AstraZeneca

Clinical Study Protocol	
Drug Substance	Roxadustat
Study Code	D5740C00002
Version	8.0
Date	19 September 2018

A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of the Safety and Efficacy of Roxadustat in the Treatment of Anemia in Dialysis Patients

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

VERSION HISTORY

Global Clinical Study Protocol Version 8.0 is arising from:

Outside of US	Clinical Study Protocol version 7.0 (Outside of US)
US (only)	Clinical Study Protocol version 7.0 (US)

Clinical Study Protocol version 8.0
Rationale for protocol amendment: Changes were made to clarify operational and statistical aspects of the protocol, including minor editorial changes throughout the document to correct typographical errors and improve consistency and clarity. Changes to secondary efficacy in terms of addition of objectives and outcome measures as well as the ordering were made to harmonize D5740C00002 with the other phase 3 trials in the Roxadustat dialysis program (FG-4592-064, 1517-CL-0613 and FG-4592-063). 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). **Summary of changes from Clinical Study Protocol version 7.0 (US) and Clinical Study Protocol version 7.0 (Outside of US) to version 8.0:** **All below changes are updated in relevant sections of the study protocol.** **General changes throughout the document:** Estimated date of study completion changed throughout the entire document to Q3 2018. *Rationale for change:* Revision and clarification of estimated date of study completion. **Synopsis and Section 2.1. Primary safety objectives** The previous texts on primary objective is moved to the section on primary safety objective. New texts stating that pooled CV safety analyses are now described in the PSAP. *Rationale for change:* Harmonizes D5740C00002 with the other phase 3 trials in the roxadustat CKD dialysis program, to serve as a pivotal study for confirming efficacy and safety, and facilitates assessment of pooled safety across the phase 3 program. **Synopsis and Section 2.1. Primary efficacy objectives** Previous primary efficacy objective and its outcome measures is designated for US FDA. Another outcome measure designated for EU health authority, namely, Hb change from baseline (BL) to the average Hb of weeks 28 to 36, without having received rescue therapy (i.e. RBC transfusion for all subjects and ESA for roxadustat subjects) within 6 weeks prior to

and during this 8-week evaluation period is added.
Rationale for change:
Harmonizes D5740C00002 with the other phase 3 trials in the roxadustat CKD dialysis program, to serve as a pivotal study for confirming efficacy and safety, and facilitates assessment of pooled efficacy and safety across the phase 3 program.

Synopsis and Section 2.2. Secondary efficacy objectives
Here are the main changes as follows:

1. 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.
2. Proportion of total time of Hb ≥ 10 g/dL from week 28 to week 52", is added as a new outcome measure for the secondary efficacy objective based on Hb response and level during the study.
3. The secondary efficacy objective with its outcome measure related to composite rescue-therapy is replaced by a corresponding objective related to RBC transfusion. Proportion and number of subjects receiving RBC transfusion as rescue therapy are also reported.
4. The secondary efficacy objective with its outcome measure related to self-reported health status using EQ-5D-5L is removed
5. Additional secondary efficacy objectives with their outcome measures related to LDL cholesterol and IV iron are added.

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

Synopsis and Section 2.2. Secondary safety objectives
Two CV safety related secondary safety objectives are removed.
Rationale for change:
They are to be addressed in the pooled analyses across the phase 3 program according to the PSAP.

Synopsis and Section 8.2 Sample size estimate
The description of the determination of the sample size related to CV safety has been shortened.
Rationale for change:
Reference to a more detailed description of the requirements for sample size to address CV safety for this indication is made to the pooled statistical analysis plan.

Section 3.1 Inclusion criteria
Clarification of inclusion criterion 3 in order to show wording in previous versions of the protocol prior to US amendment ver 6.0 and outside of US amendment ver 7.0 (changed to recruit incident dialysis patients only) as the inclusion criteria was changed to include incident dialysis patients only for the REMAINDER of the study.
Rationale for change: Clarification.

Section 3.9.2 Permanent discontinuation from investigational product

Addition of reason for permanent discontinuation by investigator: "Patients who receive organ transplantation during the study"
Rationale for change: Clarification that subjects who receive organ transplantation should discontinue investigational products.

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 for change: Clarification.

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

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

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 for change: Clarification.

Section 5.1.1 Secondary efficacy assessments
The title of this section is changed to "Efficacy assessment".
Rationale:
Assessment of Hemoglobin level specified in 5.1.1.1 is for both the primary and some of the secondary efficacy endpoints.

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

Table 1: Study Plan, Table 2: Laboratory Safety Variables from Section 5.2.2, and Section 5.7.1 Storage, use, re-use and destruction of biological samples
Added that hepcidin and hsCRP will be analyzed from biomarker samples.
Rationale for change: Hepcidin and hsCRP will be analyzed from biomarker samples.

Section 5.6.1 Collection of pharmacogenetic samples
CCI [redacted]
Rationale for change: Clarification.

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.

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.

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

8.3.3 Safety Analysis Set (SAS)

Treatment groups to which SAS subjects belong is further clarified, and the censoring rule of OT+28 is removed.

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.

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.

8.4 Outcome measures for analyses

The text structure of this section is re-organized and subsections specific to primary and secondary efficacy endpoints efficacy are added.

Rationale for change:

For structure clarification.

Here are the changes in texts related to "primary efficacy endpoint" as follows:

1. A specific subsection with two parts, one for US FDA and the other for EU health authority, is created.
2. The previous primary efficacy endpoint is designated for US FDA, and its description is moved under its corresponding part with the following clarification:
   a. The texts, "Details of the ANCOVA multiple imputation will be provided in Section 8.5.2.", are changed to "Details of the ANCOVA multiple imputation will be provided in the SAP".
   b. Hb measurement from the central lab is specified. Calculation of baseline Hb and the censoring rule for the post baseline Hb are defined.
3. Another primary efficacy endpoint designated for EU health authority is added as a separate part.

Rationale for change:

For clarification and to be harmonized with the primary efficacy objective of the other phase 3 studies in the program.

Here are the changes in texts related to "efficacy related endpoint" as follows:

1. The texts, "efficacy related endpoint", are removed.
2. The secondary efficacy endpoints are presented in four subsections, 8.4.2-8.4.5, four for Hb-related response, one for lipid reduction, one for RBC rescue therapy and one for IV iron use.
3. Texts under "Evaluation of the need for rescue therapy" together with its bullet point on time-to-first administration of RBC are moved under the subsection specific for RBC rescue therapy with more details added. The other bullet point on time-to-first receiving RBC transfusion or ESA as rescue therapy is now an exploratory, rather than a secondary, efficacy endpoint (see SAP).
4. Additional secondary efficacy endpoints are added, three related to Hb response, one to lipid reduction, one to RBC rescue therapy use and one to IV iron use.

Rationale for change:

To harmonize with the secondary efficacy objectives of the other phase 3 studies in the program with clinically important variables for this indication.

Here are the changes in texts under "Primary safety endpoint" and "Additional safety composite endpoints" as follows:

1. A specified section, Section 8.5 entitled "Adjudicated CV Events Analyses for Safety Assessments", is created to address CV safety of the study.
2. Previous texts under these two parts are moved under this section and replaced by new texts, in which CV safety endpoint analyses according to the PSAP using adjudicated events are emphasized.

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

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 Event 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 studies.

8.5.1 Stratification variables
Here are the changes as follows:

1. The section number is changed from 8.5.1 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 harmonize with the other phase 3 studies in the program.

8.5.2. Analysis of the primary efficacy variable
Here are the changes as follow:

1. This section is split into two sections, 8.6.2 is entitled "Analysis of primary efficacy endpoint for US", and 8.6.3 "Analysis of primary efficacy endpoint for EU", respectively.
2. The word, "variable", is changed to "endpoint".
3. Previous texts under this section are shortened and moved under Section 8.6.2,specific for the endpoint designated for US FDA. The analysis data set is changed from FAS to ITT.
4. New texts on the analysis of the primary efficacy endpoint designated for EU authority are added under Section 8.6.3.

Rationale for change:
For clarification and to harmonize with the primary efficacy objective of the other phase 3

studies in the program.

8.5.3 Analysis of the primary safety variable

Here are the changes as follow:

1. The section number is changed from 8.5.3 to 8.6.4.
2. The title of this section "Analysis of the primary safety variable", is changed to "CV safety endpoint analyses"
3. Previous texts under this section are replaced by new texts on CV safety endpoint analyses according to the PSAP using adjudicated pooled data across the all phase 3 studies in the program are added.

Rationale for change:

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

8.5.4 Analysis of the secondary variables

Here are the changes as follow:

1. The section number is changed from 8.5.4 to 8.6.5
2. The section title is changed to "Analysis of the secondary efficacy endpoints".
3. PPS is used for the first secondary efficacy endpoint on non-inferiority, on treatment analysis for the endpoint of RBC transfusion as rescue therapy, and ITT for the remaining secondary efficacy endpoints.
4. Time-to-event analyses including time-to-first MACE+, time-to-first CSE and time-to-first rescue therapy (composite) are removed.
5. Additional secondary efficacy endpoints are added, three related to Hb-response, one to LDL cholesterol, and one to IV iron use and one related to RBC transfusion as rescue therapy.
6. The list of the secondary endpoints is re-ordered.

8.5.5 Additional Secondary Analyses

This section is removed.

Rationale for change:

All the secondary analyses are highlighted in "Analysis of the secondary efficacy endpoints".

8.5.6 Testing order

This section is removed.

Rationale for change:

To avoid repeating the related texts specified in "Analysis of the secondary efficacy endpoints"

<u>Changes relevant only between Clinical Study Protocol version 7.0 (Outside of US) and version 8.0:</u>

Synopsis - International Co-ordinating Investigator (ICI)

Exchange of International Coordinating Investigator (ICI). The new International Co-ordinating Investigator is Dr Steven Fishbane:

Steven Fishbane, MD

Chief Division of Kidney Diseases and Hypertension
North Shore University Hospital
100 Community Drive, 2nd Floor
Great Neck, NY 11021
USA

Rationale for change:
Replacement for the previous International Co-ordinating Investigator that resigned from the International Co-ordinating Investigator role.

