PRO questionnaires: FACT-An, SF-36			X							X						X						X				

Table 1 Study Plan

	Screening[a]			Treatment (-4d to +2d)																			EOT (-4d to +2d)	EOS (4wks after EOT+4d)
	Up to 6 wks		Rand (wk 0)	wk 1 ☎	wk 2	4	6	8	10	12	14	16	18	20	24	28	32	36	40	44	48	52	60	every 8 wks		
Visit[b]	*1*	*2*	*3*	*4*	*5*	*7*	*9*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*23*	*24*	*25*	*27*	*29, 31, 33, 35, 37, 39 etc…*		
PGIC										X						X						X				
EQ-5D-5L[k]			X							X						X						X		every 24 wks		
SAE recording	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE recording			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication recording	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dose adjustment review[l]						X		X		X		X		X	X	X	X	X	X	X	X	X	X	X		
Confirm study drug being taken correctly				X																						
Study drug dispensing[m]			X[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Rand. = Randomization; EOT = End of Treatment; EOS= End of Study; Wk = Week

a Additional screening visit(s) may be conducted as needed (see Section 4.1.2)
b Please be attentive to visit # which are not consecutive due to removal of some visits from Study Plan.
c Targeted physical examination only.
d Height measured only at screening visit 1.
e Perform HR and BP measurements in triplicates after being comfortably at rest in a seated position quietly for at least 5 min.
f Collect from female patients of childbearing potential only.
g For Hemocue Hb, use blood sample from lavender top tube collected for central laboratory Hb or CBC, not fingerstick
h Hemoglobin is included in the CBC testing panel.
i Only at week 4: patients should NOT take their morning dose on the day of PK collection. The medication should be taken after the sampling. Sample should be taken pre-dose.
j Collect pre-dose.
k After suspected CSE event (MI, stroke, unstable angina, heart failure, DVT, PE, vascular access thrombosis or hypertensive emergency), collect EQ-5D-5L at next regularly scheduled visit
l Dose adjustment review every 4 weeks until week 52, every 8th week thereafter. Hemocue values will be used for all dose adjustments, with baseline values from Hemocue values at randomization. In the event of excessive erythropoiesis dose can be adjusted at any time, see Section 7.2.3.
m Dispensation every second week from Day 1 to week 20, every 4 weeks from week 20 to 52, every 8 weeks thereafter. In the event of excessive erythropoiesis dose can be adjusted at any time, see Section 7.2.3.
n Receipt of the first dose of study drug defines Day 1
o BP measurements in triplicates if one of the BP at visit 1 was out of range

4.1 Enrollment/screening period

During the screening period consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be randomized in the study. Patients must provide written informed consent before any screening tests or assessments are performed.

4.1.1 Screening visits

Procedures will be performed according to the Study Plan, Table 1.

The screening period will consist of a minimum of two screening visits to be performed at least 7 days apart. All screening procedures should be completed within 6 weeks. The site must ensure that study drug is available at study site before the randomization visit is scheduled.

The Hb inclusion criteria will be based on central laboratory assessment and may be repeated during the screening period. Eligible patients should have a mean (calculated by the Investigator) of two most recent central laboratory Hb values during the screening period, obtained at least 7 days apart, that is <10.0 g/dL.

4.1.2 Additional screening assessments

If a patient's laboratory results or blood pressure (BP) do not meet the eligibility criteria, the laboratory assessment or BP may be repeated within the screening period. The visits must be at least 7 days apart.

For example, an additional central laboratory Hb value may be collected if necessary. The mean of two most recent Hb values during the screening period, obtained at least 7 days apart, will be used to calculate the patient's eligibility. Iron, vitamin B12 and folate laboratory tests may be repeated during the screening period after supplementation if necessary. Similarly BP may be repeated after adjustment of antihypertensive medications. Liver function test (LFT) parameters may not be repeated if found exclusionary at screening without a prior approval from the AstraZeneca study physician.

A screen-fail patient may be re-screened if deemed appropriate by the investigator. Where possible, an approval should be obtained from the AstraZeneca study physician prior to re-screening. Two re-screening periods are allowed.

For all screen failures, the reason(s) will be documented.

4.2 Treatment period

Procedures for this period are included in the Study Plan, Table 1.

The treatment period begins on the first day of dosing with study treatment (Day 1, week 0). Day 1 is the first treatment day. All Randomization study assessments are to be performed prior to first study drug administration.

During the treatment period, patients will be contacted by phone at week 1 to assure that study drug is being taken correctly. The patients will attend study visits every 2 weeks from week 0 to 20, every 4 weeks thereafter until week 52, and every 8 weeks from week 52 until study closure is declared. The patient's next scheduled visit will then be the EOT visit marking the end of the treatment period. At the EOT visit, the physicians caring for the patient will decide upon treatment the patient should receive as part of his/her ongoing clinical care.

The study is event-driven and will be closed when the target number of CV events has been accrued.

In case of premature discontinuation of study medication, see Section 3.9.

4.3 Follow-up period

After the treatment period (ending with the EOT visit), study patients will proceed to the 4-week post-treatment follow-up period (ending with the EOS visit).

Procedures will be performed according to the Study Plan, Table 1.

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded in the electronic Case Report Forms (eCRF) as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRF will be archived at the study center.

5.1 Efficacy assessments

5.1.1 Efficacy assessments

5.1.1.1 Hemoglobin level

Assessment of the efficacy of study treatments will be based on Hb assessed by central laboratory. Dose adjustments will be based on Hb assessed by Hemocue using the blood sample from lavender top tube collected for central laboratory Hb or CBC, not by fingerstick.

For timings of the Hb assessments, see Table 1.

5.1.1.2 Use of rescue therapy

Use of rescue therapy (erythropoietin analogue, IV iron and RBC transfusion) will be identified using standard questioning of the patient at each visit or by information that the investigator may receive as part of standard medical practice. The use will be recorded in the appropriate section of the eCRF. For further information see Section 7.7.4.

5.2 Safety assessments

Safety will be assessed throughout the study. A complete baseline profile of each patient will be established through demographics, medical history, clinical laboratory values, vital signs, physical assessments and electrocardiograms (ECGs). During the course of the study, vital signs, complete and targeted physical assessments, laboratory tests and ECGs will be performed at regular intervals. Adverse events, serious adverse events (SAEs) and ongoing concomitant medication usage will be monitored and recorded throughout the study. SAE reports will be evaluated individually to assess for the impact of the event, if any, on the overall safety of the product and on the study itself. Cumulative AEs will be monitored throughout the study. SAEs and AEs will be followed until resolved, stable or until the patient's EOS visit. See Section 6 for details on AE and SAE reporting.

Safety will be assessed through:

- Adverse events
- Laboratory parameters
- Vital signs (blood pressure, heart rate, ECG)
- Adjudicated cardiovascular, cerebrovascular and thrombotic/thromboembolic events

5.2.1 Cardiovascular events

MACE+ events (death, non-fatal MI, non-fatal stroke, heart failure requiring hospitalization and unstable angina leading to hospitalization) should be reported as SAEs in the eCRF. Deep vein thrombosis, pulmonary embolism, vascular access thrombosis and hypertensive emergencies will also be reported and adjudicated.

SAEs will be screened against a pre-specified list of MedDRA preferred terms to identify potential MACE+ events plus the rest of the CV events listed above. When a potential CV event is identified, the principal investigator will be contacted to collect supporting medical records; once the clinical endpoint packet is compiled, blinded adjudication of candidate CV events will be conducted by the Independent Endpoint Review Committee (IERC) as described in the IERC charter.

Independent Event Review Committee Charter (IERC) contains complete information regarding the cardiovascular events and criteria for adjudication.

5.2.2 Laboratory assessments

Blood samples for determination of clinical chemistry, hematology, lipid panel, serology, vitamin B12, folate and serum iron profile will be taken at the times indicated in Table 1 and analyzed by Covance Central Laboratory Services.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

The following laboratory variables will be measured (blood, serum or plasma will be specified in the laboratory manual):

Laboratory Variables

Hematology/Hemostasis	**Clinical Chemistry**
Hemoglobin (Hb)	Creatinine
Hematocrit	Creatinine kinase
Leukocyte count	Bilirubin, total
Leukocyte differential count (absolute count)	Alkaline phosphatase (ALP)
Platelet count	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
Serology	Gamma-glutamyl transferase (GGT)
Hepatitis B surface antigen	Albumin
Hepatitis C antibody	Potassium
Human immunodeficiency virus (HIV)	Calcium, total
	Sodium
Additional Laboratory Analytes	Chloride
Vitamin B12	Magnesium
Folate	Bicarbonate
hsCRP*, hepcidin*	Phosphorus
Lipid Panel	Glucose
Total cholesterol	Uric Acid
HDL	Total protein
Triglycerides	Lactate dehydrogenase
Calculated low-density lipoprotein (LDL)	Blood urea nitrogen
	Serum hCG pregnancy test
	Iron Profile
	Iron

Laboratory Variables

Hematology/Hemostasis	Clinical Chemistry
	Ferritin
	Total iron binding capacity (TIBC)
	Transferrin saturation (TSAT)

* = will be analyzed using biomarker specimens

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at center as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported (see Section 6.3).

Note: In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin - Hy's Law', for further instructions.

Additional laboratory assessments performed for purposes other than general safety evaluation are also listed in Table 2.

5.2.3 Physical examination

A **comprehensive** physical examination will be conducted according to Study Plan, Table 1. This examination will include general appearance and the following body regions and systems: General appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, respiratory, abdomen, neurological and any other, if deemed necessary.

Height is measured only at screening. Weight is measured at screening, at randomization and then at specific time points as described in the Study Plan, Table 1.

A **targeted** physical examination (general appearance, cardiovascular, respiratory and abdomen) will be conducted throughout the study as described in Study Plan, Table 1. Any clinically relevant adverse change will be recorded as an AE in the eCRF (see Section 6.3.6).

5.2.4 ECG

5.2.4.1 Resting 12-lead ECG

Standard 12-lead ECGs will be performed on all patients at specific time points as described in the Study Plan, Table 1, as to local routines. A single ECG will be taken after the patient has been resting in the supine position for 5 minutes. Any abnormalities must be evaluated in clinical context (based on patient's medical history and concomitant medication) and the investigator should determine if it is clinically significant. Clinically significant abnormalities should be reported as an AE. Only the visit, ECG date, heart rate, RR Interval, PR Interval,

QRS Interval, QT Interval, overall interpretation and relevant comments will be recorded in the eCRF. ECG recordings will be kept as source documents.

5.2.5 Vital signs

The vital signs, blood pressure and heart rate, will be assessed at the visits as described in the Study Plan, Table 1 and recorded in the eCRF.

5.2.5.1 Heart rate and Blood pressure

At most visits, HR and BP will be measured according to usual clinical practice. On specific visits indicated in Table 1, HR and BP will be measured in triplicates after the patient has been comfortably at rest in a seated position for at least 5 min. The position of the patient should be comfortable with the arm where the blood pressure is recorded to be within the level of heart (the middle of the cuff on the upper arm is at the level of the right atrium (the midpoint of the sternum). The patient will be instructed to relax as much as possible and to not talk during the measurement procedure. Preferably measurement will be done with an electronic automated oscillometric device. The same device should preferably be used for the patient during the course of the study and in the same arm. BP will be measured in triplicate with at least one-minute intervals between measurements. All the three readings will be reported in the eCRF.

The HR will be assessed by pulse palpation of radial artery for 30 seconds immediately after each recording of the BP. It could be also performed with an oscillometric device if this is used for BP measurement. The triplicate HR assessments will be recorded in the eCRF.

5.3 Other assessments

5.3.1 Patient reported outcomes

All study patients will be asked to complete the Health Related Quality of life (HRQoL) questionnaires at time points indicated in the Study Plan, Table 1.

5.3.1.1 Short Form 36 – (SF-36)

The SF-36 version 2, standard is a general HRQoL instrument designed to assess generic health concepts relevant across age, disease and treatment groups. It is aimed at both adults and adolescents aged eighteen years and older. The SF-36 consists of eight domains of health status: Physical functioning (PF) - 10 items; Role-physical - RP - 4 items; Bodily pain - 2 items; General health (GH) - 5 items; Vitality (VT) - 4 items; Social functioning (SF) - 2 items; Role emotional (RE) - 3 items; and Mental health (MH) - 5 items. Two component scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) can also be calculated. For both the SF-36 domain scores and summary scores, higher scores indicate better health status. The SF-36 standard version has a recall period of the ‘past four weeks’.

5.3.1.2 Functional Assessment of Cancer Therapy - Anemia (FACT-An)

The FACT-General (FACT-G) version 4 contains 27 items that cover four dimensions of disease-specific HRQoL: Physical well-being (PWB) - 7 items; Functional well-being (FWB) - 7 items; Social/family well-being (SWB) - 7 items; Emotional well-being (EWB) - 6 items. A subscale of 13 fatigue specific items (the Fatigue Subscale) plus seven additional items related to anemia were developed for use in conjunction with the FACT-G. The 13 fatigue items plus the seven additional items related to anemia comprise the Anemia Subscale (Additional Concerns). Administration of the FACT-G plus the Anemia Subscale is referred to as the FACT-An. The FACT-An has a recall period of the 'past seven days'. Respondents are asked to provide responses (i.e. 'Not at all', 'A little bit', 'Somewhat', 'Quite a bit' and 'Very much'), to a list of statements which are either positively or negatively phrased. For all FACT-An scales, a higher score indicates better HRQoL.