Clinical Study Protocol version 7.0 (US) and Clinical Study Protocol version 7.0 (Outside of US) were arising from:

Outside of US	Clinical Study Protocol edition 1.0 (version 5.0)
US (only)	Clinical Study Protocol version 6.0

Clinical Study Protocol version 7.0 (US) and Clinical Study Protocol version 7.0 (Outside of US) were the protocols for the recruitment of Incident Dialysis patients.

Clinical Study Protocol version 7.0 (US only)

Summary of main changes from Clinical Study Protocol version 6.0 US only to version 7.0 US only:

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

Synopsis - International Co-ordinating Investigator (ICI)

Exchange of International Coordinating Investigator (ICI). The new International Co-ordinating Investigator is Dr Steven Fishbane:

Steven Fishbane, MD
Chief Division of Kidney Diseases and Hypertension
North Shore University Hospital
100 Community Drive, 2nd Floor
Great Neck, NY 11021
USA

Rationale for change:
Replacement for the previous International Co-ordinating Investigator that resigned from the International Co-ordinating Investigator role.

Synopsis and Study objectives
Addition of a primary efficacy objective, "Evaluate the efficacy of roxadustat for the treatment

of anemia in CKD subjects on dialysis", with a corresponding outcome measure.
Rationale for change:
Harmonization of D5740C00002 with the other phase 3 trials in the roxadustat dialysis program, allowing the program to demonstrate both efficacy and safety across all populations studied.

Inclusion Criteria
Inclusion Criteria #4 has been changed, (new criteria is italicized):
Two central laboratory Hb values during the screening period, obtained at least 7 days apart, must be <12 g/dL in patients currently treated with an erythropoietin analogue or <10 g/dL in patients not currently treated with an erythropoietin analogue. Patients are considered not currently treated if they have not received either Mircera® for at least 8 weeks or any other erythropoietin analogue for at least 4 weeks prior to visit 1.
Rationale for change:
This inclusion criteria is modified to allow more incident subjects to participate by relaxing the screening Hb for subjects on an erythropoietin analogue.

Dose and schedule and Dosing of epoetin alfa (active control)
Deleted paragraphs covering self-administration.
Rationale for change:
Accommodate sites where patients are dialyzed at hours when site staff cannot be present.

Statistical considerations
Text has been added to clarify that there may be changes to endpoints and analyses to satisfy specific Regulatory Authorities in addition to what is described in this protocol.
Rationale for change:
Text has been added for clarification.

Per Protocol Set (PPS)
Section clarified with regards to important protocol deviation.
Rationale for change:
Changed nomenclature from "major protocol deviation" to "important protocol deviation". Have also clarified the important protocol deviations.

Safety analysis set (SAS)
Addition of "All available data will be included for the patients in SAS up until 28 days after last intake of study drug, or at the start of non-study drug ESA treatment, whichever is earlier. Subsequent results will be excluded."
Rationale for change:
Clarification of when patients will be censored from the SAS, e.g. for the analysis of MACE.

Outcome measures for analyses and Methods for statistical analyse
Primary efficacy and safety objectives separated and clarified.
Rationale for change:
Harmonization of D5740C00002 with the other phase 3 trials in the roxadustat dialysis

program, allowing the program to demonstrate both efficacy and safety across all populations studied.

Rationale for amendment:
The primary intent of this amendment is to add a primary efficacy objective to harmonize Study D5740C00002 with the other studies in the program and by changing the Hb Inclusion Criteria #4 to further support the enrolment of incident dialysis patients to improve representation of incident dialysis patients for the pooled analysis in the roxadustat phase 3 program. Furthermore, the amendment is updated with the name of the new International Co-ordinating Investigator and with changes and clarifications to the Dosing and Statistical sections.

Clinical Study Protocol version 7.0– (Outside of US)

Summary of main changes from Clinical Study Protocol edition 1.0 (version 5.0) to version 7.0:

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

Synopsis and Study objectives
Addition of a primary efficacy objective, "Evaluate the efficacy of roxadustat for the treatment of anemia in CKD subjects on dialysis", with a corresponding outcome measure.
Rationale for change:
Harmonization of D5740C00002 with the other phase 3 trials in the roxadustat dialysis program, allowing the program to demonstrate both efficacy and safety across all populations studied.

Synopsis, Study Design, Randomization and Sample size estimate
Sample size increased to approximately 2000 patients.
Rationale for change:
The sample size has been increased to allow for randomization of additional incident dialysis patients and to account for the lower than anticipated MACE event rate.

Synopsis, Treatment duration and dosing and Treatment Period
The expected duration of treatment is estimated to be up to 4 years.
Rationale for change:
Accounts for extension of study in Q1 2018.

Synopsis and Study timetable and end of study
Extension of study in Q1 2018.
Rationale for change:
The study end date has been changed to allow for randomization of additional incident dialysis patients.

Inclusion Criteria
Added text to modify Inclusion Criteria # 3, specifically it now reads as follows (added text is italicized):
Receiving or initiating hemodialysis or peritoneal dialysis for treatment of native kidney end-stage renal disease (ESRD) for a minimum of 2 weeks and a maximum of 4 months prior to randomization. Patients treated with hemodialysis must have access consisting of an arteriovenous fistula, AV graft, or tunneled (permanent) catheter. Patients on peritoneal dialysis must have a functioning peritoneal dialysis catheter in place.
Rationale for change:
Study D5740C00002 (Rockies) was designed to allow for both incident and stable dialysis patients to be enrolled. The incident dialysis population is recognized to have higher cardiovascular event rates, higher mortality rates, and higher ESA dose requirement for anemia therapy. Because the stable dialysis (conversion) patients were enrolled at a much more rapid rate in this phase 3 program than incident dialysis patients, there were few incident dialysis patients enrolled when the original target for this study was reached. The primary intent for this amendment is to further support the enrolment of incident dialysis patients to improve representation of incident dialysis patients for the pooled analysis in the roxadustat phase 3 program. The definition of incident dialysis patients has been modified to insure that the period of highest risk, 2 wks to 4 months, is captured.

Dose and treatment regimens
Initial dosing of Roxadustat and Epoetin Alfa will be based upon current dose at screening visit 1 for patients already receiving erythropoietin analogue therapy.
Rationale for change:
Incident dialysis patients frequently are on titrated dosing of ESA and this change simplifies the initial dosing strategy.

Dose and schedule and Dosing of epoetin alfa (active control)
Deleted paragraphs covering self-administration.
Rationale for change:
Accommodate sites where patients are dialyzed at hours when site staff cannot be present.

Per Protocol Set (PPS)
Section clarified with regards to important protocol deviation.
Rationale for change:
Changed nomenclature from “major protocol deviation” to “important protocol deviation”. Have also clarified the important protocol deviations.

Safety analysis set (SAS)
Addition of "All available data will be included for the patients in SAS up until 28 days after last intake of study drug, or at the start of non-study drug ESA treatment, whichever is earlier. Subsequent results will be excluded."
Rationale for change:
Clarification of when patients will be censored from the SAS, e.g. for the analysis of MACE.

Outcome measures for analyses and Methods for statistical analyse
Primary efficacy and safety objectives separated and clarified.
Rationale for change:
Harmonization of D5740C00002 with the other phase 3 trials in the roxadustat dialysis program, allowing the program to demonstrate both efficacy and safety across all populations studied.

Appendix A Signatories
Removed and replaced by electronic signatures.

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.

Rationale for amendment:
Study D5740C00002 was designed to allow for both incident and stable dialysis patients to be enrolled. The incident dialysis population is recognized to have higher cardiovascular event rates, higher mortality rates, and higher ESA dose requirement for anemia therapy. Because the stable dialysis (conversion) patients were enrolled at a much more rapid rate in this phase 3 program than incident dialysis patients, there were few incident dialysis patients enrolled when the original target for this study was reached. The primary intent is to further support the enrolment of incident dialysis patients to improve representation of incident dialysis patients for the pooled analysis in the roxadustat phase 3 program.

The incidence dialysis patient population is an important subset of the intended patient population for the roxadustat Phase 3 dialysis studies; including these patients will help evaluate the safety and efficacy of roxadustat in all dialysis patients.

The primary purpose of this protocol amendment is harmonization of D5740C00002 with the other phase 3 trials in the roxadustat dialysis program, allowing the program to demonstrate both efficacy and safety across populations studied. Additionally, the amendment allows further recruitment of newly initiated (incident) dialysis patients (on dialysis ≥2 weeks but ≤4 months at randomization).

Clinical Study Protocol version 6.0 (US only)

Summary of main changes from Clinical Study Protocol version 5.0 to version 6.0 US only:

- Adjustments in inclusion and exclusion criteria and dosing schedule for

Incident Dialysis patients.

- Duration of dialysis: Minimum of 2 weeks and a maximum of 4 months prior to randomization
- Hb: Two central laboratory Hb values during the screening period must be <10.5 g/dL
- Previous ESA treatment: Maximum 3 months at the time of informed consent

- Sample size increased to approximately 2000 patients
- Prolongation of study period up to 4 years.
- Initial dosing of Roxadustat and Epoetin Alfa will be based upon current dose at screening visit 1 for subjects already receiving erythropoietin analogue therapy.
- Clarification of EPO given as concomitant medication.
- CSP version 5 Appendix A Signatories has been removed and replaced by electronic signatures.
- CSP version 5 Appendix E - National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 has been removed and replaced by a reference to the document.

Rationale for amendment:
Rockies was designed to allow for both incident and stable dialysis patients to be enrolled. The incident dialysis population is recognized to have higher cardiovascular event rates, higher mortality rates, and higher ESA dose requirement for anemia therapy. Because the stable dialysis (conversion) patients were enrolled at a much more rapid rate in this phase 3 program than incident dialysis patients, there were few incident dialysis patients enrolled, especially incident dialysis patients from the US, when the original target for this study was reached. The primary intent for this US-only amendment is to further support the enrolment of US incident dialysis patients to improve representation of incident dialysis patients in the US for the pooled analysis in the roxadustat phase 3 program.