5.3.1.3 Patients' Global Impression of Change (PGIC)

The PGIC is an instrument where patients rate change in their overall health status compared to the start of the study treatment. Ratings are done on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

5.3.1.4 EuroQol Health Utility Index - (EQ-5D-5L)

The EQ-5D-5L is a self-reported questionnaire measuring utility values. The EQ-5D consists of the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The EQ-5D descriptive system comprises 5 dimensions of health: Mobility; Self-care; Usual activities; Pain/discomfort; and Anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The VAS records the respondent's self-rated health status on a graduated (0-100) scale, where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state' with higher scores for higher HRQoL. EQ-5D health states, defined by the EQ-5D descriptive system, may be converted into a single summary index by applying a formula that essentially attaches values (also called weights) to each of the levels in each dimension. The index can range from 1 for full health to 0 for being dead, but it can also be below 0 indicating a health state worse than being dead.

5.3.1.5 Administration of patient-reported outcome

All patient-reported outcomes (PRO)s are paper-based and will be administered at baseline and according to Study Plan, Table 1 and recorded in the eCRF. The questionnaires should be completed by the patient prior to any other intervention.

Each center must allocate the responsibility for the administration of the questionnaire to a specific individual (e.g., a research nurse, study coordinator) and if possible assign a back-up person to cover if that individual is absent. The AstraZeneca study team (or delegate) will provide relevant training in administration of the questionnaires. The significance and relevance of the data need to be explained carefully to participating patients so that they are motivated to comply with data collection.

The instructions for completion of the PRO questionnaires are as follows:

- The SF-36 should be completed first, thereafter the FACT-An, EQ-5D-5L and PGIC at scheduled visits
- They must be completed prior to any other study procedures (following informed consent) and before discussion of disease progress to avoid biasing the patient's responses to the questions. They must be completed in private by the patient
- The patient should be given sufficient time to complete at their own speed
- The patient should not receive help from relatives, friends or clinic staff to answer the questionnaires
- On completion, the questionnaires should be handed back to the person responsible for questionnaires who should check for completeness
- Only one answer should be recorded for each question

5.3.2 Hospitalizations

Details on hospitalizations (including emergency room/skilled nursing facility use) will be collected at each study visit. Reason, admission, discharge dates, type and reason for hospitalization will be recorded in the eCRF. Details on hospitalizations will also be collected at follow-up visits in patients who prematurely discontinued treatment (only if they have taken at least one dose of study drug), until EOS.

5.4 Pharmacokinetics

5.4.1 Collection of samples

Venous blood samples (4 mL) for determination of roxadustat concentration in plasma will be collected at week 4 and week 8. Patients will be instructed NOT to take the study medication on the day of week 4 visit (not necessary for week 8). If a dose of the study medication is scheduled for that day, the dose can be given AFTER the collection of the blood sample. For both visits the date and time of sample collection will be recorded as well date and time of the study last dosing of study medication.

Samples will be collected into appropriately labelled tubes containing sodium-heparin as anticoagulant. Immediately after collection, blood samples will be kept on melting ice until ready for centrifugation, which must be done within 30 minutes of collection. Blood samples will be centrifuged at 1500 g for 10 minutes at room temperature in order to obtain plasma. Plasma will be harvested and transferred into an appropriately labelled amber polypropylene storage tube and stored at -20°C or below, within 30 minutes of centrifugation. Samples will be stored frozen at the site until shipment. Samples will be sent to the central laboratory packed with sufficient dry ice to keep the samples frozen. All applicable shipping regulations will be followed. Further details will be provided in the laboratory manual.

5.4.2 Determination of study drug concentration

For the patients receiving roxadustat, samples for pharmacokinetic (PK) determination will be analyzed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using validated bioanalytical methods. Full details of the analytical methods used will be described in a separate bioanalytical report.

The plasma concentration data will be listed and summarized on the basis of time intervals and plotted in scattering with time relative to the immediately preceding roxadustat dosing time. A population PK analysis of data collected in the CKD- non-dialysis dependent (CKD-NDD) program will be performed using the non-linear mixed-effects modelling technique as outlined in a population PK analysis plan.

5.4.3 Storage and destruction of pharmacokinetic samples

PK samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical Report.

5.5 Pharmacodynamics

5.5.1 Collection of samples

For collection and assessment of the pharmacodynamics with respect to Hb, see Table 1 and Section 5.1.

5.5.2 Storage, re-use and destruction of pharmacodynamic samples

Pharmacodynamic samples will be disposed of during the study.

5.6 Pharmacogenetics

Pharmacogenetic samples CCI [redacted] will be collected at baseline, i.e., at randomization visit (week 0).

5.6.1 Collection of pharmacogenetic samples

The patient´s consent to participate in the pharmacogenetic research components of the study is mandatory. Patients may participate in the study without participating in genetic sampling.

The blood sample for genetic research will be obtained from the patients at randomization visit (week 0). Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any

reason the sample is not drawn at the randomization visit it may be taken at any visit until the last study visit, before starting the closure period. Only one sample should be collected per patient for genetics during the study.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

5.6.2 Storage, re-use and destruction of pharmacogenetic samples

CCI [redacted]

The results of any further analyses will be reported either in the Clinical Study Report itself or as an addendum or separately in a scientific report or publication.

CCI [redacted]

CCI [redacted]

5.7 Biomarker analysis

The patient's consent to the use of donated biological samples is mandatory. Patients may participate in the study without participating in biomarker sampling.

Blood samples will be collected at baseline, i.e. pre first dose in the study (week 0, pre-dose) and at week 24 (at any time), and may be analyzed for exploratory biomarkers to assess correlations with disease activity, effects of study drug and clinical outcomes (including CV risk).

5.7.1 Storage, use, re-use and destruction of biological samples

Biological samples will be used for analyses of hsCRP and hepcidin.
Samples for future research will be retained at AstraZeneca or its designee for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

5.7.2 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category a materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

5.7.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle. The Principal Investigator at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for future use are registered within the relevant sample tracking system at AstraZeneca.

5.7.4 Withdrawal of Informed Consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. However, this does not result in withdrawal of the patient from the study and patient should continue until the end of study. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is communicated immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed and the action documented
- Ensures the laboratory (ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal

AstraZeneca ensures the central laboratory (ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

An AE (classified by preferred term) that occurs during the double-blind treatment period will be considered a TEAE (Treatment Emergent Adverse Event) if it was not present prior to the first dose of study drug, or it was present prior to the first dose of study drug but increased in severity during the double-blind treatment period. An AE that occurs more than 28 days after the last dose of study medication will not be counted as a TEAE.

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., screening, treatment and follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Serious Adverse Events (SAEs) will be collected from the time of signature of informed consent throughout the treatment period and including the follow-up period.

Adverse Events (AEs) will be collected from randomization throughout the treatment period and including the follow-up period. See Section 3.9.3.2 for details regarding AE collection for subjects who are followed by modified follow-up after premature discontinuation of IP.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the follow up visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Intensity or changes in intensity

- The investigator should use the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. For terms not specified as part of NCI- CTCAE, the following guidelines should be used to determine grade:

    - Grade 1, Mild: Asymptomatic or mild symptoms that the patient finds easily tolerated. The event is of little concern to the patient and/or of little-or-no clinical significance; clinical or diagnostic observations only; intervention not indicated

    - **Grade 2, Moderate:** The patient has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (e.g. preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or non-invasive intervention indicated
    - **Grade 3, Severe:** The patient is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the patient and/or poses substantial risk to the patient's health or well-being; Likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization
    - **Grade 4, Life-threatening:** The patient was at immediate risk of death from the event as it occurred
    - **Grade 5, Death:** Related to AE

Grade 4 & 5 are SAE criteria and collected as SAE in the AE eCRF module. The following variables will be collected:

- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused patient's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge

- Probable cause of death, if applicable
- Date of death, if applicable
- Autopsy performed, if applicable
- Causality assessment in relation to Study procedure(s)
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures and additional study drug. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'* or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g. anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.7 Liver enzymes

If a patient meets any of the following criteria, please refer to Appendix D for further instruction: AST≥3xULN, ALT≥3xULN, total bilirubin ≥2xULN.

6.3.8 Disease progression

Changes in patient condition that are due to progression of the disease for which the investigational product is being studied (for example, anemia or CKD) should not be considered AEs or SAEs. This includes an increase in the severity of the disease under study, and an increase in the symptoms of the disease under study. Roxadustat is being studied for the treatment of anemia in CKD. CKD progression should therefore not be considered an AE or SAE. Acute kidney injury, when meeting diagnostic criteria (i.e. based on serum creatinine values or urine output), can be considered an AE or SAE. AEs or SAEs that cause anemia should be recorded, but anemia for which no cause is found other than CKD should not be reported as an AE or SAE.

6.3.9 Patients initiating dialysis during the treatment period

In patients judged on clinical grounds to require dialysis during the study, study medication should be continued until study closure, unless protocol specified reasons for investigational product discontinuation are present. Initiation of chronic dialysis should be recorded in the eCRF.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e. immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e. immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site personnel how to proceed. The reference document for definition of expectedness is the IB for the AstraZeneca drug.

6.5 Overdose

The maximum tolerated dose of roxadustat has not been established in humans. For the purposes of this study, exceeding the maximum allowed dose specified in this CSP (3.0 mg/kg or 300 mg per administration, whichever is lower) represents an overdose.

An overdose with associated AE(s) is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

An overdose without associated AE(s) is only reported on the Overdose eCRF module. If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to AstraZeneca.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca or its representative on the pregnancy form.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e. immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented as described in Section 6.6.1. To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information.

6.7 Management of IP related toxicities

Observed adverse effects demonstrated in nonclinical safety studies (refer to Section 4 of the IB) following administration of roxadustat are primarily caused by an exaggerated pharmacological response, which can be managed in the clinical setting. The dose algorithm will mitigate excessive Hb elevation.

If there are clinical concerns for a patient due to excessive elevation in Hb levels, the investigator may decide to perform a therapeutic phlebotomy instead of or in addition to, a dose hold. For overdose see Section 6.5.

6.8 Study governance and oversight

6.8.1 International coordinating investigator

The International coordinating investigator (ICI) in collaboration with AstraZeneca will be responsible for the overall design, interpretation, supervision and reporting (presented at international congresses and published in peer reviewed journals) of the study, including the development of the protocol and any protocol amendments.

6.8.2 Independent Endpoint Review Committee

An Independent Endpoint Review Committee (IERC) will be appointed and will adjudicate potential endpoint events. The committee members will not have access to individual treatment codes for any patient or clinical efficacy and safety event. The precise responsibilities and procedures applicable for the IERC will be detailed in a separate IERC charter.

6.8.3 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be appointed and will report to the International Coordinating Investigator and sponsor. The DSMB will be responsible for safeguarding the interests of the patients in the outcome study by assessing the safety of the intervention during the study and for reviewing the overall conduct of the clinical study. The DSMB will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing.

The DSMB charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the International Coordinating Investigator and sponsor.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Table 3 Identity of investigational products

Investigational product	Dosage form and strength	Manufacturer
Roxadustat	Oral tablets 20mg, 50mg and 100mg	FibroGen
Placebo	Oral tablets to match 20mg, 50mg and 100mg	FibroGen

The formulation number and batch number will be recorded in the study master file and identified in the clinical study report (CSR).

Roxadustat and matching placebo oral tablets will be packaged in bottles supplied by AstraZeneca. The tablet strengths are different in size and each strength has a matching placebo. The tablets should remain in original packaging until administration. The tablets

should be swallowed whole with water. The tablets must not be chewed, crushed or divided. The excipients include lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate and colorant Red Opadry II (contains Lecithin (Soya), FD&C Red #40 Aluminium Lake).

7.2 Dose and treatment regimens

7.2.1 Randomization

Patients will be randomized to receive roxadustat or placebo in a 1:1 ratio in a double-blind manner. Randomization schedules will be prospectively prepared. Automated randomization and assignment to treatment arm will be provided by IWRS/IVRS. The randomization in this study will be stratified by country.

The number of tablet bottles that will be dispensed may vary depending on the dose. Dispensation will be managed by IWRS/IVRS. The administration will be detailed on a dosing card. Doses administered will be recorded in the eCRF.

The administration of the first dose of study drug would mark the beginning of the treatment period. Hemocue values will be used for all dose adjustments, including baseline values from Hemocue values at randomization. Missed doses should not be replaced.

7.2.2 Starting dose and dose adjustment

The initial study drug dose (per dose occasion) is 70 mg orally administered three times a week (TIW).

The first study drug administration will be on Day 1 (week 0). Study drug doses must be administered at least 2 days apart and no more than 4 days apart (e.g., Monday , Wednesday, Friday). Study drug will be dosed TIW throughout the study treatment period unless downward dose adjustment requires a change to twice or once weekly.

Dose adjustments are permitted starting at week 4 and at intervals of every 4 weeks until week 52, every 8 weeks thereafter using the dose adjustment algorithm (see Table 4). If dose reduction is required for excessive erythropoiesis, the dose may be adjusted at any time. All dose adjustments are based on Hb values using Hemocue, a point-of-care device. Hb values will be recorded in the eCRF (during the screening period) and in IWRS (during the treatment period).

Table 4 Dose adjustment algorithm

Changes in Hb over past 4[a] weeks	Hb <10.5g/dL	Hb 10.5 to 11.9g/dL	Hb 12.0 to 12.9g/dL	Hb ≥13.0g/dL
<-1.0	↑	↑	**No change**	**Hold, then resume dosing when Hb≤11.9 g/dL, at a dose that is reduced by two dose steps**
-1.0 to 1.0	↑	**No change**	↓	
>1.0	**No change**	↓	↓	

Dose Increases and Reductions:

Dose increases (↑) and reductions (↓) are pre-set according to dose steps.