Version History up until Clinical Study Protocol edition 1.0 (version 5.0), globally

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 protocol Edition 1.0 was the resulting version number, as this was the first revision of the protocol.

Clinical Study Protocol edition 4.0, 26 September 2014

Edition 4.0 was the original protocol submitted and approved globally.

Summary of main changes from edition 3.0 to 4.0:

Concomitant medications

Deleted text `Due to a potential…at the healthcare providers discretion`

Added text to new section Statins 7.7.1.1

`When coadministered with roxadustat, hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) exposure was increased 2- to 3-fold. For patients randomized to roxadustat, 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)

Rationale:

In vitro studies indicated an inhibitory potential of roxadustat for transporters OATP1B1 and BCRP, so formal drug: drug interaction studies with simvastatin, atorvastatin and rosuvastatin were conducted. When preliminary results became available, the Clinical Study Protocol concomitant medication section was updated:

simvastatin 2-fold increase in Cmax and AUC

atorvastatin 1.3-fold increase in Cmax, 2-fold increase in AUC

rosuvastatin 4-fold increase in Cmax, 3-fold increase in AUC

The CSP already included maximum recommended statin doses based on in vitro data; rosuvastatin exposure when administered with roxadustat was higher than predicted, so the maximum recommended rosuvastatin dose was reduced from 20 mg to 10 mg daily. To avoid undertreatment of patients at high CV risk who might be randomized to placebo, investigators are asked to consider this interaction in the context of local prescribing information and lipid guidelines. Recommendations for pravastatin, pitavastatin and fluvastatin are based on predicted exposure as clinical studies were not conducted with these medications.

Concomitant medications

Addition of

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 at least 1 hour before or 3 hours after their phosphate binder.

Rationale:
In addition to new statin data, preliminary results of a drug: drug interaction study with sevelamer carbonate and calcium acetate indicate 40-50% reduced roxadustat exposure with concurrent administration. A recommendation to take roxadustat at least 1 hour before or 3 hours after phosphate binder was also added to the concomitant medication section.

Concomitant medications
Moved herbal medicine text " Use of herbal medicine…to continue at the same dose" from 7.7.1 to a new section 7.7.1.3 Herbal medicine

Rationale:
In addition, preliminary results of a drug: drug interaction study with sevelamer carbonate and calcium acetate indicate 40-50% reduced roxadustat exposure with concurrent administration. A recommendation to take roxadustat at least 1 hour before or 3 hours after phosphate binder was also added to the concomitant medication section.

Liver enzymes
Liver enzyme text exchange " For cases where a patient shows an AST or ALT ≥3xULN or total bilirubin ≥2xULN please refer to Appendix D for further instruction in cases of combined increase of aminotransferase and total bilirubin." to "If a patient meets any of the following criteria, please refer to Appendix D for further instruction:
AST≥3xULN, ALT≥3xULN, total bilirubin ≥2xULN."

Rationale:
Clarification

Clinical Study Protocol edition 3.0, 22 August 2014

Edition 3.0 was finalized but never used. Czech Republic & Russia submitted this edition to HA , but have only enrolled patients on Edition 4.0.

Summary of main changes from edition 2.0 to 3.0:

Dosing:

Starting dose and dose adjustment;

Start doses: 120 mg dose removed

120 and 350 mg dose steps removed

Dosing algorithm changes; 0.8 changed to 1.0

Single dose adjustment algorithm used throughout treatment period instead of separate algorithms for Correction and Maintenance

Maximum dose reduced from lower of 3.5 mg/kg or 400 mg to 3.0 mg/kg or 400 mg

Rationale:

Dosing simplified to reduce risk of prescriber/patient error and provide slow, steady Hb rise to and maintenance within desired range of 11+1 g/dL.

Dose algorithm was adjusted to reflect results of pharmacometric modeling and simulation using the simplified dosing regimen

Mg/kg dose cap lowered from 3.5 to align with non-dialysis. The 400 mg cap is retained, reflecting weight distribution of dialysis patients.

Definition of excessive erythropoiesis

Definition of excessive erythropoiesis simplified from before week 20 'Hb increases by >2.0 g/dL within a 2 week period' and after week 20 'Hb increases by >2.5 g/dL within a 4 week period' to a single definition, 'Hb increases by >2.0 g/dL within a 4 week period'

Rationale:

Revised to less complicated and more conservative definition of excessive erythropoiesis.

Self-administration of study drug :

Specify self-administration of study drug or epoetin alfa allowed in PD and home HD patients

Rationale:

Clarification to homogenize prescription in dialysis patients

Visit schedule

Exchange visit week 1 with phone call

Removed visits at week 3,5,7. Also after week 52, visits every 4 weeks

Visit window +-2 days to –4 days to 2

Rationale:

Enhance retention, reduce patient burden. Visits every 4 weeks align with standard of care for measurements of Hb and drug dose adjustments in dialysis patients

The visit window was lengthen to improve patient retention by making sure that investigators in dialysis clinics can capture necessary data from patients who may miss dialysis treatments that fall on scheduled visit days

Study objectives

'Vascular access thrombosis or hypertensive emergency' added to definition of composite safety endpoint

Rationale:

Consistent with list of adjudicated CV events in section 5.2.1.7

Inclusion criteria

#5-6 Ferritin & TSAT thresholds raised

Ferritin raised to ≥100ng/mL

TSAT raised to ≥20%

Rationale:

Encourage iron repletion before randomization in line with standard of care

Exclusion criteria

Deleted exclusion criteria # 3

"Current treatment with an average weekly dose of epoetin alfa……..exceeding 225µg/month`

Rationale:

Enhance patient recruitment

Exclusion criteria

#9 changed from Bosniak II to IIF

#10 added definition of uncontrolled hypertension in dialysis patients

#13 added 'that is determined to be the principal cause of anemia'

Rationale:

Allow patients with Bosniak II cysts, which are not associated with increased risk of renal cell carcinoma. Continue to exclude Bosniak IIF cysts which are associated with cancer risk.

Clarification specifying need to measure post-dialysis blood pressure and accounting for higher blood pressures observed in dialysis patients

Allows participation of patients with inflammatory disease if cause of anemia is CKD

Temporary discontinuation

Deleted study medication discontinuation for thrombocytopenia or bleeding

Rationale:

These patients may benefit from roxadustat; they will also be able to receive appropriate concomitant therapy including transfusion

Temporary discontinuation

Updated text with" Need for more than one cycle of erythropoietin analogue rescue"

Rationale:

Clarification

Supplemental iron use

Added recommendation for oral iron supplementation.

For IV iron, ferritin/TSAT thresholds changed from <30 ng/ml/<5% to <100/<20; discontinue IV iron when patient no longer iron deficient

Rationale:

Consistent with standard of care

Revised IV iron management to align with guidelines and current standard of care.

Rescue continues to be reserved for patients who are not responsive to study medication, oral & IV iron and who do not have acute blood loss, which should be managed with transfusion. To maintain as many patients as possible on study medication, one cycle of epoetin alfa rescue is permitted before permanent discontinuation of study medication.

Erythropoietin analogue administration

For erythropoietin analogue rescue, added statement that clinical judgment should not suggest iron deficiency or bleeding. Also, rescue should be discontinued when Hb >9 g/dL or (new text) 'after a 4-week cycle has been completed, whichever comes first.' Allow one cycle of rescue before permanent discontinuation of study drug.

Added statement regarding rescue with different erythropoietin analogue in epoetin alfa treated patients

Rationale:

Rescue continues to be reserved for patients who are not responsive to study medication, oral & IV iron and who do not have acute blood loss, which should be managed with transfusion. To maintain as many patients as possible on study medication, one cycle of epoetin alfa rescue is permitted before permanent discontinuation of study medication

Study plan

EQ-5D-5L continued every 24 weeks after week 52 and added at next visit after CSE event

Specify visits with triplicate HR, BP recording

Clarify complete physical exam at randomization and EOT visits

Added optional for pharmacogenetic sampling & biomarker sampling

Rationale:

More complete quality of life assessment

Safety assessments Thromboembolic events added to list of adjudicated CV events

Rationale:

For consistency

Protocol synopsis

Priority order of Secondary Objectives change

Rescue therapy before self reported health status

Rationale:

To reflect the pre-planned statistical testing order

Vascular access thrombosis and hypertensive emergency

Text exchanged to "Hypertensive emergency and vascular access thrombosis will be reported as AE and adjudicated by the IERC"

Rationale:

Clarification

Clinical Study Protocol edition 2.0, 21 May 2014
Rockies protocol Edition 2.0 was submitted and approved in the United States only, as the study began in that market.

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

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

AstraZeneca

PROTOCOL SYNOPSIS

A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of the Safety and Efficacy of Roxadustat in the Treatment of Anemia in Dialysis Patients

International Co-ordinating Investigator (ICI)

Steven Fishbane, MD

Chief Division of Kidney Diseases and Hypertension
North Shore University Hospital
100 Community Drive, 2nd Floor
Great Neck, NY 11021
USA

Study site(s) and number of subjects planned

Approximately 2000 patients will be randomized from approximately 250 centres worldwide.

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

Study design

This is a Phase 3, multicenter, randomized, open-label, active-controlled study to evaluate the efficacy and safety of roxadustat compared to epoetin alfa for the treatment of anemia in dialysis patients. Patients on hemodialysis (HD) or peritoneal dialysis (PD) who have been treated with an erythropoietin analogue or have an indication for treatment with an erythropoietin analogue will be evaluated for eligibility and randomized at a 1:1 ratio to treatment with roxadustat (with discontinuation of prior erythropoietin analogue therapy) or to an active-control group treated with epoetin alfa.

Objectives

Primary Efficacy Objective:	**Outcome Measure:**
Evaluate the efficacy of Roxadustat for the treatment of anemia in CKD subjects on dialysis.	**US FDA:** Mean change from baseline in Hb averaged over week 28 to week 52. **EU health authorities:** The EU (EMA) primary efficacy endpoint is change in Hb from BL to the average level during the evaluation period (defined as week 28 until week 36), without having received rescue therapy (i.e. RBC transfusion for all subjects or ESA for subjects treated with roxadustat) within 6 weeks prior to and during this 8-week evaluation period.