The dose steps are as follows: 20, 40, 50, 70, 100, 150, 200, 250 and 300mg.

Example: A dose increase at a dose of 70 mg results in 100 mg as the new dose. A dose reduction at a dose of 150 mg results in 100 mg as the new dose.

If patients on 20 mg TIW need dose reduction, change frequency to twice a week, i.e. 20 mg administered twice a week. If further dose reduction is needed, reduce frequency to once weekly, i.e. 20 mg administered once a week.

Note: Maximum dose is capped at the lower of 3.0 mg/kg or 300 mg per dose administration

Dose Adjustment for Excessive erythropoiesis

- If Hb increases by >2.0 g/dL within a 4 week period, reduce dose by one step.

a After week 52, adjust dose based on current Hb (increase 1 dose step if <10.5g/dL, no change if 10.5 to 11.9 g/dL, decrease 1 dose step if 12 to 12.9 g/dL)

7.2.3 Dose adjustment for excessive Erythropoiesis

Excessive erythropoiesis is defined in Table 4. In the event of excessive erythropoiesis, the dose may be adjusted at any time, even on visits without a dose adjustment review. In such cases, dose adjustment reviews are then resumed at 4-week intervals until week 52, where after there will be 8-week intervals. If a dose adjustment review is performed on week 18, then the next dose adjustment review will be scheduled on week 24, since there is no scheduled visit on week 22.

7.2.4 Dose adjustment for Hb ≥ 13.0g/dL

In the event of Hemocue Hb value ≥13.0g/dL, dosing will immediately be put on hold. Resume dosing at a subsequent visit when Hb ≤11.9 g/dL, at a dose that is reduced by two dose steps. After dosing has been resumed, the dose adjustment reviews are then continued at 4-week intervals until week 52, where after there will be 8-week intervals, following the same principle as for excessive erythropoiesis.

7.2.5 Patients initiating dialysis during the treatment period

In patients judged on clinical grounds to require dialysis during the study, study medication will be continued until study closure, unless protocol specified reasons for investigational product discontinuation are present. See Section 7.7.4 for criteria for rescue therapy in dialysis patients. Initiation of dialysis should be recorded in the eCRF.

7.3 Labelling

Labelling of the investigational products will be carried out by AstraZeneca or their designee in accordance with current Good Manufacturing Practice (GMP). The labels will fulfil GMP Annex 13 requirements for labelling and local regulatory guidelines. Label text will be translated into local language.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage.

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient. Study site personnel, if applicable or the AstraZeneca monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed. Unused and/or returned investigational products should be destroyed according to local regulations.

7.7 Concomitant and other treatments

7.7.1 Concomitant medications

Concomitant medications are any prescription or over-the-counter preparations, including herbal products and "natural remedies", used by a patient while participating in this clinical study. For all concomitant medications, an indication for its use should be provided. If the stated indication is a non-specific condition, e.g. "rash", documentation of the condition, as specific as possible, should be maintained in the patient's clinical study records as source documentation.

7.7.1.1 Statins

When coadministered with roxadustat, hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) exposure was increased 2- to 3-fold. Investigators should consider this interaction and local prescribing information when deciding on the appropriate statin dose for individual patients, bearing in mind the impact of ethnicity, other concomitant medications, renal and hepatic function. Goals of lipid lowering treatment should be maintained as clinically indicated. The recommended maximum daily statin doses are: simvastatin 20 mg, atorvastatin 40 mg, rosuvastatin 10 mg, pravastatin 40 mg, fluvastatin 40 mg (20 mg if eGFR<30), pitavastatin 2 mg (1 mg if eGFR<30).

7.7.1.2 Phosphate binders

When coadministered with phosphate binders, roxadustat exposure was reduced. Patients should be advised to discuss with the investigator before changing their phosphate binder dose or dosing time. To optimize absorption of roxadustat, subjects should take roxadustat with at least 1 hour separation from their phosphate binder.

7.7.1.3 Herbal medicines

Use of herbal medicine during the study is not prohibited but strongly discouraged. All herbal and natural remedies should be reviewed by the investigator and if considered safe, may be allowed to continue at the same dose.

7.7.2 Prohibited medications

The following medications/therapies are prohibited during the study:

- Any other investigational drug: from randomization until EOS
- Any erythropoietin analogues during the treatment period, except as rescue medication (Section 7.7.4.3)
- Iron-chelating agents (e.g. deferoxamine/desferrioxamine, deferiprone or deferaxirox therapy): from 4 weeks prior to screening until EOS
- Androgens: from randomization onwards until EOS
- Dapsone (at any dose) from randomisation to EOS
- Chronic doses of acetaminophen/paracetamol >2.0 g/day from randomization until EOS

7.7.3 Supplemental iron use

Oral iron supplementation is allowed for both treatment arms without restriction.

Oral iron is recommended for dietary supplementation to support erythropoiesis and as the first- line for prevention and treatment of iron deficiency, unless the patient is intolerant to this treatment.

In addition to scheduled assessments (Table 1), iron indices may be assessed anytime (via central lab) to evaluate iron storage status of the patients, if considered necessary by the investigator.

7.7.4 Rescue therapy guidelines

Rescue therapy guidelines are provided to optimize standardization of the use of rescue therapy by investigators and to ensure safety of the individual study patients. Rescue therapy should be recorded in the eCRF.

7.7.4.1 Intravenous iron supplementation

The use of intravenous iron is not encouraged in the setting of this placebo-controlled study. Oral iron is recommended for dietary supplementation to support erythropoiesis and as the first-line for prevention and treatment of iron deficiency, unless the patient is intolerant to this treatment.

The investigator may initiate the use of an approved IV iron supplement if:

- the patient is receiving or does not tolerate oral iron, **and**
- Hb < 8.5 g/dL **and**
- Ferritin <100 ng/ml **or** Transferrin saturation (TSAT) <20%

Study treatment may continue during IV iron administration. Ferritin and TSAT assessment is recommended 4 weeks after IV iron administration. Discontinuation of IV iron supplementation is recommended once the patient is no longer considered to be iron deficient (ferritin ≥100 ng/mL and TSAT ≥20%) or Hb >9 g/dL, whichever comes first. Use of IV iron will be recorded in the eCRF.

7.7.4.2 Red blood cell transfusion

Red blood cell (RBC) transfusion is allowed if rapid correction of anemia is required to stabilize the patient's condition (e.g. acute hemorrhage) or the investigator is of the opinion that the blood transfusion is a medical necessity. Study drug treatment may continue during or after RBC transfusion administration. Transfusion will be recorded in the eCRF.