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 as compared to epoetin alfa 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 effect of roxadustat on Low-density lipoprotein (LDL) cholesterol as compared to epoetin alfa	Mean change from baseline in LDL cholesterol from baseline to week 24
The efficacy of roxadustat 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 need for IV iron use in subjects treated with roxadustat as compared to epoetin alfa	Average monthly IV iron use
The need for RBC transfusion as rescue therapy in subjects treated with roxadustat as compared to epoetin alfa	Time-to-first (and proportion of subjects receiving) administration of red blood cell (RBC) transfusion as rescue therapy

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 subject population

Approximately 2000 anemic patients with chronic kidney disease (CKD) receiving hemodialysis or peritoneal dialysis with an indication for treatment with an erythropoietin analogue.

Duration of treatment

The study will consist of three study periods as follows:

- **Screening Period:** Up to 6 weeks
- **Treatment Period:** Patients will be randomized (1:1) to open-label treatment with either roxadustat or epoetin alfa. A study end date will be declared and common close-out will occur when the target number of CV events has been accrued. The expected duration of treatment is estimated to be up to 4 years
- **Post-Treatment Follow-Up Period**: 4 weeks

Investigational product, dosage and mode of administration

Roxadustat

Roxadustat will be administered orally three times a week (TIW). Study drug doses must be administered at least 2 days apart but no more than 4 days apart (e.g., Monday, Wednesday, Friday). Selection of roxadustat starting dose will utilize a conversion table (Section 7) for patients currently treated with an erythropoietin analogue. Patients not currently treated with an erythropoietin analogue will initiate roxadustat using a tiered weight-based dosing scheme. Patients with dry weights between 45 and 70 kg will receive 70 mg of roxadustat as starting dose. Patients with dry weights between 71 and 160 kg will receive 100 mg of roxadustat for initial dosing. Dose adjustments are permitted starting at week 4 and at intervals of every 4 weeks thereafter in order to achieve an Hb level of 11 g/dL and maintain an Hb of 11±1 g/ dL . However, dose adjustments can be done at any time if dose reduction is required for excessive erythropoiesis. Study drug will be dosed TIW throughout the study treatment period unless downward dose adjustment requires a change to twice or once weekly.

Epoetin alfa

Initial dose selection of epoetin alfa for patients treated with an erythropoietin analogue will be determined using a conversion table based on the patient's current erythropoietin analogue dose

at screening visit 1. Initial dosing of epoetin alfa for patients not currently receiving any erythropoietin at study entry will be 50 IU/kg TIW with subsequent dose adjustments to achieve an Hb level of 11 g/dL and maintain an Hb of 11±1 g/dL, consistent with approved prescribing information or the Summary of Product Characteristics for epoetin alfa.

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.

In the event of excessive erythropoiesis, the dose may be adjusted or put on hold at any time.

Statistical methods

Sample size determination

Primary efficacy variable: With at least 600 subjects, the study will provide at least 99% power to demonstrate non-inferiority of roxadustat versus epoetin alfa for the primary efficacy endpoint (i.e., Hb change from baseline to the average level during the evaluation period defined as Week 28 until Week 52). This assumes a difference (roxadustat minus epoetin alfa) of -0.30 g/dL, a non-inferiority margin for this difference of -0.75 g/dL and a standard deviation of 1.25 g/dL.

To contribute adjudicated CV events for the pooled CV analyses across the phase 3 program: approximately 2000 subjects will be randomized in a 1:1 ratio to either roxadustat or active control, i.e. epoetin alfa. The sample size for this study is driven by the overall requirement of adjudicated CV events for the phase 3 program in dialysis-treated CKD subjects (which consists of four studies in total targeting 611 subjects with MACE events). The three other studies in the study program are FG-4592-064, 1517-CL-0613, FG-4592-063.

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
CMH	Cochran-Mantel-Haenszel
CSA	Clinical Study Agreement
CSE	Composite safety endpoint
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
CV	Cardiovascular
DILI	Drug induced liver injury
DSMB	Data 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
ESRD	End-stage Renal Disease
FAS	Full Analysis Set
GGT	Gamma-glutamyl transferase
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen

Abbreviation or special term	Explanation
hCG	Human chorionic gonadotropin
HD	Hemodialysis
HIF	Hypoxia-inducible factor
HIF-PHI	Hypoxia-inducible factor 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
ICH	International Conference on Harmonisation
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.
ID	Incident Dialysis
IERC	Independent Endpoint Review Committee
iPTH	Intact parathyroid hormone
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
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 (MI) 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 hospitalisation and unstable angina requiring hospitalisation.
MI	Myocardial Infarction
MMRM	Mixed Model of Repeated Measures
NCI	National Cancer Institute
PCI	Percutanous coronary intervention
PD	Peritoneal dialysis

Abbreviation or special term	**Explanation**
PE	Pulmonary embolism
PI	Principal Investigator
PK	Pharmacokinetic
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
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), including end-stage renal disease (ESRD). It is currently in global Phase 3 clinical development and has not been marketed in any country. Roxadustat is a potent and reversible orally active hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) 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 (Semenza 1998). HIF induces expression not only of erythropoietin, but also the erythropoietin receptor and proteins that promote iron reabsorption 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 treated with dialysis 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 patients, 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 objective of the current study is to assess the efficacy, safety and tolerability, with the primary focus on Hemoglobin efficacy and CV safety of roxadustat in patients with ESRD treated by dialysis (hemodialysis [HD] or peritoneal dialysis [PD]).

1.2 Rationale for study design, doses and control groups

1.2.1 Rationale for study design

The study is designed to evaluate the efficacy and safety of roxadustat in the treatment of anemia associated with CKD in dialysis patients. The study is a randomized, open-label study with two treatment groups, roxadustat or epoetin alfa, and includes hemodialysis or peritoneal dialysis patients that have been treated with an erythropoietin analogue or have an indication for treatment with an erythropoietin analogue.

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 or a fixed starting dose regardless of weight.

Dose adjustments were allowed at regular 4-week intervals to maintain, increase or decrease the dose according to pre-specified rules. Additional rules were provided to minimize excessive erythropoiesis. These dose adjustment rules are adopted in this study with minor modifications.

For patients treated with an erythropoietin analogue at study entry, selection of initial roxadustat dose in this study will utilize a conversion table based on the patient's current erythropoietin analogue dose at screening visit 1. Patients not currently treated with erythropoietin analogue will initiate roxadustat using a tiered weight-based dose dosing scheme. Patients with dry weights between 45 and 70 kg will receive 70 mg of roxadustat as starting dose. Patients with dry weights between 71 and 160 kg will receive 100 mg of roxadustat for initial dosing.

Doses will be administered at a frequency of three times a week (TIW) throughout the study treatment period unless downward dose adjustment requires a change to twice or once weekly.

In the event of excessive erythropoiesis, the dose may be adjusted at any time. The maximum dose of roxadustat allowed will be the lower of 3.0 mg/kg or 400 mg per dose.

Patients randomized to the epoetin alfa group will receive an epoetin alfa dosing regimen with initial and subsequent dose adjustments in accordance with accepted clinical practice guidelines and approved prescribing information for epoetin alfa. The initial dose of epoetin alfa will be selected based on the erythropoietin analogue regimen used prior to the entry into the study. Patients who were not receiving an erythropoietin analogue at study entry will initially receive epoetin alfa at a dose of 50 IU/kg three times weekly. Adjustments in the total weekly dose or frequency of epoetin alfa dosing should subsequently be made to achieve an Hb of 11 g/dL and maintain Hb levels of 11±1 g/dL.

1.2.3 Rationale for control group

The control group will be treated with epoetin alfa in accordance with accepted clinical practice guidelines and approved prescribing information for epoetin alfa in this patient population. Epoetin alfa is a frequently used erythropoietin analogue agent and is approved for use in treatment of anemia associated with CKD in dialysis patients.

1.2.4 Rationale for hemoglobin level

This study seeks to achieve and maintain Hb within the range of 11±1 g/dL. This 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 2012 KDIGO guidelines suggest that erythropoietin analogues be started at Hb below 10 g/dL and should generally not be used to maintain Hb above 11.5 g/dL (Johansen et al 2010, KDIGO 2012). In

contrast, the Cleveland Clinic recommends target hemoglobin level for both predialysis CKD and ESRD patients should be 11 to 12 g/dL (Lascano et al 2010).

Unlike Hb levels above 13 g/dL where the data indicates 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 analogue (Andrews et al 201) 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). With the proposed dosing regimen, the risk of rapid rises of Hb levels is minimized. Finally, 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.

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.

Dosing of epoetin alfa in the epoetin alfa group will be consistent with approved prescribing information. Adverse and serious adverse events, and laboratory parameters including electrolytes, liver enzymes, and iron indices, will be closely monitored to ensure the safety of treatment with roxadustat or epoetin alfa.

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 repeat 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 epoetin alfa 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, open-label, active-controlled study to evaluate the efficacy and safety of roxadustat compared to epoetin alfa for the treatment of anemia due to CKD in dialysis patients (hemodialysis or peritoneal dialysis). This study is planned to randomize approximately 2000 patients from approximately 250 centers worldwide.

1.4.1 Treatment duration and dosing

The study periods are as follows:

- **Screening Period:** Up to 6 weeks

  Treatment Period: Patients will be randomized (1:1) to open-label treatment with roxadustat or epoetin alfa. Roxadustat will be started at doses of 70 mg for patients with dry weights between 45 and 70 kg and 100 mg for patients with dry weights between 71 and 160 kg. This dose will be subsequently titrated. Patients currently treated with an erythropoietin analogue and randomized to receive roxadustat will discontinue prior erythropoietin analogue therapy and initiate treatment with roxadustat at a starting dose according to Table 4 Section 7 to achieve and maintain Hb 11±1 g/dL. Epoetin alfa dosing will be done in accordance with accepted clinical practice guidelines and approved prescribing information.

  The expected duration of treatment is estimated to be up to 4 years. 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 2000 patients will be randomized at 1:1 ratio to roxadustat or epoetin alfa via an Interactive Web Response System (IWRS)/ Interactive Voice Response System (IVRS).