7.7.4.3 Initiation of Rescue with an approved erythropoietin analogue

The investigator may initiate use of an approved erythropoietin analogue if all of the following criteria are met:

- A patient's Hb level has not sufficiently responded to two or more dose increases or the maximum dose limit of the study drug has been reached, **and**
- The patient's Hb is <8.0 g/dL on two consecutive measurements drawn at least five days apart; **and**
- Clinical judgment does not suggest iron deficiency or bleeding as a cause of lack of response or rapid decline in Hb (see 7.7.4.1 and 7.7.4.2 above for addressing these conditions), **and**
- Reducing the risk of alloimmunization in transplant eligible patients and/or reduction of other RBC transfusion-related risks is a goal

The patient is not allowed to be administered both erythropoietin analogue and study drug at the same time. For patients not on dialysis, treatment with erythropoietin analogue should be

stopped when Hb >9 g/dL or after a 4-week cycle has been completed, whichever comes first. Study treatment should be resumed after the following intervals:

- Two days after stopping epoetin
- One week after stopping darbepoetin alfa
- Two weeks after stopping methoxy polyethylene glycol-epoetin beta (Mircera)

Use of erythropoietin analogues will be recorded in the eCRF.

Patients may receive 2 cycles of rescue with erythropoietin analogues. If they meet the above criteria for erythropoietin rescue for a third time, study drug should be permanently discontinued (see Section 3.9.3). Study drug should be permanently discontinued for subjects who initiate dialysis and who are clinically judged to require erythropoietin analogue therapy.

7.7.4.4 Therapeutic Phlebotomy

If there are clinical concerns for a patient due to excessive elevation in Hb levels, the investigator may decide to perform a therapeutic phlebotomy instead of, or in addition to, a dose hold. This should be documented and discussed with the study AstraZeneca study physician.

7.7.4.5 Other concomitant treatment

Other medication than described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections in the eCRF.

7.8 Post Study Access to Study Treatment

After end of treatment with study drug, patients should be managed according to local standard of care.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified. Analyses will be performed by AstraZeneca or its representatives.

A comprehensive SAP will be prepared prior to database lock.

8.2 Sample size estimate

Primary efficacy endpoint: A sample size of 450 subjects will have > 99% power to detect a 0.75 g/dL difference in mean Hb values between the two treatment groups, assuming that the common standard deviation is 1.2 g/dL, using an analysis of variance (ANOVA) test with a 0.05 two-sided significance level.

To contribute adjudicated CV safety events for the pooled CV analyses across the phase 3 program: approximately 2600 subjects are planned to be randomized in a 1:1 ratio to either roxadustat or placebo. The sample size in this study is driven by the overall requirement of adjudicated CV events for the phase 3 program in CKD-NDD (which consists of 3 studies in total targeting 465 subjects with MACE events). The two other placebo-controlled studies in the study program are FGCL-4592-060 and 1517-CL-0608.

Further information related to the sample size determination can be found in the study statistical analysis plan and the pooled statistical analysis plan.

8.3 Definitions of analysis sets

8.3.1 Intention To Treat Analysis Set (ITT)

All subjects who have been randomized to study treatment will be included irrespective of their protocol adherence and continued participation in the study. Subjects will be analysed according to their randomized study medication irrespective of intake of study medication.

8.3.2 Per Protocol Set (PPS)

All randomized subjects without important protocol deviations and who have received at least 8 weeks of study treatment and have valid corresponding Hb measurements from the central laboratory will be included in the PPS. Subjects will be analysed according to their randomized study medication irrespective of intake of study medication. Subjects with an important protocol deviation will be included in the PPS up to the time point when the violation was met. For criteria for PPS exclusion, see Table 1 in the SAP. Further details of important protocol deviations are available in a Protocol Deviation Plan. Subjects will be censored at the earliest of date of an important protocol deviation, the EOS visit, or 28 days after last intake of study drug.

8.3.3 Safety analysis set

All subjects who received at least one dose of randomized study drug will be included in the Safety Analysis Set. Throughout the safety results sections, erroneously treated subjects will be accounted for in the actual treatment group. If a subject has received both treatments, only the initial period will be utilized. Subjects will be censored 28 days after last intake of study drug. The Safety Analysis Set may also be referred to as On-treatment+28 (OT+28).

8.3.4 Full Analysis Set (FAS)

The FAS consists of all subjects in the ITT analysis set who received at least one dose of study drug and have baseline and at least one post-dose Hb assessment. If actual study medication received differs from the randomized treatment arm, the randomized treatment arm will be used for analysis for the FAS. This analysis set is primarily used for EX-US submissions.

8.3.5 Subjects who will not be included in any analysis sets

Subjects or sites identified prior to unblinding with major Good Clinical Practice violations and where the integrity of the data is strongly questioned through thorough independent investigations will be excluded from all analyses and all analysis sets. This includes but are not limited to subjects who have been identified to be part of a potential fraud investigation, subjects who have not signed an informed consent, subjects randomized in error (e.g. a subject considered to be a screen fail but by mistake randomized in the IWRS due to a technical error). Further, subjects being randomized more than once will only contribute to the analysis one time. These patients will be analyzed according to their first assigned randomization number and treatment code. All AE's reported for the subjects will be assigned to the subject´s first randomization number. All subjects excluded from all analysis sets will be properly documented.

8.4 Outcome measures for analyses

8.4.1 Primary efficacy endpoint

US FDA: The primary efficacy endpoint for the US is the mean change from baseline in Hb averaged over week 28 to week 52. A multiple imputation approach with analysis of covariance (ANCOVA) will be applied as a method to handle missing data. Details of the multiple imputation ANCOVA are provided in the SAP.

Hb results obtained from the central laboratory will be used for all Hb efficacy analyses. Baseline Hb is defined as the mean of the three last central laboratory Hb values from the screening and randomization visits.

Hb values under the influence of a rescue therapy will not be censored.

EU health authorities: The primary efficacy endpoint is whether patients achieved Hb response as described below.

- Hb response (Yes/No), where Yes is defined as:

    - Hb ≥ 11.0 g/dL and Hb increase from baseline by ≥ 1.0 g/dL, for subjects with baseline Hb > 8.0 g/dL; or

    - Hb increase from baseline by ≥ 2.0 g/dL, for subjects with baseline Hb ≤ 8.0 g/dL

  at two consecutive visits [dates] (with available data) separated at least 5 days during the first 24 weeks of treatment without having received rescue therapy (RBC transfusion, ESA, or IV iron) prior to Hb response. Subjects who have discontinued study medication or received rescue therapy before a Hb response could be achieved will be considered as a non-responder.

8.4.2 Hb related secondary efficacy endpoints

The Hb related secondary efficacy variables are:

- The EU primary endpoint is the first secondary efficacy endpoint the analysis for FDA

- Mean change in Hb from baseline to the subjects mean level between week 28 to week 52 in subjects with baseline high-sensitivity C-reactive protein (hsCRP) greater than the Upper Limit Normal (ULN)

- Proportion of total time of Hb ≥ 10 g/dL from week 28 to week 52. The proportion of total time will be computed as follows: For each subject, the recorded Hb values will first be linearly interpolated between measurements. The time this interpolated curve is ≥10 g/dL will be computed and subsequently divided by the time between the measurements at week 28 and week 52. Patients without any Hb measurements from week 28 will not be considered for this variable.

- Proportion of total time of Hb within the interval of 10-12 g/dL from week 28 to week 52. The proportion of total time will be computed as follows: For each subject, the recorded Hb values will first be linearly interpolated between measurements. The time this interpolated curve is within 10-12 g/dL will be computed and subsequently divided by the time between the measurements at week 28 and week 52. Patients without any Hb measurements from week 28 will not be considered for this variable.

8.4.3 Lipid related secondary efficacy endpoints

To evaluate the roxadustat effect on lipids, the following variable will be evaluated

- Mean change in LDL cholesterol from baseline to week 24.

8.4.4 Rescue therapy related secondary efficacy endpoints

The need for rescue therapy will be evaluated as:

- Time-to-first (and proportion of subjects receiving) instance of receiving intravenous (IV) iron, red blood cell (RBC) transfusions, or erythropoietin analogue as rescue therapy (rescue therapy guidelines are specified in the clinical study protocol (CSP), Section 7.7.4).
- Time-to-first (and proportion of subjects receiving) instance of receiving red blood cell (RBC) transfusions as rescue therapy.

and will be computed, as the number of days plus one between the day of first dose of study drug and the date of the first occurrence of rescue therapy, or if no event has occurred before censoring, the date of censoring.

8.4.5 36-Item Short Form Health Survey

The SF-36 is a QoL instrument designed to assess generic health concepts relevant across age, disease, and treatment groups. It is aimed at both adults and adolescents aged eighteen years and older. The SF-36 consists of eight domains of health status: Physical functioning (10 items), Role-physical (4 items), Bodily pain (2 items), General health (5 items), Vitality (4 items), Social functioning (2 items), Role emotional (3 items) and Mental health (5 items). Two component scores, the Physical Component Summary and the Mental Component Summary can also be calculated. For both the SF-36 domain scores and summary scores, higher scores indicate better health status. The SF-36 has a recall period of the 'past four weeks'.

- Change from baseline in SF-36 Physical Functioning (PF) sub-score
- Change from baseline in SF-36 Vitality (VT) sub-score

The SF-36 scores will be computed according to its documentation

8.4.6 CKD progression related secondary efficacy endpoints

To evaluate the effect of roxadustat on the CKD progression prior to initiation of dialysis/kidney transplant, the following variable will be analyzed:

- Annual rate of eGFR change in log scale, calculated as the slope of log (eGFR values), prior to initiation of dialysis/kidney transplant

8.5 Adjudicated CV Events Analyses for Safety Assessments

The CV events described in Section 5.2.1 will be adjudicated by the Independent Event Review Committee (IERC) according to the IERC charter. The same adjudication committee will be used for three phase 3 studies, FG-4592-060, 1517-CL-608 and D5740C00001, in the CKD-NDD program. Analyses of these adjudicated events are described in a separate pooled analysis plan.

8.6 Methods for statistical analyses

A detailed Statistical Analysis Plan (SAP) will be finalized prior to database lock. Any significant changes to the analyses described in this protocol will be highlighted in the SAP and the Clinical Study Report (CSR). Moreover further details of the statistical analyses are provided in the SAP.

8.6.1 Stratification variables

The randomization in this study will only be stratified by country. The stratification variables for the other two studies in the program will be used in the analyses for this study as covariates. The variables are:

1. Baseline eGFR (≤ 30 mL/min/1.73 m2 vs > 30 mL/min/1.73 m2)
2. Baseline Hb (≤ 8 g/dL vs > 8 g/dL)
3. cardiovascular/cerebrovascular/thromboembolic medical history (Yes vs. No)
4. geographical region (US vs Ex-US)

Baseline Hb and baseline eGFR will be included in the analyses as continuous covariates, not as dichotomous factors, unless specified otherwise. Throughout this document, the variable cardiovascular/cerebrovascular/thromboembolic medical history will be shortened as CV history.

CV history at baseline will be defined for subjects with history of any of the following diseases:

- Myocardial infarction
- Percutaneous coronary intervention
- Coronary artery bypass
- Cardiac failure congestive
- Ischaemic stroke
- Haemorrhagic stroke
- Cerebrovascular accident

8.6.2 Analysis of the primary efficacy endpoint for US

Mean change in Hb from baseline to the subjects mean level from week 28 to week 52 will analysed with multiple imputation ANCOVA as described in the SAP. The model will contain

terms for the treatment, baseline Hb measurement, baseline eGFR, geographic region and CV history. Superiority of roxadustat compared to placebo will be declared, and this test as successful, if the lower bound of the 2-sided 95% confidence interval of the difference between roxadustat and placebo exceeds 0 g/dL. The ITT analysis set will be used.

8.6.3 Analysis of the primary efficacy endpoint for EU (Secondary Endpoint for FDA)

Hb response (Yes/No), where Yes is defined as:

- Hb ≥ 11.0 g/dL and Hb increase from baseline by ≥ 1.0 g/dL, for subjects with baseline Hb > 8.0 g/dL; or

- Hb increase from baseline by ≥ 2.0 g/dL, for subjects with baseline Hb ≤ 8.0 g/dL

at two consecutive visits [dates] (with available data) separated at least 5 days during the first 24 weeks of treatment without having received rescue therapy (RBC transfusion, ESA, or IV iron) prior to Hb response. The first date of the two consecutive visits will be used as the date of response. The second date of the two consecutive visits will be used when evaluating the presence or absence of rescue therapy. The proportion of responders in the primary efficacy variable will be compared using a Cochran–Mantel–Haenszel (CMH) test adjusting for the region, history of CV, baseline Hb (<=8, >8 g/dL) and baseline eGFR (<=30, >30 mL/min/1.73 m2), comparing roxadustat to placebo. The FAS will be used.

8.6.4 CV safety endpoint analyses

The CV safety evaluation strategy is to conduct pooled analyses of adjudicated data across the study program to ensure that the overall number of events is high enough to provide adequate power. Thus, all analyses of CV safety will be conducted in accordance with the PSAP.

8.6.5 Analysis of the secondary efficacy endpoints

Secondary efficacy endpoints will be tested using a fixed sequence approach to adjust for multiple testing. If the p-value from a test is less than 0.05, the test will be declared as successful and the analysis will continue to the next comparison in the sequence. Formal statistical hypothesis testing will be stopped as soon as a test is accompanied by a p-value ≥0.05. The FAS will be used on the first secondary endpoint, OT+28 will be used for the two secondary endpoints related to rescue therapy, and the ITT analysis set will be used for all the remaining secondary endpoints.