1.4.3 Starting dose of study drug

For more details see Section 7.

Roxadustat

Patients currently treated with an erythropoietin analogue who are randomized to the roxadustat group will discontinue prior erythropoietin analogue therapy and initiate treatment with roxadustat at a starting dose according to Section 7. Patients not currently treated with an erythropoietin analogue will initiate roxadustat with dose selection based on body weight. Roxadustat will be dosed orally three times a week (TIW) throughout the Treatment Period unless dose reduction is required based on Hb levels.

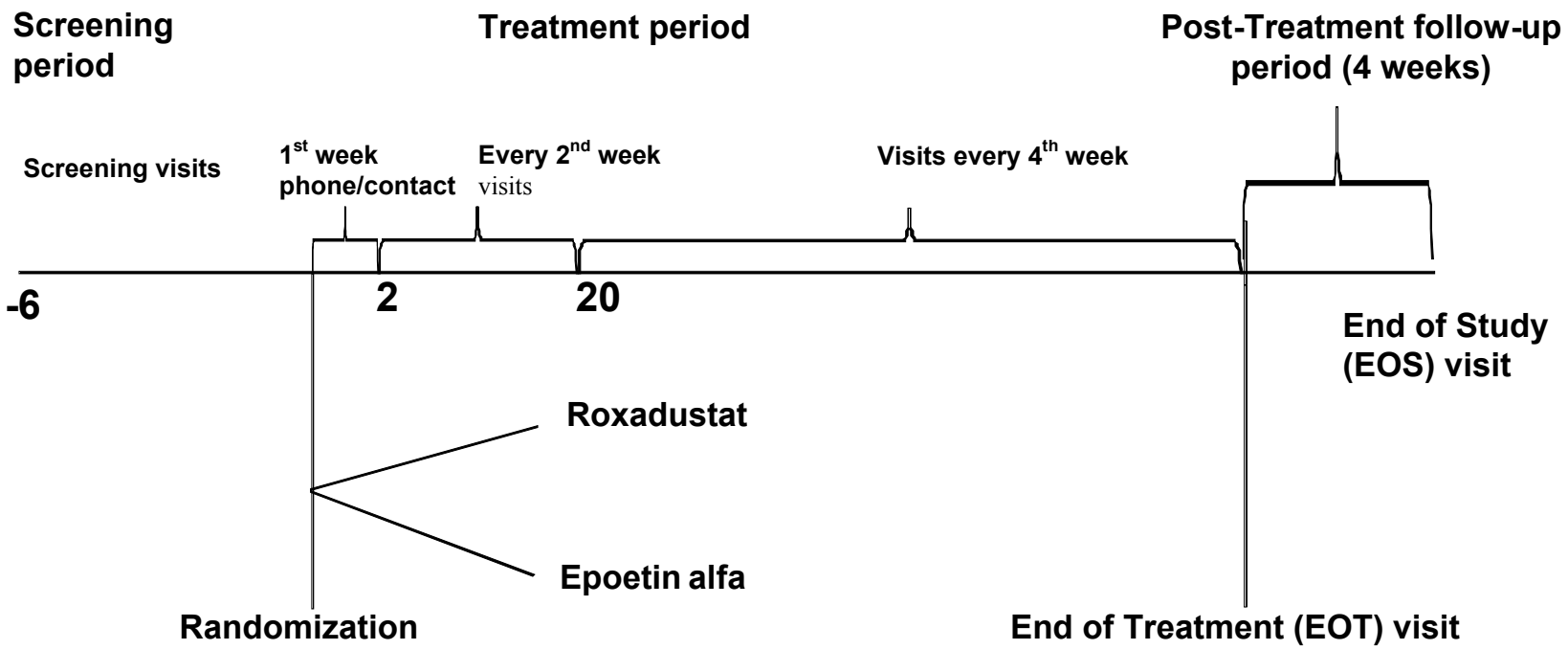
Epoetin alfa

Patients currently treated with erythropoietin analogue who are randomized to the epoetin alfa active control group will be treated with epoetin alfa dosing regimen as described in Section 7. Initial dosing of epoetin alfa in patients not currently treated with erythropoietin analogue will be 50 IU/kg TIW with subsequent dose adjustments of erythropoietin analogue made based on Hb levels consistent with approved prescribing information.

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



2. STUDY OBJECTIVES

2.1 Primary objectives

Primary Efficacy Objective:	**Outcome Measure:**
Evaluate the efficacy of Roxadustat for the treatment of anemia in CKD subjects on dialysis.	**US FDA:** Mean change from baseline in Hb averaged over week 28 to week 52. **EU health authorities:** The EU (EMA) primary efficacy endpoint is change in Hb from BL to the average level during the evaluation period (defined as week 28 until week 36), without having received rescue therapy (i.e. RBC transfusion for all subjects or ESA for subjects treated with roxadustat) within 6 weeks prior to and during this 8-week evaluation period.

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 as compared to epoetin alfa 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 effect of roxadustat on Low-density lipoprotein (LDL) cholesterol as compared to epoetin alfa	Mean change from baseline in LDL cholesterol from baseline to week 24
The efficacy of roxadustat 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 need for IV iron use in subjects treated with roxadustat as compared to epoetin alfa	Average monthly IV iron use

Secondary Efficacy Objectives:	**Outcome Measure:**
The need for RBC transfusion as rescue therapy in subjects treated with roxadustat as compared to epoetin alfa	Time-to-first (and proportion of subjects receiving) administration of red blood cell (RBC) transfusion as rescue therapy

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. SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject 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 subjects should fulfil the following criteria:

1. Provision of Informed Consent prior to any study specific procedures

2. Age ≥18 years at screening visit 1

3. **Previous versions of the protocol prior to US amendment ver 6.0 and outside of US amendment ver 7.0:**
   Receiving or initiating hemodialysis or peritoneal dialysis for treatment of native kidney end-stage renal disease (ESRD) at least 30 days prior to visit 1. Patients treated with hemodialysis must have access consisting of an arteriovenous fistula, AV graft, or tunneled (permanent) catheter. Patients on peritoneal dialysis must have a functioning peritoneal dialysis catheter in place.

   Starting with US amendment ver. 6.0 and outside of US amendment ver 7.0 (changed to recruit incident dialysis patients only):

   Receiving or initiating hemodialysis or peritoneal dialysis for treatment of native kidney end-stage renal disease (ESRD) for a minimum of 2 weeks and a maximum of 4 months prior to randomization. Patients treated with hemodialysis must have access consisting of an arteriovenous fistula, AV graft, or tunneled (permanent) catheter. Patients on peritoneal dialysis must have a functioning peritoneal dialysis catheter in place.

4. Two central laboratory Hb values during the screening period, obtained at least 7 days apart, must be <12 g/dL in patients currently treated with an erythropoietin analogue or <10 g/dL in patients not currently treated with an erythropoietin analogue. Patients are considered not currently treated if they have not received either Mircera® for at least 8 weeks or any other erythropoietin analogue for at least 4 weeks prior to visit 1.

5. Ferritin ≥100 ng/mL at randomization (obtained from screening visit)

6. TSAT ≥20% 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) ≤3x 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 (prescribed dry weight)

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 randomisation in the present study
3. New York Heart Association Class III or IV congestive heart failure at enrolment

4. Myocardial infarction, acute coronary syndrome, stroke, seizure or a thrombotic/thromboembolic event (e.g., deep vein thrombosis or pulmonary embolism) within 12 weeks prior to randomization

5. History of chronic liver disease (e.g., chronic infectious hepatitis, chronic auto-immune liver disease, cirrhosis or fibrosis of the liver)

6. 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

7. Known and untreated retinal vein occlusion or known and untreated proliferative diabetic retinopathy (risk for retinal vein thrombosis)

8. 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.

9. Uncontrolled hypertension at the time of randomization (defined as systolic BP ≥180 mmHg or diastolic BP ≥100 mmHg on repeated measurement post-dialysis in hemodialysis patients or at any time in peritoneal dialysis patients), contraindication to epoetin alfa treatment (e.g., pure red cell aplasia, hypersensitivity or know inability to tolerate epoetin alfa)

10. 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.

11. Positive for any of the following: human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus antibody (anti-HCV Ab)

12. Chronic inflammatory diseases such as rheumatoid arthritis, SLE, ankylosing spondylitis, psoriatic arthritis or inflammatory bowel disease that is determined to be the principal cause of anemia

13. Known hemosiderosis, hemochromatosis or hypercoagulable condition

14. Any prior organ transplant with the exception of an autologous renal transplant or a renal transplant that was subsequently removed ("explanted") or **scheduled** organ transplantation date

15. Any red blood cell (RBC) transfusion during the screening period

16. Any current condition leading to active significant blood loss

17. Any prior treatment with roxadustat or a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI)

18. 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 the month preceding 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)

19. History of alcohol or drug abuse within 2 years prior to randomization

20. Females of childbearing potential, unless using contraception as detailed in the protocol or sexual abstinence (see Section 3.8)

21. Pregnant or breastfeeding females

22. Known allergy to the investigational product or any of its ingredients

23. 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 subjects see Section 3.4.

3.3 Subject enrolment and randomization

Investigator(s) should keep a record, the subject screening log, of subjects 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 enrolment number, beginning with 'E#', through the IVRS/IWRS
- Determine patient eligibility, see Section 3.1and 3.2.
- Assign eligible patient unique randomization code through the IVRS/IWRS

If a patient withdraws from participation in the study, his/her enrolment/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 subjects

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 blocked randomization schedule by country will be produced.

3.6 Methods for ensuring blinding (Not applicable)

3.7 Methods for unblinding (Not applicable)

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.

If epoetin alfa is supplied by AstraZeneca, see Section 7.1.2 for dose restrictions at study entry.

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, study medication must be discontinued or interrupted temporarily.

For decisions around discontinuation the AstraZeneca study physician can be consulted as appropriate.