1. The EU primary endpoint is the first secondary efficacy endpoint for FDA (see above)

2. Mean change in Hb from baseline to the subjects mean level from week 28 to week 52 in subjects with baseline hsCRP greater than the Upper Limit Normal (ULN) will be analysed analogously as the primary efficacy endpoint. Superiority of roxadustat compared to placebo will be declared, and this test as successful, if the lower bound of

the 2-sided 95% confidence interval of the difference between roxadustat and placebo exceeds 0 g/dL.

3. Proportion of total time of interpolated Hb values ≥ 10 g/dL from week 28 until week 52 will be estimated for each subject and used as dependent variable. The difference between roxadustat and placebo will be compared using ANCOVA with treatment group, geographic region and CV history as fixed factors and baseline Hb and baseline eGFR as covariates. Superiority between the groups will be declared, and this test as successful, if the lower bound of the 2-sided confidence interval of the difference between roxadustat and placebo exceeds 0.

4. Proportion of total time of interpolated Hb values within the interval 10-12 g/dL from week 28 until week 52 will be estimated for each subject and used as dependent variable. The difference between roxadustat and placebo will be compared using ANCOVA with treatment group, geographic region and CV history as fixed factors and baseline Hb and baseline eGFR as covariates. Superiority between the groups will be declared, and this test as successful, if the lower bound of the 2-sided confidence interval of the difference between roxadustat and placebo exceeds 0.

5. Mean change from baseline in LDL cholesterol to week 24 will be analysed using ANCOVA. Baseline Hb, baseline eGFR and baseline LDL will be used as covariates and treatment arm, CV history and geographic region as fixed effects. Superiority will be declared if the upper bound of the 2-sided 95% confidence interval of the difference between roxadustat and placebo exceeds 0.

6. Time-to-first (and proportion of subjects receiving) rescue therapy (composite) of any of IV iron, RBC transfusion or erythropoietin analogue as rescue therapy, will be analyzed using the Cox proportional hazard model with OT+28. Baseline Hb, baseline eGFR, geographic region, and CV history will be included as covariates. Superiority will be claimed, and this test successful, if the upper limit of the 2-sided 95% CI for the hazard ratio is less than or equal 1.0.

7. Time-to-first (and proportion of subjects receiving) RBC transfusion as rescue therapy, will be analyzed using the Cox proportional hazard model with OT+28. Baseline Hb, baseline eGFR, geographic region, and CV history will be included as covariates. Superiority will be claimed, and this test successful, if the upper limit of the 2-sided 95% CI for the hazard ratio is less than or equal 1.0.

8. Mean change in SF-36 Vitality (VT) sub-score from baseline to average VT sub-score of weeks 12-28 will be analyzed using MMRM with treatment, visit, treatment-by-visit interaction, and baseline covariates, including the baseline score, baseline Hb, baseline eGFR, and geographic region and CV history, as fixed effects and subject as a random effect. Superiority between roxadustat and placebo will be declared, and this test

successful, if the lower bound of the 2-sided confidence interval for the difference between roxadustat and placebo exceeds 0.

9. Annual rate of eGFR change in log scale prior to initiation of dialysis/kidney transplant will be estimated with MMRM using all post-baseline log (eGFR values) prior to initiation of dialysis/kidney transplant. Baseline eGFR in log scale, baseline Hb and geographic region, CV history, treatment group and post-baseline eGFR measurement time will be treated as fixed effects, and subject and time as random effects, i.e. random intercept and slope.

10. Mean change in SF-36 Physical Functioning (PF) sub-score from baseline to average PF sub-score of weeks 12-28 will be analyzed using MMRM with treatment, visit, treatment-by-visit interaction, and baseline covariates, including the baseline score, baseline Hb, baseline eGFR, and geographic region and CV history, as fixed effects and subject as a random effect. Superiority between roxadustat and placebo will be declared, and this test successful, if the lower bound of the 2-sided confidence interval for the difference between roxadustat and placebo exceeds 0.

8.6.6 **Subgroup analysis**

Defined in the SAP.

8.6.7 **Interim analysis**

No interim analysis specific to this study will be conducted.

8.6.8 **Sensitivity analysis**

Defined in the SAP.

8.6.9 **Exploratory analysis**

Exploratory analyses are specified in the SAP.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigators
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly and the action is documented and reported to the patient

The AstraZeneca representative will be available between visits if the Investigators or other staff at the center needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Study agreements

The Principal Investigator at each center should comply with all the terms, conditions and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients. In all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'. The study is expected to start in Q2 2014 and is estimated to end by Q3 2018.

The study may be terminated at individual centers if the study procedures are not being performed according to GCP or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with roxadustat.

9.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Center staff.

Data will be entered in the WBDC system at the study site. Trained site staff will be responsible for entering the data on the observation, tests and assessments specified in the protocol into the WBDC system and according to the eCRF instructions. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be Source Data Verified, reviewed/queried and updated as needed.

The principal Investigator is responsible for signing the eCRF and this can be delegated to a trained sub-investigator.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, signed and locked, a clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked. A copy of the eCRF will be archived at the study site when the study has been locked.

When the completed paper Case Report Forms for the PRO questionnaires have been completed by the patients, the data are to be entered ongoing into the eCRF by the site staff.

Dictionary coding

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the latest version of the AstraZeneca Drug Dictionary. Classification coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Center.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory (ies) internal or external to AstraZeneca.

Management of external data

The data collected through third party sources will be obtained and reconciled against study data. The AstraZeneca Data Management Center determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). The AstraZeneca Data Management Center will ensure that the data collection tool (IVRS/ IWRS, etc.) will be tested/validated as needed. External reconciliation will be done with the clinical database as applicable.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The informed consent form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

An Ethics Committee/Institutional Review Board (IRB) should approve the final study protocol, including the final version of the informed consent form and any other written

information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee and to the study site staff.

The opinion of the Ethics Committee/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The Ethics Committee/IRB should approve all advertising used to recruit patients for the study. AstraZeneca should approve any modifications to the informed consent forms that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrollment of any patient into the study, the national regulatory authority approves the final study protocol, including the final version of the informed consent forms or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the Ethics Committees/ Institutional Review Board (IRB) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed informed consent form(s) is/are stored in the Investigator’s Study File
- Ensure a copy of the signed informed consent form(s) is/are is given to the patient

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section10.3.

If a protocol amendment requires a change to a center's informed consent form, AstraZeneca and the center's Ethics Committee are to approve the revised informed consent form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority or an Ethics Committee may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted and data were recorded, analyzed and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH) and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

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Appendix A Not Applicable

Appendix B Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious.

These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'yes' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'no'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix C International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 - Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin – Hy's Law

1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥ 3x ULN **and** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination while there is no alternative causation:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver CRF Modules as information becomes available

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met. No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of
    'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

SIGNATURE PAGE

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