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
   - Need for more than one cycle of erythropoietin analogue rescue in patients treated with Roxadustat
   - Patients who receive organ transplantation during the study

Each permanent discontinuation from study medication should be communicated to the study team. For decisions around permanent discontinuation the AstraZeneca study physician can be consulted as appropriate. 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.

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.

All discontinued patients unless consent withdrawal will be followed up for vital status and hospitalizations until study closure (see Section 3.9.3.2).

If the patient permanently discontinues study medication prior to closure of the study, there should be several different options for their 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 (Table 1), or if needed with reduced frequency until end of study is declared (i.e., when the prespecified number of primary events has been reached). The patient will then return for their EOS visit **as soon as feasible**, but no later than 60 days after the study closure has been declared. It is essential that the patients attend the EOS visit in person whenever possible.

At PTDV, the physicians caring for the patient will decide upon treatment the patient should receive as part of his/her ongoing clinical care.

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 such patients 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. However, if a patient has permanently discontinued study drug and a PTDV has been performed, study drug should not be restarted.

If patient has been treated with erythropoietin analogue as rescue, see Section 7.7.4 for guidance on when study drug treatment 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 withdraw from the study (i.e., discontinue study medication permanently and withdraw from visit assessments), without prejudice to further treatment (withdrawal of consent). Withdrawal of consent from the study must be ascertained and 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. 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 fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (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 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 enrolment/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

During study visits, all assessments including laboratory tests and physical examinations should be completed prior to initiation of the hemodialysis (HD) procedure in patients receiving HD. The EQ-5D-5L quality of life assessments should be completed prior to any intervention (e.g., start of dialysis in HD patients) and at approximately the same time of the day. Blood samples for Hb measurement and safety laboratory tests will be obtained according to 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**	**56**	**60**	**every 4 wks**		
Visit[o]	***1***	***2***	***3***	***4***	***5***	***7***	***9***	***11***	***12***	***13***	***14***	***15***	***16***	***17***	***18***	***19***	***20***	***21***	***22***	***23***	***24***	***25***	***26***	***27***	***etc***		
Written informed consent	X																										
Eligibility criteria	X	X	X																								
Demographics and medical history	X																										
Physical examination	X[b]		X							X[b]					X[b]											X	
Height[c], weight[d]	X		X							X					X			X				X			every 24 wks[t]	X	
12-lead ECG			X							X					X											X	
Blood pressure, Heart rate	X[e]	X	X[e,q]			X		X		X[e]		X		X	X[e]	X	X	X	X	X	X	X	X[e]	X	X	X, every 24 wks X[e,t]	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	

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**	**56**	**60**	**every 4 wks**		
Visit[o]	***1***	***2***	***3***	***4***	***5***	***7***	***9***	***11***	***12***	***13***	***14***	***15***	***16***	***17***	***18***	***19***	***20***	***21***	***22***	***23***	***24***	***25***	***26***	***27***	***etc***		
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	X		
Hemoglobin (Central lab)		X			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				X	
Clinical chemistry	X		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	
Intact parathyroid hormone (PTH)			X												X						X				every 24wks[t]		
Population PK sampling[p]						X[i]		X																			
Pharmacogenetic sampling (optional)			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**	**56**	**60**	**every 4 wks**		
Visit[o]	***1***	***2***	***3***	***4***	***5***	***7***	***9***	***11***	***12***	***13***	***14***	***15***	***16***	***17***	***18***	***19***	***20***	***21***	***22***	***23***	***24***	***25***	***26***	***27***	***etc***		
Biomarker sampling(optional) hsCRP, hepcidin			X[j]												X												
EQ-5D-5L[k]			X							X						X						X			every 24 wks[t]		
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	X
AE recording			X[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	V	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	X
Dose adjustment review[m]						X		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[n]			X[r]		X	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 Targeted physical examination only.
c Height measured only at screening visit 1.
d Dry weight; the dry weight measured after the patient's most recent dialysis can be recorded.
e BP should be measured prior to the hemodialysis procedure. HR and BP should be measured in triplicate 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 predose.
j Collect pre-dose.
k After suspected CSE event (MI, stroke, unstable angina, heart failure, DVT, PE, hypertensive emergency or vascular access thrombosis), collect EQ-5D-5L at next regularly scheduled visit.
l Baseline dialysis related signs and symptoms will be recorded at randomization and AEs will be recorded starting from the first dose administration
m Dose adjustment review every 4 weeks. Hemocue values measured from venous blood samples, collected in lavender tube, will be used for all dose adjustments with baseline value from Hemocue values at randomization. In the event of excessive erythropoiesis dose can be adjusted at any time see Section 7.2.3.4.
n Dispensation every second week from Day 1 to week 20, every 4 weeks thereafter. In the event of excessive erythropoiesis dose can be adjusted at any time see Section 7.2.3.4.
o Please be attentive to visit # which are not consecutive due to removal of some visits from Study plan
p PK sampling is done only for patients assigned to the roxadustat treatment arm.
q Refer to exclusion criterion 1: if ANY of the 3 measurements is exclusionary before dialysis on the day of randomization, then a BP measurement should be done after dialysis to confirm eligibility.
r Receipt of the first dose of study drug defines Study Day 1.
s Randomization may occur up to 2 weeks after the screening period ends, in order to allow for synchronization with the patient`s existing dosing schedule
t Every 24 weeks should be calculated from week 48 for Intact parathyroid hormone (PTH) and from week 52 for Weight, Blood pressure/Heart rate and EQ-5D-5L.

4.1 Enrolment/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.

Patients in screening currently treated with erythropoietin analogue will continue their existing erythropoietin analogue therapy during the enrolment/screening period.

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 visits to be performed at least 7 days apart. All screening procedures should be completed within 6 weeks. The site must ensure that roxadustat and epoetin alfa are available at study site before the randomization visit is scheduled. The Hb inclusion criteria will be based on central laboratory assessments and may be repeated during the screening period. Eligible patients should have two **central laboratory Hb** values 7 days apart (during the screening period). <12. g/dL in patients currently treated with an erythropoietin analogue or <10.0 g/dL in patients not currently treated with an erythropoietin analogue.

4.1.2 Additional screening assessments

If a patient's laboratory results do not meet the eligibility criteria or the patient is considered to have uncontrolled hypertension, the laboratory assessment may be repeated within the screening period. The visits must be at least 7 days apart.

For example, an additional central laboratory Hb may be collected, if necessary, at least 7 days after the second screening visit if the screening visit 1 or visit 2 Hb level is ≥12 g/dL in patients currently treated with an erythropoietin analogue. Similarly an additional central laboratory Hb may be collected, if necessary, at least 7 days after the second screening visit if the screening visit 1 or visit 2 Hb level is ≥10 in patients not treated with epoetin alpha or other erythropoietin analogue for at least 4 weeks prior to visit 1.

Iron, vitamin B12 and folate laboratory tests may be repeated during the screening period after supplementation, if necessary. The liver function test (LFT) parameters may not be repeated if found exclusionary at screening without a prior approval from the AstraZeneca study physician 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.

Instructions will be provided for collection and recording of baseline dialysis symptoms.

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 rescreening periods are allowed.

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

4.2 Treatment period

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

The treatment period begins on the first day of dosing with study treatment (Day 1, week 0). Day 1 is preferably a scheduled treatment date according to the existing erythropoietin analogue treatment regimen.

The first day of dosing should not occur less than 2 days from the last dose of epoetin alfa or epoetin beta, less than 7 days since the last dose of darbepoetin alfa or less than 14 days since the last dose of Mircera®. All Day 1 study assessments are to be performed prior to first study drug administration; in hemodialysis patients, study assessments should also be performed prior to or at initiation of the dialysis procedure for patients treated with epoetin alfa prior to randomization.

During the treatment period, the patient will be contacted by telephone at week 1. Patient will attend study visits every 2 weeks from randomization to week 20 and every 4 weeks thereafter 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. Treatment duration is estimated to be up to 4 years.

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

4.3 Follow-up period

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

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

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 centre.

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 medication (erythropoietin analogue use in the roxadustat group only or 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 in 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 (AE), 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 and will be adjudicated. 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):

Table 2 Laboratory Safety 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 Analyses	Chloride
Vitamin B12	Magnesium
Folate	Bicarbonate
Intact Parathyroid hormone (iPTH)	Phosphorus
hsCRP*, hepcidin*	Glucose
Lipid Panel	Uric Acid

Total cholesterol	Total protein
HDL	Lactate dehydrogenase
Triglycerides	Blood urea nitrogen
Calculated low-density lipoprotein (LDL)	
	Serum hCG pregnancy test
	Iron Profile
	Iron
	Ferritin
	Total iron binding capacity (TIBC)
	Transferrin saturation (TSAT)

* = will be analysed from specimens obtained in subjects who consent to biobanking blood samples

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 centre 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 the Study Plan, Table 1, and recorded in the source documents. 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 recorded at screening, randomization visit, 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 the 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 (HR), 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 and recorded.

On specific visits indicated in Table 1, HR and BP will be measured in triplicate 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. Blood pressure will be measured in triplicate with at least one-minute intervals between measurements. In HD patients BP and HR will be assessed prior to initiation of the dialysis procedures. In peritoneal dialysis (PD) patients BP and HR will be assessed when they come to the clinic. All the three readings will be reported in the eCRF.

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

Blood pressure measurements are to be obtained prior to initiation of each dialysis procedure.

5.3 Other assessments

5.3.1 Patient reported outcomes

All study patients will be asked to complete the Euro Quality of life (QoL) Health Utility Index questionnaire at time points indicated in the Study Plan, Table 1. The questionnaires should be completed by the patient prior any other intervention.

5.3.1.1 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.

5.3.1.2 Administration of patient-reported outcome

All patient-reported outcomes (PROs) are paper-based and will be administered at baseline and according to Study plan, Table 1 and recorded in the eCRF.

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 questionnaire. 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 questionnaire are as follows:

- The EQ-5D-5L 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 questionnaire. However, if the patient is unable to read the questionnaire (e.g. is visually impaired) the questionnaire may be read out by trained clinic staff and responses recorded
- On completion of the questionnaire it should be handed back to the person responsible for questionnaire 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 and 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 the projected date of the EOS visit.

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, only for patients taking roxadustat. 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 as the last dosing date and time 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 drug concentration

For the patients receiving roxadustat, samples for pharmacokinetic (PK) determination will be analysed 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, summarized on the basis of time intervals and plotted in scattering with time relative to the immediate preceding roxadustat dosing time. A population PK analysis of data collected in the CKD dialysis 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 (week 0) randomization visit.

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 (week 0) randomization visit. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an 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., at (week0, **pre-dose**) randomization visit and at week 24 (at any time), and may be analysed 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 centre keeps full traceability of collected biological samples from the patients while in storage at the centre 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 further use are registered in the AstraZeneca Biobank during the entire life cycle.

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. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an optional part of the study, then the patient may continue in the study.

The Principal Investigator:

- Ensures patients' withdrawal of Informed Consent to the use of donated samples is notified 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 are 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.

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 hospitalisation or prolongation of existing hospitalisation
- 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 jeopardise the subject 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 (after first dose of investigational product) throughout the treatment period and including the follow-up period.

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 collect 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 are 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
- Date of death
- Autopsy performed
- 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, 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 D to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient, care provider 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 summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, 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≥3x ULN, ALT≥3x ULN, total bilirubin ≥2x ULN.

6.3.8 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Worsening of CKD should be considered a disease progression and not an AE and events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

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 CRF.

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/listedness 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 400 mg per administration, whichever is lower) represents an overdose.

An overdose with associated AEs 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 symptoms 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 levels.

If there are clinical concerns for 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 in collaboration with the sponsor 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) committee 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 the 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 product

Investigational product	Dosage form and strength	Manufacturer
Roxadustat	Oral tablets 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).

The only epoetin alfa to be used in the study is Procrit®, Eprex® and Epogen®, will be reimbursed in countries where this is possible, or otherwise centrally supplied by AstraZeneca.

7.1.1 Roxadustat

Roxadustat oral tablets will be packed in bottles and supplied by AstraZeneca. The tablet strengths are different in size. The tablets should remain in original packaging until administration. The tablets must not be chewed, crushed or divided but should be swallowed whole with water.

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).

7.1.2 Epoetin alfa

The only epoetin alfa to be used in the study is Procrit®, Eprex® and Epogen®.

In countries where epoetin alfa is not expected to be marketed for the duration of study, or where local regulations prevent reimbursement, Eprex will be centrally supplied by AstraZeneca. In these centrally supplied countries only, patients requiring Eprex doses >45,000 IU/week or 15,000IU/administration should not be enrolled.

7.2 Dose and treatment regimens

7.2.1 Randomization

Eligible patients will be randomized to receive either roxadustat or epoetin alfa in a 1:1 ratio. 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 (or amount of epoetin alfa supplied by AstraZeneca) 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.

7.2.2 Dose and schedule

The first dose of study drug should be administered on Day 1 (week 0), and will mark the beginning of the treatment period. This should correspond to a day when the next dose of erythropoietin analogue would have been administered in patient currently treated with erythropoietin analogue. All randomization visit study procedures including laboratory blood draws are to be completed prior to administration of the first dose of study drug. All dose adjustments should be based on Hb values using Hemocue, a point-of-care device, at visits specified in Table 1. Hb values will be recorded in the eCRF (screening) and IWRS (during treatment period).

Missed dose should not be replaced.

7.2.3 Dosing of Roxadustat

Roxadustat will be dosed orally three times a week (TIW) throughout the treatment period unless dose reduction is required based on Hb levels. For hemodialysis patients, it is recommended that roxadustat is taken after completion of the hemodialysis session.

7.2.3.1 Patients treated with erythropoietin analogue at study entry

Patients randomized to roxadustat will discontinue any prior erythropoietin analogue therapy and start roxadustat. The starting dose of roxadustat will be based on the current erythropoietin analogue dose at screening visit 1 (Table 4). If the mean hemoglobin during the screening phase (e.g. the average of central laboratory values at visit 1 and visit 2 or the average of the values at visit 2 and the retest of visit 2 value, if applicable) is less than 10 g/dL, the starting dose will be

increased by one dose step. For example, a patient being treated with an average of 10,000 IU of epoetin alfa per week with a Hb value of 11 g/dL during the screening period would take roxadustat 150 mg orally, three times a week (TIW). In contrast, a patient being treated with an average of 10,000 IU of epoetin alfa per week who had a screening Hb of 9 g/dL during the screening period would take roxadustat 200 mg orally TIW.

Table 4 Initial dosing of roxadustat for patients treated with an erythropoietin analogue at study entry

Epoetin alfa or beta [a] (IU/week)	Darbepoetin alfa [a,b] (µg/week)	Mircera® [c] (µg/month)	Roxadustat dose [d] (mg/dose) TIW
<5,000	<25	<80	70
5,000 to ≤8,000	25-40	80-120	100
>8,000 to 16,000	40-80	120-200	150
>16,000	>80	>200	200[e]

a Current weekly dose at screening visit 1
b If darbepoetin is used once every 2 weeks, use half dose given every 2 weeks to determine the roxadustat starting dose.
c Current monthly dose at screening visit 1.
d Starting dose will be 1 step higher if the mean central Hb value from the last 2 screening visits is <10 g/dL.
e If the initial dose of 200 mg exceeds the maximum dose of 3.0 mg/kg, then 150 mg should be chosen as the starting dose

7.2.3.2 Patients not treated with erythropoietin analogue at study entry

The initial roxadustat dose (administered TIW) is based on a tiered, weight-based dosing scheme (Table 5). For example, a patient that has a dry weight of 80 kg would initiate roxadustat treatment with 100 mg orally TIW.

Table 5 Initial dosing of roxadustat dose for patients not taking erythropoietin analogue at study entry

Dry Weight (kg)	Roxadustat dose, mg TIW
45-70	70
>70-160	100

7.2.3.3 Roxadustat dose adjustments

Roxadustat dose will remain constant during the first 4 weeks of the treatment period, unless a dose reduction is required for excessive erythropoiesis. Dose may be adjusted at week 4 and every 4 weeks thereafter in accordance b to achieve and maintain Hb 11±1 g/dL. Dose adjustment is based on Hb assessed by Hemocue.

Table 6 Roxadustat dose adjustments

Changes in Hb over past 4 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, 300, and 400 mg.

Example: A dose increase at a dose of 70 mg results in 100 mg as the new dose. A dose reduction at a dose150 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 400 mg per dose administration.

Dose Adjustment for Excessive Erythropoiesis:

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

7.2.3.4 Dose adjustment for excessive erythropoiesis

Excessive erythropoiesis is defined in Table 6. In the event of excessive erythropoiesis, the dose may be adjusted, even on visits without a dose adjustment review. In such cases, dose adjustment reviews are then resumed at 4-week intervals. If a dose adjustment review is scheduled on week 18, then the next dose adjustment review will be scheduled on week 24, since there is no scheduled visit on week 22.

7.2.3.5 Dose adjustments for excessive Hb ≥ 13.0g/dL

In the event of 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 following the same principle as for excessive erythropoiesis.

7.2.4 Dosing of epoetin alfa (active control)

7.2.4.1 Patients treated with epoetin alfa or beta at study entry

All patients who are randomized to the epoetin alfa group should initially receive epoetin alfa TIW with the exception of patients who were treated with epoetin alfa using a less frequent dosing regimen (for example, twice weekly dosing) prior to study entry. The initial dose of epoetin alfa will be the actual dose given at the time of screening visit 1.

7.2.4.2 Patients treated with darbepoetin alfa or Mircera® at study entry

Patients treated with darbepoetin alfa or Mircera® who are randomized to the epoetin alfa group will initially receive epoetin alfa at doses based on a conversion factor as described in Table 7.

Table 7 Initial dosing of epoetin alfa for patients treated with darbepoetin alfa or Mircera® at study entry

	Conversion Ratio	Examples of converted initial epoetin alfa dose (IU/week)[d]
Darbepoetin alfa (µg/week) [a]	x 200	40 µg/week x 200 = 8,000 IU/week
Mircera® (µg/month) [b]	x 70 to 80	100 µg/month x 70=7,000 IU/week
	(Lower conversion ratio can be used for lower Mircera® dose)[c]	200 µg/month x 80=16,000 IU/week

a Current weekly dose at screening visit 1
b Current monthly dose at screening visit 1
c Per discretion of investigator
d May be rounded if deemed necessary

7.2.4.3 Patients not treated with erythropoietin at study entry

Patients who are not currently treated with erythropoietin analogue at study entry who are randomized to the epoetin alfa group will be treated with epoetin alfa with an initial dose of 50 IU/kg TIW. Dose adjustments should not occur more frequently than every 4 weeks and be made in a manner consistent with local approved prescribing information for epoetin alfa. In countries where no local guideline is available, Handling Instruction including Summary of Product Characteristics will be provided as guideline for dosing by AstraZeneca.

7.3 Labelling

Labelling of roxadustat and centrally sourced epoetin alfa will be carried out by AstraZeneca or their designee in accordance with current Good Manufacturing Practise (GMP). The labels will fulfil GMPAnnex 13 requirements for labelling and local regulatory guidelines. The 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 at the site 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. For patients randomized to roxadustat, 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 medicine

Use of herbal medicine during the study is not prohibited but strongly discouraged. All herbal and natural remidies 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 treatments/medications are prohibited during the study:

- Any other investigational drug: from randomization until EOS.
- Any erythropoietin analogue during the treatment period except for study medication or rescue medication (see Section 7.7.4.2)
- 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 randomization onwards until 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 route of treatment.

In subjects receiving roxadustat, the investigator may initiate the use of an approved IV iron supplement if:

- A patient's Hb level has not sufficiently responded to two or more dose increases of study drug, and
- Ferritin <100 ng/ml or transferring saturation (TSAT) <20%

Study treatment may continue during 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%). Use of IV iron will be recorded in the eCRF. In subjects receiving epoetin alfa, IV iron supplementation will be given according to standard of care.

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

7.7.4.1 Red blood cell transfusion

Red blood cell (RBC) transfusion is allowed in either roxadustat or epoetin alfa treated patients 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.

7.7.4.2 Erythropoietin analogue administration in patients randomized to roxadustat

For patients randomized to roxadustat, 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 <8.5 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 all immunization 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 an erythropoietin analogue and study drug at the same time. Treatment with an 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)

If more than one cycle of erythropoietin analogue rescue is required, the investigator should permanently discontinue study drug. Use of erythropoietin analogues will be recorded in the eCRF.

Note: For patients randomized to epoetin alfa, the investigator may initiate use of a different erythropoietin analogue if clinically indicated. Use of the different erythropoietin analogue will be recorded in the eCRF and will be considered rescue therapy.

7.7.4.3 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.

7.7.5 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

Analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will be prepared prior to database lock. It is recognized that Regulatory Authorities might require different efficacy and/or safety endpoints or alternate analyses for approval. The endpoints and analyses described in this protocol are intended for the US (FDA) submission. Regional SAPs will fully describe any changes to endpoints or analyses that differ from those described in this protocol.

8.2 Sample size estimate

Primary efficacy variable: With at least 600 subjects, the study will provide at least 99% power to demonstrate non-inferiority of roxadustat versus epoetin alfa for the primary efficacy endpoint (i.e., Hb change from baseline to the average level during the evaluation period defined as Week 28 until Week 52). This assumes a difference (roxadustat minus epoetin alfa) of -0.30 g/dL, a non-inferiority margin for this difference of -0.75 g/dL and a standard deviation of 1.25 g/dL.

To contribute adjudicated CV events for the pooled CV analyses across the phase 3 program: approximately 2000 subjects will be randomized in a 1:1 ratio to either roxadustat or active control, i.e. epoetin alfa. The sample size for this study is driven by the overall requirement of adjudicated CV events for the phase 3 program in dialysis-treated CKD subjects (which consists of four studies in total targeting 611 subjects with MACE events). The three other studies in the study program are FG-4592-064, 1517-CL-0613, FG-4592-063.

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 last intake of study drug.

8.3.3 Safety analysis set (SAS)

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. On-treatment analyses will be emphasized.

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 Database lock (breaking of Sponsor blindness, open-label study) 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 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 ANCOVA multiple imputation 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 the mean change from baseline in Hb averaged over week 28 to week 36, without having received rescue therapy (i.e. RBC transfusion for all subjects or ESA for subjects treated with roxadustat) within 6 weeks prior to and during this 8-week evaluation period.

8.4.2 Hb related secondary efficacy endpoints:

The Hb related secondary efficacy endpoints are:

- The EU primary endpoint is the first secondary efficacy endpoint.
- 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 measurement 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 from baseline in LDL cholesterol to week 24.

8.4.4 IV iron related secondary efficacy variable endpoints:

The use of IV iron will be investigated with the variable:

- Average monthly IV iron use per subject during, week 36 to EOS (monthly defined as a period of 4 weeks).

8.4.5 Rescue therapy related secondary efficacy endpoints:

The need for rescue therapy will be evaluated as

- Time-to-first (and proportion of subjects receiving) administration of red blood cell (RBC) transfusion as rescue therapy (rescue therapy guidelines are specified in the CSP, Section 7.7.4).

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 four phase 3 studies, FG-4592-064, 1517-CL-0613, FG-4592-063, and D5740C00002, in the CKD-DD 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 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, with addition of incident vs stable dialysis. The stratification variables are:

1. Baseline Hb (≤ 10.5 g/dL vs > 10.5 g/dL)
2. cardiovascular/cerebrovascular/thromboembolic medical history (Yes vs. No)
3. geographical region (US vs. Ex-US)
4. incident vs. stable dialysis (dialysis duration ≤4 months vs >4 months from the randomization date)

Baseline Hb will be included in the analyses as a continuous covariate, hence, not as a dichotomous factor, unless specified otherwise. Throughout this document, the variable

cardiovascular/cerebrovascular/thromboembolic medical history will be shortened as CV history, and the variable incident vs stable dialysis will be shortened as dialysis duration

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 analyzed with multiple imputation ANCOVA as described in the SAP. The model will contain terms for the baseline Hb measurement, treatment arm, CV history, geographic region and dialysis duration. Non-inferiority of roxadustat compared to epoetin alfa 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 epoetin alfa exceeds -0.75 g/dL. The ITT analysis set will be used.

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

The primary efficacy endpoint for EU is Hb change from baseline (BL) to the average Hb of weeks 28 to 36, without having received rescue therapy (i.e. RBC transfusion for all subjects and ESA for roxadustat subjects) within 6 weeks prior to and during this 8-week evaluation period and will be analysed using MMRM. The model will contain terms for the baseline Hb measurement, treatment arm, visit, visit by treatment, CV history, geographic region and dialysis duration. Data up to visit of Week 52 will be included in the model. Non-inferiority of roxadustat compared to epoetin alfa 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 epoetin alfa exceeds -0.75 g/dL. The PPS will be used for non-inferiority. In addition to the comparison based on the PPS population, to address the formal test for non-inferiority, results will also be provided based on the FAS population, to allow also for a potential superiority comparison. The latter test is not part of the formal testing sequence.

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 PPS will be used on the first secondary endpoint for non-inferiority, on treatment analysis will be used on the secondary endpoint related to RBC transfusion as rescue therapy, and the ITT analysis set will be used for all the remaining secondary endpoints.

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

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

3. 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 epoetin alfa 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 epoetin alfa exceeds 0 g/dL.

4. 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 epoetin alfa will be compared using ANCOVA. Baseline Hb will be used as a covariate and the treatment groups, CV history, geographic region and dialysis duration as fixed effects. Non-inferiority between the groups 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 epoetin alfa exceeds -0.15.

5. 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 epoetin alfa will be compared using ANCOVA. Baseline Hb will be used as a covariate and the treatment groups, CV history, geographic region and dialysis duration as fixed effects. Non-inferiority between the groups 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 epoetin alfa exceeds -0.15.

6. The average monthly IV iron use during Week 36 to EOS will be compared between the two treatment groups using a Wilcoxon Rank Sum test. Superiority will be declared if the p-value is less than 0.05.

7. Time-to-first (and proportion of subjects receiving) RBC transfusion as rescue therapy. The baseline Hb, geographic region, dialysis duration and CV history will be included as covariates.

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

As 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 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 centre 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 centre 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 and 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 centres 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 Centre 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 questionnaire has 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 Centre.

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 Centre 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 Centre 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 Forms 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/Institutional Review Board should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee/Institutional Review Board 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 enrolment of any patient into the study, the national regulatory authority will approve 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/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 centre 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 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 10.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre'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

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, 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, analysed, 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 centre.

11. LIST OF REFERENCES

Andrews et al 2014
Andrews DA, Pyrah ITG, Boren BM, Tannehill-Gregg SH, Lightfoot-Dunn RM. High Hematocrit Resulting from Administration of Erythropoiesis-stimulating Agents Is Not Fully Predictive of Mortality or Toxicities in Preclinical Species.
Toxicol Pathol 2014;42(3):510-23

Gandra et al 2010
Gandra SR, Finkelstein FO, Bennett AV, Lewis EF, Brazg T, Martin ML. Impact of erythropoiesis-stimulating agents on energy and physical function in nondialysis CKD patients with anemia: A systematic review. *Am J Kidney Dis* 2010;55(3):519-34

Hicks et al 2014
Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A et al. ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on

Clinical Data Standards Writing Committee to Develop Cardiovascular Endpoints Data Standards. *Circulation* 2015; 131: 1-109

Johansen et al 2010
Johansen KL, Finkelstein FO, Revicki DA, Gitlin M, Evans C, Mayne TJ. Systematic Review and Meta-analysis of Exercise Tolerance and Physical Functioning in Dialysis Patients Treated With Erythropoiesis-Stimulating Agents. *Am J Kidney Dis* 2010;55(3):535-48

KDIGO 2012
Kidney Disease Improving Global Outcomes (KDIGO) 2012. Clinical Practice Guideline for Anaemia in Chronic Kidney Disease. *Kidney International Supplements* 2012;2(4):279-335

Lascano et al 2010
Lascano ME, Schreiber MJ, Nurko S. *Chronic Kidney Disease*. Cleveland Clinic 2010. Available at:
http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/nephrology/chronic-kidney-disease/

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

Peyssonnaux et al 2008
Peyssonnaux CV, Nizet, Johnson RS. Role of the hypoxia inducible factors HIF in iron metabolism. *Cell Cycle* 2008;7(1):28-32

Pfeffer et al 2009
Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU et al. A trial of darbepoeitin alfa in type 2 diabetes and chronic kidney disease.
N Engl J Med 2009;361(21):2019-32

Phrommintikul et al 2010
Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis.
The Lancet 2010;369(9559):381-8

Semenza 1998
Semenza GL. Hypoxia-inducible factor 1: master regulator of O_2 homeostasis.
Curr Opin Genet Dev 1998;8(5):588-94

Singh 2010
Singh AK. The FDA's Perspective on the Risk for Rapid Rise in Haemoglobin in Treating CKD Anaemia: Quo Vadis. Renal Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. *Clin J Am Soc Nephrol* 2010;5:553-6

Skali et al 2011

Skali H, Parving H-H, Parfrey PS, Burdmann EA, Lewis EF, Ivanovich P et al . Stroke in Patients With Type 2 Diabetes Mellitus, Chronic Kidney Disease, and Anemia Treated With Darbepoetin Alfa. The Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) Experience. *Circulation* 2011;124:2903-2908

Strippoli et al 2004
Strippoli GFM, Craig JC, Manno C, Schena FP. Haemoglobin Targets for the Anemia of Chronic Kidney Disease: A Meta-analysis of Randomized, Controlled Trials. *J Am Soc Nephrol* 2004;15(12):3154-65

Yu et al 2013
Yu P, Chou J, Zong M, Neff T, Schaddelee M. Similar PK/PD profiles were observed following comparable doses of FG-4592 in haemodialysis (HD) patients. World Congress of Nephrology Hong Kong 31 May - 4 June 2013, Poster SU437

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 'related' 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 'not related'.

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) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication 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 **together with** 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:

- 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

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